QUINOLIZIDINES. XXIX.\(^1\) PREPARATION OF (−)-DIHYDRO-CORYNANTHEOL

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Abstract—An alternative, total synthesis of the indoloquinolizidine alkaloid (−)-dihydrocorynantheol (−)-1, adaptable to that on a gram scale preparation, has been achieved via a "lactim ether route". The route started with an initial condensation between the lactim ether [(+)-4] and 3-(chloroacetyl)indole and proceeded through the lactam ketone [(+)-5], oxazolium salt (6), N-substituted lactam [(+)-8], quaternary iminium salt (9), and tetracyclic ester [(−)-11].

As part of a study on the chiral synthesis of indoloquinolizidine alkaloids in this laboratory, it was necessary to prepare (−)-dihydrocorynantheol (corynan-17-ol) (−)-1\(^2\) in gram quantity. This Corynanthe-type alkaloid has been isolated from the bark\(^3\) and stem bark\(^4\) of Aspidosperma maragravanum Woodson (Apocynaceae); the bark of A. auriculatum;\(^5\) the leaves of Amsonia tabernaemontana Walt. (Apocynaceae);\(^6\) the leaves of Mitragyna parvifolia (Roxb.) Korth (Rubiaceae);\(^7\) the bark of Hunteria zeylanica

\[ (-)-1 \]

\[ (-)-2: R = \text{MeO} \]

\[ (-)-3: R = \text{H} \]

(Apocynaceae); the trunk bark of Ochrosia moorei (Apocynaceae); the root bark and trunk bark of Aspidosperma marcgravianum; the roots of Rhazya stricta Decsne. (Apocynaceae); the stem bark of Strychnos johnsonii Hutch et M. B. Mass (Logani-
caceae); the stem bark of Ochrosia alyxioides Guillaumin; and the aerial part of Aspidosperma oblongum. Semisynthetic (-)-1 has been prepared from various alkaloids such as dihydrocorynantheine, geissoschizol, quinine, ajmalicine, and guettardine. In 1985, Suzuki et al. reported a milligram scale synthesis of (-)-1 starting from (R)-1,2-isopropylidenglyceraldehyde. This has been the only total synthesis of (-)-1 reported so far. However, a repetition of any one of these preparative methods for attaining our purpose would encounter a difficulty in securing the plant materials (for extraction) or the starting alkaloids (for the partial synthesis) and/or the target alkaloid in sufficient amounts. On the other hand, our recent total syntheses of (+)-1 (in a formal sense) and the Netsosperma alkaloids (-)-ochrop-posinine and (-)-ochromianine through the “lactim ether route” would take the lead in designing a synthetic route to (-)-1. We therefore decided to follow a chiral, 10,11-unsubstituted version of these syntheses, as shown in Scheme 1, in the present study.

The initial step was coupling of the lactim ether with 3-(chloroacetyl)-indole, which proceeded in HCONMe2 at 60°C in the presence of KBr for 72 h, giving the lactam ketone in 68% yield. Treatment of (+)-5 with POCl3 in boiling toluene for 3 h afforded the oxazolium chloride, which was characterized as the crystalline perchlorate salt [(+)-7]. The crude chloride salt [(+)-7] was then reduced by catalytic hydrogenation (Pt/H2, EtOH, 1 atm, room temperature, 3 h) to furnish the lactam [(+)-8] in 52% overall yield [from (+)-5]. Conversion of (+)-8 into the tetracyclic ester [(-)-11] through the quaternary iminium salt [characterized as the crystalline perchlorate salt [(+)-10]] was effected in 91% overall yield by means of Bischler-Napieralski cyclization (POCl3, boiling toluene, 1 h) followed by catalytic hydrogenation (Pt/H2, EtOH, 1 atm, room temperature, 1 h). The hydrogen at C(3) of [(-)-11 was assigned the α configuration by the analogy with catalytic hydrogenation of similar systems, and the appearance of absorption bands, attributable to a trans-quinolizidine ring, in the IR spectrum of [(-)-11 in CHCl3 supported the correctness of this
In conclusion, the above results represent an alternative, total synthesis of \((-\text{-})\)-dihydrocorynantheol \((-\text{-})\)-1 since the starting lactim ether \((+\text{-})\)-4 is easily available not only by partially synthetic means [from the major Cinchona alkaloids (e. g., cinchonine) through cinchotoipon ethyl ester]^{25b} but also by totally synthetic means.\(^{27}\) This new synthetic route to \((-\text{-})\)-1, adaptable to its preparation on a gram-size scale, exemplifies the usefulness of our "lactim ether route"\(^{22-26}\) for chiral syntheses of the Corynanthe-type indoloquinolizidine alkaloids. After completion of the present work, Fukumoto's group\(^{30}\) has reported yet another total synthesis of \((-\text{-})\)-1, together with a semisynthetic route from yohimbine.

Assignment. On reduction with LiAlH\(_4\) in tetrahydrofuran (THF) at room temperature for 30 min, \((-\text{-})\)-11 produced the desired alkaloid \([-\text{-})\]-I in quantitative yield. The correctness of the structure of the synthetic \((-\text{-})\)-1 was confirmed by comparison of its melting point, specific rotation, and spectral data with those reported for authentic samples of natural and semisynthetic origin.
EXPERIMENTAL

General Notes All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. See refs. 1 and 22b for details of chromatography, instrumentation, and measurements. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

(4R,5R)-5-Ethyl-1-[2-(1H-indol-3-yl)-2-oxoethyl]-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-5]. A mixture of (+)-4₂₅b,₂₇ (2.76 g, 11.4 mmol), 3-(chloroacetyl)indole₃₁ (2.30 g, 11.9 mmol), and KBr (3.37 g, 28.3 mmol) in HCONMe₂ (14 ml) was stirred at 60°C for 72 h. The reaction mixture was concentrated in vacuo, and the residue was partitioned by extraction with a mixture of H₂O (120 ml) and CH₂Cl₂ (120 ml). The CH₂Cl₂ extracts were washed successively with saturated aqueous NaHCO₃ and H₂O, then dried, and concentrated to leave a brown oil (3.98 g). Purification of the oil by flash chromatography₃² (silica gel, AcOEt) afforded (+)-5 (2.86 g, 68%) as a faintly orangy solid, mp 140-141.5°C. Recrystallization from AcOEt yielded an analytical sample as colorless needles, mp 146-147°C; [α]D²⁴ +38.0° (c 0.498, EtOH); ms m/z: 370 (M+); uv λmax (EtOH) 241 nm (ε 13800), 260.5 (sh) (9400), 298 (13600); ir νmax (Nujol) cm⁻¹: 3180 (NH), 1727 (ester CO), 1660 (ArCO), 1620 (lactam CO); ¹H nmr (CDCl₃) δ: 0.93 (3H, t, J = 7 Hz, CCH₂Me), 1.27 (3H, t, J = 7 Hz, OCH₂Me), 1.3-3.6 (10H, m, CCH₂Me, C(3)-H's, C(4)-H, C(5)-H, C(6)-H's, and CH₂CO₂Et), 4.15 (2H, q, J = 7 Hz, OCH₂Me), 4.50 (2H, s, COCH₂N), 7.1-7.4 (3H, m, C(5')-H, C(6')-H, and C(7')-H), 7.77 (1H, d, J = 3 Hz, C(2')-H), 8.1-8.3 (1H, m, C(4')-H), 9.93 (1H, br, NH).³³ Anal. Calcd for C₁₁H₁₆N₂O₄: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.23; H, 7.27; N, 7.32. The uv and ¹H nmr spectra of this sample were virtually identical with those of (+)-5.²¹¹

(6R,7R)-7-(2-Ethoxy-2-oxoethyl)-6-ethyl-2-(1H-indol-3-yl)-5,6,7,8-tetrahydrooxazolo-[3,2-alpyridinium Chloride (6). A mixture of (+)-5 (1.48 g, 4.0 mmol) and POCl₃ (12.3 g, 80.2 mmol) in dry toluene (100 ml) was heated under reflux in an atmosphere of N₂
for 3 h. The reaction mixture was concentrated in vacuo, and the residue was washed with hexane (4 × 3 ml) to leave crude 6 (2.24 g) as a reddish purple solid. This sample was directly used in the next hydrogenation step without further purification.

(6R,7R)-7-[2-Ethoxy-2-oxoethyl]-6-ethyl-2-(1H-indol-3-yl)-5,6,7,8-tetrahydrooxazolo-[3,2-a]pyridinium Perchlorate [(+)-7]. A small sample (ca. 0.5 mmol) of crude 6 was triturated with a solution of NaClO₄·H₂O (140 mg, 1 mmol) in H₂O (7 ml). The dark brown gum that resulted was filtered off, washed with H₂O, then dried, and triturated with hexane to give crude (+)-7 as a brown solid. Recrystallization of the solid from CHCl₃ furnished an analytical sample as colorless needles, mp 131-132°C; [α]D²⁶ +66.4° (c 0.503, EtOH); uv λmax (EtOH) 241.5 nm (sh) (ε 12500), 249 (sh) (10900), 308 (15500); ir νmax (Nujol) cm⁻¹: 3315 (NH), 1722 (ester CO), 1657 (C=N+), 1625 (C=C); ¹H nmr (Me₂SO-d₆) δ: 0.95 (3H, t, J = 7 Hz, CCH₂Me), 1.23 (3H, t, J = 7 Hz, OCH₂Me), 1.35-4.45 [10H, m, C(CH₃)₂Me, C(5)-H's, C(6)-H, C(7)-H, C(8)-H's, and CH₂CO₂Et], 4.13 (2H, q, J = 7 Hz, OCH₂Me), 7.15-7.9 [4H, m, C(4')-H, C(5')-H, C(6')-H, and C(7')-H], 8.07 [1H, d, J = 2.5 Hz, C(2')-H], 8.30 [1H, s, C(3')-H], 11.98 (1H, br, NH). Anal. Calcd for C₂₁H₂₅N₂O₇Cl: C, 55.69; H, 5.56; N, 6.19. Found: C, 55.43; H, 5.60; N, 6.08.

(4R,5R)-5-Ethyl-1-[2-(1H-indol-3-yl)ethyl]-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-8]. A solution of crude 6 (vide supra) (2.24 g) in EtOH (165 ml) was hydrogenated over Adams catalyst (315 mg) at atmospheric pressure and room temperature for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The residue was partitioned by extraction with a mixture of H₂O (80 ml) and CH₂Cl₂ (80 ml). The CH₂Cl₂ extracts were washed successively with H₂O and saturated aqueous NaCl, dried, and concentrated to leave a brown oil (1.25 g). Purification of the oil by flash chromatography [silica gel, AcOEt-hexane (5 : 1, v/v)] gave (+)-8 [737 mg, 52% overall yield from (+)-5] as a faintly brownish solid, mp 121-123.5°C. Recrystallization of the solid from AcOEt-hexane (1 : 1, v/v) yielded an analytical sample of (+)-8 as almost colorless prisms, mp 124.5-125.5°C; [α]D¹⁷ +86.2° (c 0.499, EtOH); ms m/z: 356 (M⁺); uv λmax (EtOH) 274.5 nm (sh) (ε 5400), 282.5 (6000), 291 (5180); ir νmax (Nujol) cm⁻¹: 3155 (NH), 1725 (ester CO), 1620 (lactam CO); ¹H nmr (CDCl₃) δ: 0.75
(3H, t, J = 7 Hz, CCH₂Me), 1.26 (3H, t, J = 7 Hz, OCH₂Me), 1.05-3.3 (12H, m, CCH₂Me, CH₂Ar, C(3)-H's, C(4)-H, C(5)-H, C(6)-H's, and CH₂CO₂Et), 3.55-3.8 (2H, m, CH₂CH₂Ar), 4.13 (2H, q, J = 7 Hz, OCH₂Me), 7.0-7.7 (5H, m, aromatic protons), 8.11 (1H, br, NH). Anal. Calcd for C₂₁H₂₈N₂O₃: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.80; H, 7.96; N, 7.64. The uv and 1H nmr spectra of this sample were virtually identical with those of (±)-8.²¹

3,4-Didehydro-17-ethoxy-17-oxocorynanium Chloride (9). A mixture of (+)-8 (535 mg, 1.5 mmol) and POCl₃ (1.38 g, 9.0 mmol) in dry toluene (9 ml) was heated under reflux in an atmosphere of N₂ for 1 h. After cooling, the reaction mixture was concentrated in vacuo, and the residue was partitioned by extraction with a mixture of CHCl₃ (40 ml) and H₂O (15 ml). The CHCl₃ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave crude 9 (622 mg) as a brown glass. This sample was directly used in the next hydrogenation step without further purification.

3,4-Didehydro-17-ethoxy-17-oxocorynanum Perchlorate ([+]-10). A small sample (127 mg) of crude 9 was dissolved in MeOH (1 ml), and a solution of NaClO₄·H₂O (126 mg, 0.897 mmol) in MeOH (0.5 ml) was added. The yellowish crystals that deposited were filtered off, washed successively with MeOH (0.5 ml) and H₂O (2 ml), and dried to give (+)-10 [121 mg, 92% overall yield from (+)-8], mp 183.5-185°C (decomp). Recrystallization from MeOH–ether (2:1, v/v) provided an analytical sample as almost colorless needles, mp 193.5-194.5°C (decomp); [α]D²³ +84.0° (c 0.499, MeOH); uv λmax (EtOH) 246 nm (ε 10600), 354 (19200); ir νmax (Nujol) cm⁻¹: 3270 (NH), 1643 (C=N+); 1H nmr (Me₂SO-d₆) δ: 0.92 (3H, t, J = 7 Hz, CCH₂Me), 1.23 (3H, t, J = 7 Hz, OCH₂Me), 1.3-4.1 (14H, m, CCH₂Me, C(5)-H's, C(6)-H's, C(14)-H's, C(15)-H, C(20)-H, C(21)-H's, and C(16)-H's), 4.14 (2H, q, J = 7 Hz, OCH₂Me), 7.05-7.8 (4H, m, aromatic protons), 12.25 (1H, br, NH). Anal. Calcd for C₂₁H₂₇N₂O₆Cl: C, 57.47; H, 6.20; N, 6.38. Found: C, 57.24; H, 6.20; N, 6.38.

Corynan-17-oic Acid Ethyl Ester ([−]-11). A solution of crude 9 (vide supra) (622 mg) in EtOH (60 ml) was hydrogenated over Adams catalyst (60 mg) at atmospheric pressure
and room temperature for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to leave an oil, which was dissolved in H2O (100 ml). The resulting aqueous solution was made alkaline with 10% aqueous Na2CO3 and then extracted with benzene. The benzene extracts were combined, washed with saturated aqueous NaCl, dried, and concentrated to leave a dark greenish glass (492 mg). Purification of the glass by flash chromatography furnished (-)-11 [464 mg, 91% overall yield from (+)-8] as a faintly yellowish glass [lit., mp 54–55°C]; [α]D24 +4.6° (c 0.521, EtOH) [lit.,34 α]D25 –12° (c and solvent unspecified)]; ms m/z: 340 (M+); uv λmax (EtOH) 225.5 nm (ε 36200), 274.5 (sh) (7000), 282 (7440), 290 (6250); ir νmax (CHCl3) cm⁻¹: 3475 (free NH), 3375 (associated NH), 2805, 2755 (trans-quinolizidine ring29), 1724 (ester CO); ¹H nmr (CDCl3) δ: 0.92 (3H, t, J = 7 Hz, CCH2Me), 1.29 (3H, t, J = 7 Hz, OCH2Me), 1.1–3.35 [15H, m, CCH2Me, C(3)-H, C(5)-H’s, C(6)-H’s, C(14)-H’s, C(15)-H, C(20)-H, C(21)-H’s, and C(16)-H’s], 4.18 (2H, q, J = 7 Hz, OCH2Me), 6.95–7.55 (4H, m, aromatic protons), 7.80 (1H, br, NH). The ¹H nmr and mass spectral data were in agreement with those reported for authentic (-)-11. In an attempt to crystallize the above sample, however, it turned dark.

Corynan-17-ol (Dihydrocorynantheol) [(-)-1]. A solution of (-)-11 (447 mg, 1.31 mmol) in dry tetrahydrofuran (THF) (9 ml) was added dropwise to a stirred, ice-cooled suspension of LiAlH4 (149 mg, 3.93 mmol) in dry THF (9 ml) over a period of 15 min. After the resulting mixture had been stirred at room temperature for 30 min, THF (1 ml), H2O (0.1 ml), 10% aqueous NaOH (0.1 ml), and H2O (0.2 ml) were added in that order under ice-cooling. Stirring was continued at room temperature for 30 min, and the insoluble material that resulted was filtered off and washed with THF (30 ml). The filtrate and washings were combined, dried over anhydrous K2CO3, and concentrated to leave (-)-1 (390 mg, 100%) as a yellowish solid, mp 178.5–182°C. Recrystallization of the solid from AcOEt–hexane (1:1, v/v) yielded an analytical sample as colorless needles, mp 184.5–186°C (lit., mp 181–183°C;3 185–187°C;16 184–185°C17); [α]D21 +35.4° (c 0.486, pyridine) [lit., [α]D27 +34° (c 0.47, pyridine);3 [α]D23 +37±2° (c 0.938, pyridine)16]; [α]D22 +14.2° (c 0.921, CHCl3);35 [α]D23 +13.0° (c 0.508, CHCl3–EtOH
(100 : 1, v/v]); ms m/z: 298 (M+); uv λ<sub>max</sub> (EtOH) 225.5 nm (ε 38100), 273.5 (sh) (7340), 282 (7820), 289.5 (6530); ir ν<sub>max</sub> (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3625 (OH), 3480 (NH), 3295 (associated OH and NH), 2810, 2755 (trans-quinolizidine ring<sup>29</sup>); <sup>1</sup>H nmr (CDCl<sub>3</sub>) δ: 0.92 [3H, t, J = 6.5 Hz, C(18)-H's], 1.61 (1H, br, OH), 1.05–3.3 [15H, m, C(14)-H's, C(15)-H, C(16)-H's, C(19)-H's, C(20)-H, C(3)-H, C(5)-H's, C(6)-H's, and C(21)-H's], 3.65–3.85 [2H, m, C(17)-H's], 7.0–7.55 (4H, m, aromatic protons), 8.80 (1H, br, NH). Anal. Calcd for C<sub>19</sub>H<sub>26</sub>N<sub>2</sub>O: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.32; H, 8.82; N, 9.35.

The uv, ir, <sup>1</sup>H nmr, and mass spectral data were virtually identical with those<sup>16,17,20</sup> reported for authentic (-)-1.

ACKNOWLEDGMENT

We are pleased to acknowledge the support of this work by a grant from the Japan Research Foundation for Optically Active Compounds.

REFERENCES


2. Unless otherwise stated, the structural formulas of optically active compounds in this paper represent their absolute configurations.


33. For convenience, each position of the indole ring is indicated by a primed number.
35. The optical rotation in CHCl₃ showed a tendency to decrease slowly during measurement.

Received, 20th December, 1990