Synthesis of (±)-Thalictricavine, Berlambine, and (±)-Canadine from a Common Intermediate

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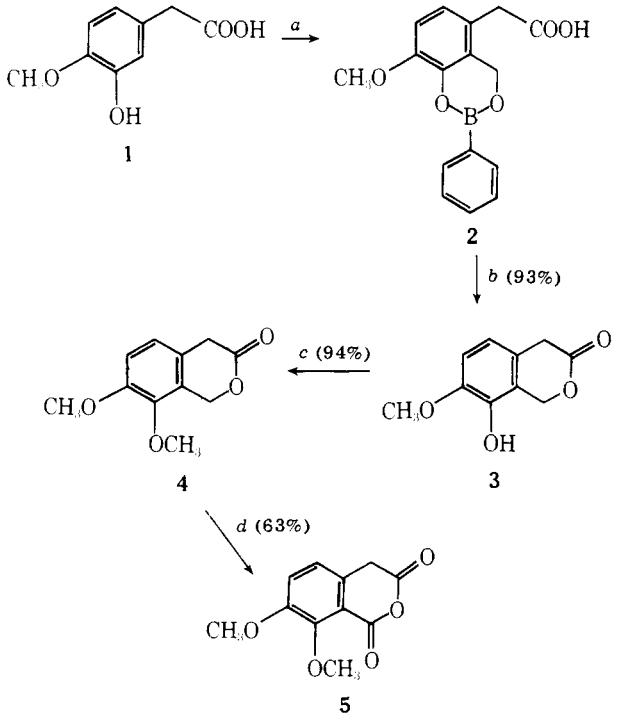
The protoberberine alkaloids (±)-thalictricavine (12), berlambine (8), and (±)-canadine (9) have been synthesized from *cis*-2,3-methylenedioxy-8-oxo-9,10-dimethoxy-13-carboxytetrahydroprotoberberine (7).

The protoberberine alkaloids thalictricavine (12), berlambine (8), and canadine (9) differ only in the substitution pattern and oxidation state of the C ring.[1] We have recently been interested in the possibility that these metabolites could be prepared from the appropriately substituted *cis*-13-carboxytetrahydroprotoberberine 7. The preparation of canadine (9) would also constitute a formal synthesis of berberine, lambertine, and ophiocarpine, which differ only in the oxidation state of the C ring and are chemically interconvertible.[1b,3]

The challenging 9,10-dioxygenation pattern displayed by most of the naturally occurring protoberberines has recently stimulated work involving a variety of approaches to the synthesis of this system.[1a-d,4] In the present instance, our method[2] requires an intermediate 3,4-dimethoxyhomophthalic anhydride (5, Scheme I), which dictates the 9,10-dimethoxy substitution pattern of the protoberberine resulting from its condensation with norhydrastinine (6). Although a synthesis of the required anhydride 5 has been previously reported,[5] the methods demand extensive modification to be practicable and the route is too long.[6] We now report the synthesis shown in Scheme I.

Scheme I



[a] (1) $PhB(OH)_2$, toluene, reflux (1 h); (2) paraformaldehyde, 3 Å molecular sieves, 100 °C (46 h). [b] H_2O, reflux (2 h). [c] Dimethyl sulfate, Me_2CO, K_2CO_3, reflux (2 h). [d] (1) $KMnO_4$, aqueous KOH, room temperature (16 h); (2) AcCl, reflux (2 h).

Anchimerically assisted hydroxymethylation of the readily available homoisovanillic acid (1)[7] in the presence of phenylboric acid and paraformaldehyde is known to proceed ortho to the phenol, yielding intermediate 2, which may be hydrolyzed without isolation to the lactone 3.[4j] The troublesome loss of paraformaldehyde from the reaction mixture by its solidification in the condenser during the reported procedure[4j] can be avoided by performing the reaction over molecular sieves in a bomb. The corresponding methyl ether 4 was then oxidized with potassium permanganate in aqueous potassium hydroxide, and the crude intermediate diacid was converted without purification to the anhydride 5.

Condensation of norhydrastinine (6) with 3,4-dimethoxyhomophthalic anhydride (5, Scheme II) proceeded exothermally in chloroform to afford a mixture of cis and trans isomers which was converted to the thermodynamically more stable cis diastereomer 7 (J_{AB} = 4 Hz)[2] on heating in acetic acid. Although it is known that the classical Hunsdiecker reaction rarely gives good results on unsaturated systems,[8] we initially attempted to convert the cis acid 7 to berlambine (8) by decarboxylative halogenation[9-11] followed by dehydrohalogenation. Mercuric oxide and bromine gave a complex mixture of products, and lead tetraacetate with cuprous iodide also gave unsatisfactory results. However, when the cis acid 7 was treated with lead tetraacetate in the presence of cupric acetate, potassium acetate, acetic acid, and dimethylformamide, a 65% yield of the desired berlambine (8) was obtained directly. Aluminum hydride reduction of berlambine in ether afforded (±)-canadine (9).

The NMR spectrum of the methyl ester 10, prepared by treatment of the corresponding acid 7 with diazomethane, displayed the singlet at δ 3.46 anticipated for the pseudoaxial methoxycarbonyl protons which are shielded by the aromatic rings.[2] Reduction of 10 with lithium aluminum hydride afforded the amino alcohol 11. The mesylate of 11 was then reduced to (±)-thalictricavine by sodium borohydride in refluxing ethanol. The NMR spectrum of our synthetic (±)-thalictricavine (12) displayed the C-13 methyl doublet at δ 0.95, the C-8 methylene AB quartet with doublets at δ 4.27 and 3.50 (J = 16 Hz), and the C-14 methine doublet at δ 3.72 (J = 3 Hz) of the natural product.[1a,12]

Experimental Section

All reactions were performed under a nitrogen atmosphere unless otherwise noted, and solvents were removed on a rotary evaporator under reduced pressure. Melting points were taken on a Thomas Hoover Unimelt or a Meltemp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 60-MHz instrument or a JEOL PFT-100 spectrometer, and except where noted, in $CDCl_3$ solvent. Chemical shifts are reported in parts per million relative to Me_4Si as an internal standard. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Mass spectra were determined on a Dupont 21-492B double-focusing spectrometer using an ion source temperature of 200–280 °C, an ionization potential of 70 eV, and an ionizing current of 100 μA. Microanalyses were performed by Dr. C. S. Yeh and associates at Purdue University.

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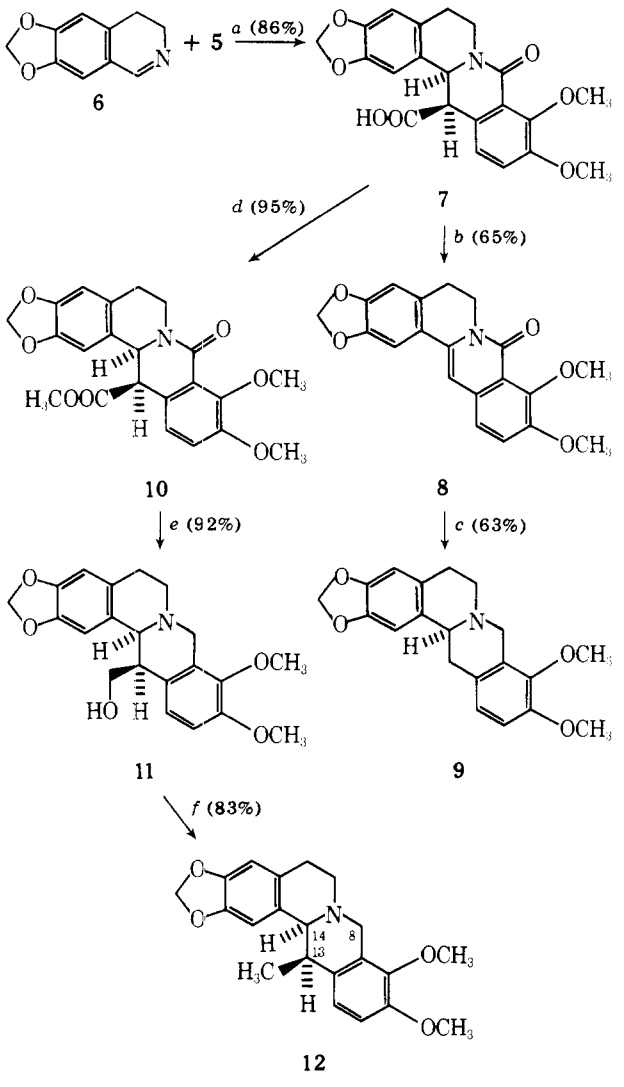
Scheme II



[a] (1) $CHCl_3$, room temperature (30 min); (2) AcOH, reflux (24 h). [b] (1) $Pb(OAc)_4$, $Cu(OAc)_2$, AcOH, DMF, room temperature (0.5 h); (2) 100 °C (0.5 h). [c] $LiAlH_4$, $AlCl_3$, Et_2O, room temperature (16 h). [d] CH_2N_2, Et_2O–EtOH, 0 °C (2 h). [e] $LiAlH_4$, THF–Et_2O (3:1), reflux (16 h). [f] (1) MsCl, pyridine, 35 °C (4 h); (2) $NaBH_4$, EtOH, reflux (48 h).

7-Methoxy-8-hydroxyisochroman-3-one (3). To homoisovanillic acid[7] (1; 6.08 g, 33.4 mmol) was added phenylboric acid (8.00 g, 65.6 mmol) and toluene (190 mL). The mixture was heated at reflux for 1 h, and H_2O (~1 mL) was collected in a Dean-Stark trap. The hot solution was poured over molecular sieves (3 Å, 4.26 g) in a stainless steel bomb. Paraformaldehyde (7.26 g) was added along with enough toluene (~2–3 mL) to bring the level of the solution to 0.25 in. from the brim. The bomb was sealed and heated on a steam bath for 46 h. The bomb was opened and the hot solution filtered. The toluene was evaporated, and water (75 mL) was added to the residue. After heating at reflux for 2 h, the mixture was cooled to room temperature and extracted with CH_2Cl_2 (200 mL). The solution was dried ($MgSO_4$) and the solvent evaporated. The residue was stirred in Et_2O (60 mL) for 3 h and the solid lactone 3 (6.03 g, 93%) filtered: mp 173–175 °C (lit.[4j] mp 183–185 °C); IR (KBr) 3500–3300, 1725 cm^{-1}; NMR ($CDCl_3$–pyridine-d_5, 5:1) δ 10.25 (br s, 1 H, exchangeable with D_2O), 6.92 (d, J = 8 Hz, 1 H), 6.68 (d, J = 8 Hz, 1 H), 5.53 (s, 2 H), 3.82 (s, 2 H), 3.67 (s, 3 H).

3,4-Dimethoxyhomophthalic Anhydride (5). The dimethoxy lactone 4[4j] (2.00 g, 9.6 mmol) was dissolved in H_2O (20 mL) containing KOH (1.08 g). To this was added a solution of $KMnO_4$ (3.0 g, 19 mmol) in H_2O (150 mL). The mixture was allowed to stir at room temperature for 16 h, after which the mixture was filtered through Celite. The filtrate was acidified with HCl to pH 1, saturated with NaCl, and extracted with Et_2O (2 × 150 mL). The Et_2O layers were extracted with 5% $NaHCO_3$ (2 × 150 mL). The combined $NaHCO_3$ extracts were washed with benzene (150 mL), acidified (HCl), saturated with NaCl, and extracted with Et_2O (3 × 150 mL). The Et_2O was dried ($MgSO_4$) and evaporated to give a colorless oil (2.26 g, 98%) which would not crystallize. The oil was heated in refluxing AcCl (50 mL) for 2 h, the mixture was concentrated to 5 mL, and Et_2O (50 mL) was added. Upon standing overnight the product (1.34 g, 63%) crystallized out of solution: mp 115–117 °C (lit.[5] mp 104–105 °C); IR (KBr) 2960, 1790, 1750, 1255 cm^{-1}; NMR δ 7.27 (d, 1 H, J = 9 Hz), 7.02 (d, 1 H, J = 9 Hz), 4.00 (s, 2 H), 3.97 (s, 3 H), 3.92 (s, 3 H).

***cis*-2,3-Methylenedioxy-8-oxo-9,10-dimethoxy-13-carboxytetrahydroprotoberberine (7).** 3,4-Dimethoxyhomophthalic anhydride (5; 2.00 g, 9.00 mmol) was added to a stirred solution of norhydrastinine (6; 1.58 g, 9.00 mmol) in $CHCl_3$ (10 mL). A vigorous exothermic reaction occurred, and the mixture was stirred at room temperature for 1 h. Evaporation of the solvent left a yellow powder, which was heated in refluxing AcOH (50 mL) for 16 h. The AcOH was evaporated, and the oily residue was dissolved in CH_3CN (100 mL). The product (3.08 g, 86%) crystallized in colorless plates: mp 246–247 °C dec; IR (KBr) 3300–2700, 1710, 1615, 1235 cm^{-1}; NMR ($CDCl_3$–pyridine-d_5, 5:1) δ 10.65 (br, 1 H, exchangeable with D_2O), 7.18 (d, 1 H, J = 8 Hz), 7.05 (d, 1 H, J = 8 Hz), 6.83 (s, 1 H), 6.67 (s, 1 H), 5.97 (s, 2 H), 5.10 (d, J = 4 Hz, 1 H), 4.90 (m, 1 H), 4.10 (obscured d, 1 H), 4.10 (s, 3 H), 3.93 (s, 3 H), 2.93 (m, 3 H); mass spectrum, *m/e* (rel intensity) 397 (M^+, 34), 362 (45), 235 (38), 221 (54), 194 (82), 179 (100), 176 (96).

Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.45; H, 5.07; N, 3.54.

Berlambine (8). To a solution of the cis acid 7 (100 mg, 0.25 mmol), KOAc (250 mg, 2.55 mmol), $Cu(OAc)_2$ (15 mg, 75 μmol), and AcOH (0.150 mL) in dry DMF (2 mL) was added $Pb(OAc)_4$ (112 mg, 0.25 mmol). Additional DMF (3 mL) was added, and the solution was purged with N_2 at room temperature with stirring for 0.5 h. The mixture was then heated at 100 °C for 0.5 h. The mixture was poured into H_2O (50 mL). The H_2O phase was extracted with toluene (3 × 30 mL). The toluene phase was washed with 5% $NaHCO_3$ (2 × 30 mL) and H_2O (30 mL), dried ($MgSO_4$), and evaporated to give a pale yellow powder (68 mg, 69%), mp 191–196 °C. Recrystallization from 50% EtOH–H_2O gave pure berlambine (57 mg, 65%): mp 192–195 °C (lit.[13] mp 200 °C); IR (KBr) 2900, 1640, 1270 cm^{-1}; NMR (80 MHz) δ 7.29 (s, 2 H), 7.21 (s, 1 H), 6.71 (s, 2 H), 6.00 (s, 2 H), 4.29 (t, J = 6 Hz, 2 H), 4.01 (s, 3 H), 3.94 (s, 3 H), 2.88 (t, J = 6 Hz, 2 H); mass spectrum, *m/e* (rel intensity) 351 (M^+, 100), 337 (70), 323 (33), 292 (21), 236 (30).

(±)-Canadine (9). $AlCl_3$ (86 mg, 0.64 mmol) was added to a suspension of $LiAlH_4$ (73 mg, 1.92 mmol) in Et_2O (15 mL) at 0 °C. The mixture was allowed to warm to room temperature with constant stirring for 1 h. Berlambine (8; 250 mg, 0.71 mmol) was added to the ethereal AlH_3 mixture. The mixture was stirred at room temperature for 16 h, after which the excess hydride was decomposed by the addition of H_2O (78 μL), 15% NaOH (78 μL), and H_2O (234 μL). The aluminates were removed by filtration and washed with toluene (50 mL). The combined filtrates were dried ($MgSO_4$) and evaporated to give a yellow powder (180 mg, 75%), mp 152–158 °C, which rapidly turned brown. Recrystallization from 50% aqueous MeOH (10 mL) gave canadine (150 mg, 63%): mp 163–165 °C (lit.[14] mp 172 °C); IR (KBr) 2900, 2800, 2710, 1580, 1235 cm^{-1}; NMR (80 MHz) δ 6.82 (s, 2 H), 6.72 (s, 1 H), 6.58 (s, 1 H), 5.91 (s, 2 H), 4.25 (d, J = 16 Hz, 1 H), 3.84 (s, 7 H), 3.50 (d, J = 16 Hz, 1 H), 3.49–2.61 (m, 6 H); mass spectrum, *m/e* (rel intensity) 339 (M^+, 50), 176 (28), 175 (30), 163 (100), 143 (63), 142 (35).

***cis*-2,3-Methylenedioxy-8-oxo-9,10-dimethoxy-13-methoxycarbonyltetrahydroprotoberberine (10).** The acid 9 (2.70 g, 6.79 mmol) was slowly added to a solution of diazomethane (~3 g) in Et_2O–EtOH at 0 °C. After 3 h at 0 °C the excess diazomethane was decomposed by addition of AcOH. The solvent was evaporated to give crystalline product (2.65 g, 95%): mp 185–187 °C; IR (KBr) 2910, 1720, 1640, 1260 cm^{-1}; NMR δ 7.10 (s, 2 H), 6.75 (s, 1 H), 6.68 (s, 1 H), 6.00 (s, 2 H), 5.10 (d, J = 4 Hz, 1 H), 4.95 (m, 1 H), 4.10 (s, 3 H), 4.00 (obscured d, 1 H), 3.95 (s, 3 H), 3.46 (s, 3 H), 2.90 (m, 3 H); mass spectrum, *m/e* (rel intensity) 411 (M^+, 7), 235 (100), 208 (25), 192 (33), 186 (7), 160 (5). Calcd for $C_{22}H_{21}NO_7$: *m/e* 411.1318. Found: *m/e* 411.134.

Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.15; N, 3.40. Found: C, 64.20; H, 5.25; N, 3.18.

***cis*-2,3-Methylenedioxy-9,10-dimethoxy-13-hydroxymethyltetrahydroprotoberberine (11).** $LiAlH_4$ (0.79 g, 20.8 mmol) was carefully added to a solution of cis ester 10 (2.2 g, 5.3 mmol) in THF (135 mL) and Et_2O (45 mL). The mixture was heated at reflux for 16 h. The mixture was cooled and the excess hydride decomposed by the addition of H_2O (0.8 mL), 15% NaOH (0.8 mL), and finally H_2O (2.4 mL). The aluminates were filtered and washed with THF (2 × 100 mL). The combined filtrates were dried ($MgSO_4$) and evaporated to

yield a solid (1.81 g, 92%), mp 238–241 °C dec. An analytical sample was recrystallized from 95% EtOH: mp 240–241 °C; IR (KBr) 3300, 2880, 2820, 1230 cm^{-1}; NMR δ 7.15 (d, J = 8 Hz, 1 H), 6.98 (d, J = 8 Hz, 1 H), 6.67 (s, 2 H), 5.97 (s, 2 H), 5.72 (br, 1 H, exchangeable with D_2O), 4.32 (d, J = 16 Hz, 1 H), 3.90 (s, 8 H), 3.78 (d, J = 3 Hz, 1 H), 3.53 (d, J = 16 Hz, 1 H), 3.35–2.40 (m, 5 H); mass spectrum, m/e (rel intensity) 369 (M^+, 100), 348 (43), 194 (99), 179 (46), 166 (41), 155 (59).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.17; H, 6.32; N, 3.56.

(±)-Thalictricavine (12). Methanesulfonyl chloride (520 μL, 6.7 mmol) was added to a solution of the cis alcohol **11** (1.33 g, 3.60 mmol) in pyridine (10 mL). The solution was stirred at 35 °C for 3.5 h and then poured into H_2O (100 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 100 mL). The combined $CHCl_3$ layers were dried ($MgSO_4$) and evaporated. The last traces of pyridine were removed at 35 °C (0.1 mm) to afford the mesylate as a light brown oil (1.6 g, 100%). The oil was suspended in 95% EtOH (100 mL). $NaBH_4$ (0.95 g, 25 mmol) was added to the stirred mixture. The mixture was heated at reflux for 48 h and then poured into H_2O (100 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 100 mL). The $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated to yield the crude product. The powder was triturated with Et_2O (10 mL), filtered, washed again with Et_2O (20 mL), and dried to afford pure (±)-thalictricavine (1.05 g, 83%): mp 204–206 °C (lit.[15] mp 205–207 °C); IR (KBr) 2910, 2795, 2760, 1240 cm^{-1}; NMR δ 6.90 (s, 2 H), 6.72 (s, 1 H), 6.62 (s, 1 H), 5.92 (s, 2 H), 4.27 (d, J = 16 Hz, 1 H), 3.90 (s, 6 H), 3.72 (d, J = 3 Hz, 1 H), 3.50 (d, J = 16 Hz, 1 H), 3.45–2.25 (m, 5 H), 0.95 (d, J = 7 Hz, 3 H); mass spectrum, m/e (rel intensity) 353 (M^+, 40), 338 (7), 179 (15), 178 (100), 162 (22).

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Registry No.—**1**, 1131-94-8; **3**, 56201-87-7; **4**, 4697-59-0; **5**, 68408-56-0; **6**, 6882-28-6; **7**, 68408-57-1; **8**, 549-21-3; **9**, 29074-38-2; **10**, 68408-58-2; **11**, 38969-51-6; **12**, 38969-46-9; phenylboric acid, 98-80-6.

References and Notes

(1) For previous work on the synthesis of these natural products, see (a) T. Kametani, T. Sugai, Y. Shoji, T. Honda, F. Satoh, and K. Fukumoto, *J. Chem. Soc., Perkin Trans 1*, 1151 (1977); (b) T. Kametani, I. Noguchi, K. Saito, and S. Kaneda, *J. Chem. Soc. C*, 2036 (1969); (c) T. Kametani, K. Fukumoto, T. Terui, K. Yamaki, and E. Taguchi, *ibid.*, 2709 (1971); (d) R. Rajaraman, B. R. Pai, M. S. Premila, and H. Suguna, *Indian J. Chem., Sect. B*, **15B**, 876 (1977); (e) W. H. Perkin, Jr., J. N. Ray, and R. Robinson, *J. Chem. Soc.*, 127, 740 (1925); (f) R. D. Haworth, J. B. Koepfli, and W. H. Perkin, Jr., *ibid.*, 548 (1927), and references cited therein.

(2) (a) M. Cushman, J. Gentry, and F. W. Dekow, *J. Org. Chem.*, **42**, 1111 (1977); (b) M. A. Haimova, N. M. Mollov, S. C. Ivanova, A. I. Dimitrova, and V. I. Ognyanov, *Tetrahedron*, **33**, 331 (1977).

(3) (a) I. W. Elliott, Jr., *J. Heterocycl. Chem.*, **4**, 639 (1967); (b) M. Hanaoka, C. Mukai, and Y. Arata, *Heterocycles*, **6**, 895 (1977).

(4) (a) R. T. Dean and H. Rapoport, *J. Org. Chem.*, **43**, 2115 (1978); (b) H.-C. Chiang, *Tai-wan Yao Hseuh Tsa Chih*, **28**, 111 (1977); (c) M. Shamma, A. S. Rothenberg, G. S. Jayatilake, and S. F. Hussain, *Tetrahedron*, **34**, 635 (1978); (d) I. Ninomiya, H. Takasugi, and T. Naito, *Heterocycles*, **1**, 17 (1973); A. A. Bindra, M. S. Wadia, and N. L. Dutta, *Indian J. Chem.*, **7**, 744 (1969); (e) S. Rajeswari, H. Suguna, and B. R. Pai, *Collect. Czech. Chem. Commun.*, **42**, 2207 (1977); (f) H.-C. Chiang and E. Brochmann-Hanssen, *J. Org. Chem.*, **42**, 3190 (1977); (g) T. Kametani, H. Matsumoto, Y. Satoh, H. Nemoto, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 376 (1977); (h) C. K. Bradsher and N. L. Dutta, *J. Am. Chem. Soc.*, **82**, 1145 (1960); (i) A. R. Battersby, R. Southgate, J. Staunton, and M. Hirst, *J. Chem. Soc. C*, 1052 (1966); (j) W. Nagata, H. Itazaki, K. Okada, T. Wakabayashi, K. Shibata, and N. Tokutake, *Chem. Pharm. Bull.*, **23**, 2867 (1975); (k) B. R. Pai, T. Natarajan, G. Manikumar, R. Rajaraman, and H. Suguna, *J. Org. Chem.*, **43**, 1992 (1978).

(5) R. D. Haworth, J. B. Koepfli, and W. H. Perkin, Jr., *J. Chem. Soc.*, 548 (1927).

(6) M. Cushman and F. W. Dekow, *Tetrahedron*, **34**, 1435 (1978).

(7) R. Grewe and H. Fisher, *Chem. Ber.*, **96**, 1520 (1963).

(8) J. March, "Advanced Organic Chemistry. Reactions, Mechanisms, and Structure", 2nd ed., McGraw-Hill, New York, 1977, p 668.

(9) D. E. Applequist and N. D. Werner, *J. Org. Chem.*, **28**, 48 (1963).

(10) F. W. Baker, H. D. Holtz, and L. M. Stock, *J. Org. Chem.*, **28**, 514 (1963).

(11) J. A. Davis, J. Herynk, S. Carroll, J. Bunds, and D. Johnson, *J. Org. Chem.*, **30**, 415 (1965).

(12) C. K. Yu, D. B. MacLean, R. G. A. Rodrigo, and R. H. F. Manske, *Can. J. Chem.*, **48**, 3673 (1970).

(13) M. Tomita and T. Kugo, *Yakugaku Zasshi*, **79**, 317 (1959).

(14) "The Merck Index", 9th ed., Merck and Co., Inc., Rahway, N.J.

(15) C. Tani, N. Takao, S. Takao, and K. Tagahara, *Yakugaku Zasshi*, **82**, 751 (1962).

Subsessiline: Structure Revision and Synthesis

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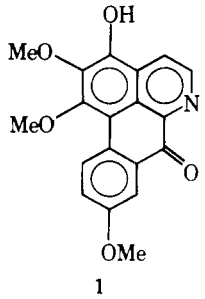
The total synthesis of the oxoaporphine alkaloid subsessiline is reported. Comparision with the natural product has shown subsessiline to be 9-hydroxy-1,2,3-trimethoxy-7*H*-dibenzo[*de*,*g*]quinolin-7-one (**2**), rather than the 3-hydroxy isomer (**1**), as previously assumed.

Of the more than 20 known oxoaporphine alkaloids, only a few are phenolic in nature.[1] Among these, subsessiline, which has been assigned structure **1**,[2] contains the unusual feature of a phenolic function at the C_3 position of the aporphine system. In connection with other alkaloid structural studies in progress in our laboratory, we have now synthesized 9-hydroxy-1,2,3-trimethoxy-7*H*-dibenzo[*de*,*g*]quinolin-7-one (**2**). The latter substance unexpectedly proved to be identical with natural subsessiline, the structure of which must therefore be revised from **1** to **2**.



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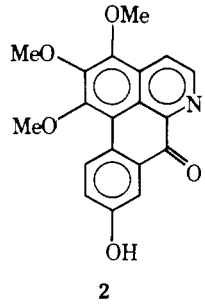

2

Results and Discussion

The synthetic route to **2** which was employed involved, as a key step, the alkylation of the known Reissert compound 2-benzoyl-1,2-dihydro-5,6,7-trimethoxyisoquinaldonitrile (**10**)[3] with the previously unreported halide 2-nitro-5-(benzyloxy)benzyl chloride (**9**). A good practical preparation of halide **9** was devised starting from *m*-hydroxybenzaldehyde (**3**) and proceeding via intermediates **4**–**8**. A closely related synthesis of 2-nitro-5-hydroxybenzaldehyde (**6**) has already been described which proceeds via bis(3-formylphenyl) carbonate;[4] our variation has the advantage of not requiring the use of phosgene.

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