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).

Acknowledgment. This investigation was supported by Grant 1 RO1 CA19204, awarded by the National Cancer Institute, DHEW.

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

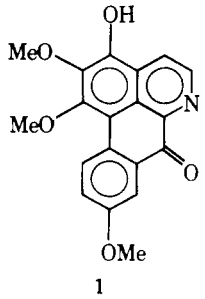
Jerry W. Skiles and Michael P. Cava*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

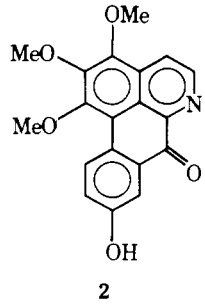
Received July 21, 1978

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**.



1

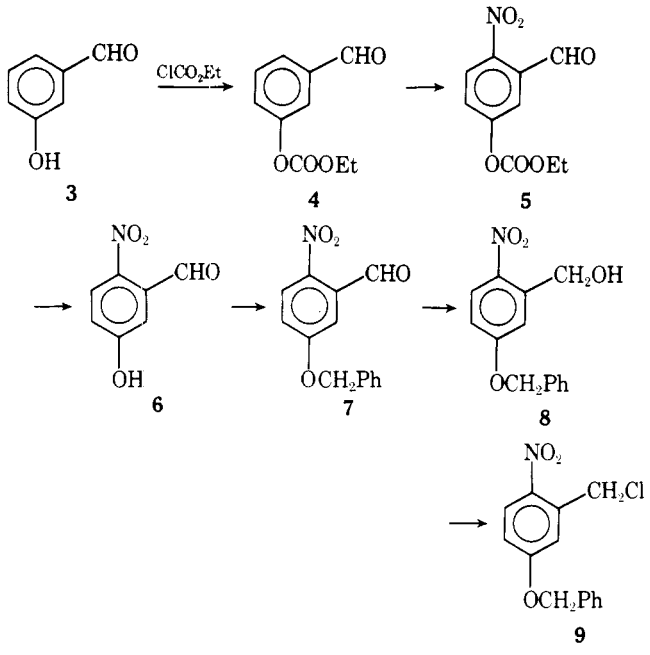


2

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.

0022-3263/79/1944-0409$01.00/0



Alkylation of Reissert compound **10** by halide **9** proceeded cleanly and in high yield in benzene solution, using potassium hydroxide as the base and either a crown ether or a phase-transfer salt as the catalyst.[5] The resulting alkylated Reissert compound **11** was best converted to the benzylisoquinoline **12** (67% yield) by mild treatment with Triton B.[3] Examination of the mother liquors from this reaction led to the isolation of three byproducts: methyl benzoate, 1-cyano-5,6,7-trimethoxyisoquinoline (**13**), and 2-nitro-5-(benzyloxy)toluene (**14**).[7] Whereas benzylisoquinoline **12** results from the usual cyanide elimination process (path A), compounds **13** and **14** result from a competing process (path B) in which the stabilized anion of the nitrotoluene **14** is eliminated.

Reduction of the nitro benzyl ether **12** by hydrazine in the presence of palladium afforded a high yield of the aminophenol **15**. Hydrogenolysis of the *O*-benzyl protecting group could be avoided by reducing **12** catalytically in the presence of platinum and potassium carbonate, when the desired amine **16** was obtained almost quantitatively.

Under carefully defined conditions, Pschorr cyclization of a 6′-aminobenzylisoquinoline is accompanied by concomitant oxidation of the C-ring to give a 7-oxoaporphine; this method has been used in the synthesis of both imenine[6] and homomoschatoline.[8] In a similar manner, amine **16** afforded, in 18% yield, orange prisms of the 7-oxoaporphine benzyl ether **17**. Hydrogenolysis of the latter in the presence of palladium gave, in 84% yield, red prisms of 9-hydroxy-1,2,3-trimethoxy-7*H*-dibenzo[*de*,*g*]quinolin-7-one (**2**). Direct comparison of synthetic **2** with subsessiline of natural origin showed the two samples to be identical. Consequently, subsessiline is represented by structure **2** rather than the originally assigned[2] structure **1**.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were carried out by Midwest Microlabs, Indianapolis, Indiana.

Infrared spectra were recorded (KBr) on a Perkin-Elmer Model 137 IR spectrophotometer.

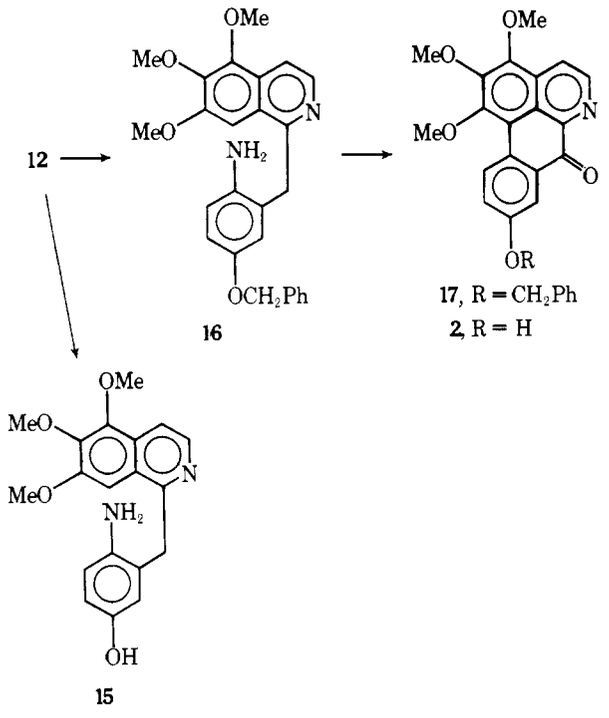
Nuclear magnetic resonance spectra were obtained on Varian A-60A, Varian HA-100D, Varian HA-220, and JEOL 100-MHz NMR instruments. All spectra were recorded in $CDCl_3$ (Me_4Si standard) unless otherwise noted.

Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 UV–vis spectrophotometer using matched 1.0-cm quartz cells. The wavelengths of all ultraviolet absorptions (λ_{max}) are reported in nanometers (nm) and are uncorrected.

Low-resolution mass spectra were recorded on a Perkin-Elmer Model 270B mass spectrometer. High-resolution mass spectra were determined by Dr. C. E. Costello of Massachusetts Institute of Technology.

Ethyl 3-Formylphenyl Carbonate (4). 3-Hydroxybenzaldehyde (**3**; 15.0 g, 0.123 mol) was dissolved in dry pyridine (100 mL). The solution was cooled in an ice bath, and ethyl chloroformate (20 mL) was added dropwise over a period of 30 min. The resulting solution was stirred for 2 h at room temperature. The solvent was evaporated and water (150 mL) added. The product was extracted into ether, and the extract was washed consecutively with water, 5% HCl, 5% cold NaOH, and again with water. The dried organic extract was evaporated to give the product as a dark red syrup (23 g, 97%) which was directly nitrated: NMR δ 1.34 (t, 3 H, J = 7.0 Hz, CH_3), 4.33 (q, 2 H, J = 7.0 Hz, CH_2), 7.36–7.89 (m, 4 H), 9.88 (s, 1 H, CHO).

Ethyl 3-Formyl-4-nitrophenyl Carbonate (5). Ethyl 3-formylphenyl carbonate (**4**; 14.0 g, 0.0722 mol) was dissolved in concentrated sulfuric acid (135 mL). The solution was cooled to −5 °C, and a solution of fuming nitric acid (3.44 mL, sp gr = 1.49, 0.0814 mol) in 25 mL of concentrated H_2SO_4 was added dropwise over 15 min at −5 to



0 °C. Stirring was continued at −5 to 0 °C for 1 h. Water (500 mL) was added dropwise at 0–10 °C, and the product was extracted into chloroform. Evaporation of the washed and dried solvent gave a gum which crystallized from ether as pale yellow needles (13.0 g, 76%), mp 60–61 °C. The product was directly hydrolyzed as described below.

2-Nitro-5-hydroxybenzaldehyde (6). Ethyl 3-formyl-4-nitrophenyl carbonate (**5**; 5.0 g, 0.021 mol) was added to 30 mL of 10% NaOH, and the mixture was stirred under argon at room temperature for 1 h. The dark brown solution was cooled in an ice bath and neutralized to pH 6 by the careful addition of glacial acetic acid (foaming). The mixture was cooled to 5 °C, stirred for 10 min, and then filtered. Crystallization of the crude solid from ethanol–water afforded yellow needles (3.19 g, 91%): mp 167–168 °C (lit.[4] mp 168–169 °C); IR 3175 (OH), 1684 (CHO), 1527 (NO_2), 1333 (NO_2) cm^{-1}; NMR (Me_2SO-d_6) δ 1.93 (s, 1 H, OH), 7.03 (dd, 1 H, $J_{3,4}$ = 9.0 Hz, $J_{4,6}$ = 2.5 Hz, C_4-H), 7.03 (d, 1 H, $J_{4,6}$ = 2.5 Hz, C_6-H), 8.08 (d, 1 H, $J_{3,4}$ = 9.0 Hz, C_3-H), 10.35 (s, 1 H, CHO).

2-Nitro-5-(benzyloxy)benzaldehyde (7). A mixture of 2-nitro-5-hydroxybenzaldehyde (**6**; 9.4 g, 0.0563 mol), anhydrous K_2CO_3 (10.0 g, 0.0725 mol), benzyl chloride (8.8 g, 0.0696 mol), and 150 mL of dry dimethylformamide was heated in an oil bath at 100–110 °C for 2.5 h under argon with vigorous stirring. The reaction mixture was cooled to 20 °C, and about 70 mL of water was added slowly with stirring until the mixture became permanently turbid. The contents of the flask were scratched with a glass rod until crystal formation was well under way. Slow addition of water was continued until a total of 175 mL was introduced. The mixture was cooled to 5 °C, filtered, and washed with water. Crystallization from ethanol afforded yellow needles (13.3 g, 92%): mp 70–72 °C (lit.[4] mp 71–73 °C); IR 1733 (C=O), 1531 (NO_2), 1344 (NO_2) cm^{-1}; NMR δ 5.15 (s, 2 H, OCH_2), 7.16 (dd, $J_{3,4}$ = 9.0 Hz, $J_{4,6}$ = 3.0 Hz, C_4-H), 7.29 (d, 1 H, $J_{4,6}$ = 3.0 Hz, C_6-H), 7.38 (br s, 5 H, Ph), 8.09 (d, 1 H, $J_{3,4}$ = 9.0 Hz, C_3-H), 10.41 (s, 1 H, CHO).

2-Nitro-5-(benzyloxy)benzyl Alcohol (8). 2-Nitro-5-(benzyloxy)benzaldehyde (**7**; 2.0 g, 7.78 mmol) was dissolved in 50 mL of methanol and cooled in an ice bath. Sodium borohydride (0.500 g, 0.013 mol) was added portionwise over 10 min, and then the mixture was stirred at room temperature for 45 min. Most of the solvent was evaporated, 100 mL of water was added, and the product was extracted into chloroform. Evaporation of the dried solvent gave a solid which was crystallized from ether to give pale yellow needles (1.73 g, 86%): mp 89–91 °C; IR 3311 (OH), 1506 (NO_2), 1326 (NO_2) cm^{-1}; NMR δ 2.89 (br s, 1 H, OH), 4.96 (s, 2 H, CH_2), 5.14 (s, 2 H, OCH_2Ph), 6.93 (dd, 1 H, $J_{3,4}$ = 9.0 Hz, $J_{4,6}$ = 3.0 Hz, C_4-H), 7.31 (d, 1 H, $J_{4,6}$ = 3.0 Hz, C_6-H), 7.39 (br s, 5 H, Ph), 8.14 (d, 1 H, $J_{3,4}$ = 9.0 Hz, C_3-H).

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.87; H, 4.90; N, 5.41. Found: C, 64.87; H, 4.90; N, 5.34.

2-Nitro-5-(benzyloxy)benzyl Chloride (9). 2-Nitro-5-(benzyloxy)benzyl alcohol (2.60 g, 10.0 mmol) was dissolved in 50 mL of dry benzene, and 10 drops of pyridine was added. Thionyl chloride (2.0 mL) was added in one portion, and the resulting mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo, 50 mL of water was added, and the product was extracted several times into hot hexane. Evaporation of the washed and dried extract afforded bright yellow prisms of **9** (1.97 g, 73%): mp 62–63 °C; NMR δ 4.91 (s, 2 H, CH_2Cl), 5.10 (s, 2 H, OCH_2Ph), 6.92 (dd, 1 H, $J_{3,4}$ = 9.0 Hz, $J_{4,6}$ = 3.0 Hz, C_4-H), 7.23 (d, 1 H, $J_{4,6}$ = 3.0 Hz, C_6-H), 7.28–7.50 (br s, 5 H, Ph), 8.05 (d, 1 H, $J_{3,4}$ = 9.0 Hz, C_3-H).

Anal. Calcd for $C_{14}H_{12}ClNO_3$: C, 60.54; H, 4.32; N, 5.05; Cl, 12.79. Found: C, 60.65; H, 4.72; N, 4.86; Cl, 12.65.

2-Benzoyl-1-[5-(benzyloxy)-2-nitrobenzyl]-1,2-dihydro-5,6,7-trimethoxyisoquinaldonitrile (11). A. Phase-Transfer Catalysis. In a 100-mL three-neck flask fitted with a serum cap and a gas inlet adapter extending to the bottom of the flask were placed 2-benzoyl-1,2-dihydro-5,6,7-trimethoxyisoquinaldonitrile (**10**; 3.00 g, 8.57 mmol),[3] 2-nitro-5-(benzyloxy)benzyl chloride (2.50 g, 9.01 mmol), and 100 mg of cetrimonium bromide. Benzene (100 mL) was added, and argon was bubbled through the resulting mixture for 10 min. Sodium hydroxide (10 mL of a 50% by weight aqueous solution) was added in one portion and the resulting mixture stirred at room temperature for 1.5 h; argon was bubbled through the solvent during the entire reaction period. The flask was cooled in an ice bath, the contents were acidified to pH 6 with 5% sulfuric acid, and the product was extracted several times into benzene. Evaporation of the washed and dried solvent gave a gum which was chromatographed on silica, eluting with benzene. On scratching under ether the product crystallized as bright yellow prisms; it was recrystallized from 95% ethanol to give bright yellow prisms of **11** (4.36 g, 86%): mp 156–157 °C; NMR δ 3.60 (s, 3 H, OCH_3), 3.91 (s, 6 H, $2OCH_3$), 4.23 (pair of doublets, 2 H, J_{gem} = 13.0 Hz, $\Delta_{A,B}$ = 47.0 Hz, δ_A = 3.84, δ_B = 4.62, benzylic protons), 5.21 (s, 2 H, OCH_2), 6.00 (d, 1 H, $J_{3,4}$ = 8.0 Hz, C_4-H), 6.36 (d, 1 H, $J_{3,4}$ = 8.0 Hz, C_3-H), 6.37 (s, 1 H, C_8-H), 6.96 (dd, 1 H, $J_{3,4}$ = 9.0 Hz, $J_{4,6}$ = 3.0 Hz, C_4-H), 7.25 (d, 1 H, $J_{4,6}$ = 3.0 Hz, C_6-H), 7.35–7.76 (m, 10 H), 7.79 (d, 1 H, $J_{3,4}$ = 9.0 Hz, C_3-H).

Anal. Calcd for $C_{34}H_{29}N_3O_7$: C, 69.04; H, 4.91; N, 7.11. Found: C, 68.96; H, 5.00; N, 7.22.

B. Crown Ether Catalysis. In a 100-mL three-neck flask fitted with a serum cap and a gas inlet adapter extending to the bottom of the flask were placed 2-benzoyl-1,2-dihydro-5,6,7-trimethoxyisoquinaldonitrile (**10**; 875 mg, 2.5 mmol),[3] 2-nitro-5-(benzyloxy)benzyl chloride (694 mg, 2.50 mmol), and dicyclohexyl 18-crown-6 ether (100 mg). Dry benzene was added, and the system was flushed with argon for 5 min. Finely ground potassium hydroxide pellets (3) were added in one portion. The resulting mixture was stirred vigorously for 2 h at room temperature. The reaction mixture was cooled in an ice bath and acidified to pH 6 with 5% sulfuric acid. The product was extracted several times into benzene. The usual workup, followed by chromatography on silica, eluting with benzene, gave bright yellow prisms of **11** after crystallization from ether (449 mg, 76%), mp 156–157 °C.

1-[2-Nitro-5-(benzyloxy)benzyl]-5,6,7-trimethoxyisoquinoline (12). Nitrile **11** (4.0 g, 6.77 mmol) was placed in a 100-mL three-neck flask fitted with a serum cap and a gas inlet adapter extending to the bottom of the flask, and 25 mL of dry dimethylformamide was added. The system was flushed with argon for 10 min, and the Triton B (2 mL, 40% methanolic benzyltrimethylammonium hydroxide) was syringed in. An instantaneous deep blue color resulted. The mixture was stirred at room temperature under argon for 45 min. The deep blue mixture was cooled in an ice bath and diluted with water. The product was extracted several times into chloroform. Evaporation of the washed and dried extract gave a pale yellow oil which crystallized from ether to afford the nitroisoquinoline **12** as pale yellow needles (2.050 g, 67%): mp 154–156 °C; NMR δ 3.88 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 4.93 (s, 2 H, CH_2), 4.96 (s, 2 H, OCH_2), 6.83 (d, 1 H, $J_{4,6}$ = 3.0 Hz, C_6-H), 6.87 (dd, 1 H, $J_{3,4}$ = 9.0 Hz, $J_{4,6}$ = 3.0 Hz, C_4-H), 7.13 (s, 1 H, C_8-H), 7.24 (s, 5 H, Ph), 7.75 (d, 1 H, $J_{3,4}$ = 5.5 Hz, C_4-H), 8.04 (d, 1 H, $J_{3,4}$ = 9.0 Hz, C_3-H), 8.30 (d, 1 H, $J_{3,4}$ = 5.5 Hz, C_3-H).

Anal. Calcd for $C_{26}H_{24}N_2O_6$: C, 67.83; H, 5.22; N, 6.09. Found: C, 67.56; H, 5.14; N, 6.06.

The ether filtrate from the above recrystallization was concentrated, and the residue was chromatographed on silica, eluting first with benzene and then with chloroform to give three components. Fraction A, the least polar fraction, gave methyl benzoate (110 mg, 3.5%) as a pale yellow oil whose NMR and IR spectra were identical with those of an authentic sample.

Fraction B gave 2-nitro-5-(benzyloxy)toluene (**14**; 444 mg, 14.3%) as pale yellow needles from hexane: mp 73–74 °C (lit.[7] mp 72–73 °C); NMR δ 2.53 (s, 3 H, CH_3), 5.05 (s, 2 H, OCH_2), 6.78 (dd, 1 H, $J_{3,4}$ =

9.0 Hz, $J_{4,6}$ = 3.0 Hz, C_4-H), 6.84 (d, 1 H, $J_{4,6}$ = 3.0 Hz, C_6-H), 7.33 (s, 5 H, Ph), 7.97 (d, 1 H, $J_{3,4}$ = 9.0 Hz, C_3-H).

Fraction C, the most polar fraction, proved to be 1-cyano-5,6,7-trimethoxyisoquinoline (**13**), which was identical (IR and NMR) with an authentic sample. Crystallization from methanol gave **13** as colorless needles (451 mg, 14.5%), mp 119–120 °C (lit.[6] mp 119–120 °C).

4-Amino-α-(5,6,7-trimethoxy-1-isoquinolyl)-*m*-cresol (15). Isoquinoline **12** (500 mg, 1.09 mmol) was dissolved in 100 mL of absolute ethanol, and anhydrous hydrazine (0.50 mL) was added. The system was placed under argon, and a slurry of 10% palladium on carbon (50 mg) in a small amount of ethanol was added. The argon inlet adapter was removed and the system warmed to 45–50 °C with vigorous stirring for 1 h. The catalyst was filtered off and the solvent evaporated. Water (100 mL) was added to the residue, and the product was extracted several times into chloroform. The combined washed and dried chloroform extract was evaporated to give the product (**15**) as a white chalky material which crystallized from methanol as colorless microcrystalline prisms (333 mg, 90%): mp 181–183 °C; NMR δ 3.90 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.35 (s, 2 H, CH_2), 5.15 (br s, 2 H, NH_2 and OH), 6.40–6.80 (m, 3 H), 7.33 (s, 1 H), 7.65 (s, 1 H, $J_{3,4}$ = 5.5 Hz, C_4-H), 8.08 (d, 1 H, $J_{3,4}$ = 5.5 Hz, C_3-H).

High-resolution mass spectrum calcd for $C_{19}H_{20}N_2O_4$: 340.14230. Found: 340.14028.

1-[2-Amino-5-(benzyloxy)benzyl]-5,6,7-trimethoxyisoquinoline (16). Isoquinoline **12** (460 mg, 1.00 mmol) was dissolved in 75 mL of methanol, and 50 mg of potassium carbonate was added. A slurry of Adams' catalyst (PtO_2, 50 mg) in methanol (50 mL) was added. The resulting mixture was hydrogenated in a Parr apparatus at an initial pressure of 45 psi for 3 h. The catalyst was filtered off and the solvent evaporated. Water (50 mL) was added to the residue, and the product was extracted several times into chloroform. Evaporation of the washed and dried extract gave a pale yellow oil which crystallized slowly from methanol, affording colorless prisms of **16** (413 mg, 96%): mp 72–74 °C; NMR δ 3.84 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.22 (br s, 2 H, concentration dependent NH_2), 4.37 (s, 2 H, CH_2), 4.83 (s, 2 H, OCH_2), 6.44 (dd, 1 H, $J_{3,4}$ = 9.0 Hz, $J_{4,6}$ = 3.0 Hz, C_4-H), 6.64 (d, 1 H, $J_{3,4}$ = 9.0 Hz, C_3-H), 6.89 (d, 1 H, $J_{4,6}$ = 3.0 Hz, C_6-H), 7.23 (s, 5 H, Ph), 7.68 (d, 1 H, $J_{3,4}$ = 5.5 Hz, C_4-H), 8.28 (d, 1 H, $J_{3,4}$ = 5.5 Hz, C_3-H).

High-resolution mass spectrum calcd for $C_{26}H_{26}N_2O_4$: 430.18925. Found: 430.18777.

9-(Benzyloxy)-1,2,3-trimethoxy-7*H*-dibenzo[*de,g*]quinolin-7-one (17). Aminoisoquinoline **16** (714 mg, 1.66 mmol) was dissolved in 30 mL of methanol, and 2 mL of 2 N sulfuric acid was added. The resulting solution was cooled to 0–5 °C, and a solution of $NaNO_2$ (725 mg, 10.5 mmol) in a small amount of water was added dropwise. The resulting mixture was stirred for 45 min at 0–10 °C. Sulfamic acid (725 mg) dissolved in a small amount of water was added portionwise with stirring. Excess copper–bronze was then added, causing a rapid evolution of nitrogen. The reaction was stirred at room temperature for 30 min, and then additional copper–bronze was added. The resulting mixture was heated to 50–55 °C for 2 h with vigorous stirring, the copper was filtered off, and most of the methanol was evaporated. Water was added to the residue, and the solution was basified to pH 8–9 with concentrated ammonium hydroxide. The precipitate was extracted into chloroform, and the extract was washed with water, then 5% NaOH, and again with water and dried over sodium sulfate. Evaporation of the solvent gave a dark black gum which was purified on silica TLC plates, developing first with chloroform and then with chloroform–methanol. A bright orange band was isolated from the polar zone. The orange band was further purified by dry-column chromatography on silica, eluting with purified ethyl acetate. The product crystallized from acetone to afford **17** as bright orange prisms (128 mg, 18%): mp 181–182 °C; IR (KBr) 1658 cm^{-1}; *m/e* 427 (M^+, 100), 412 (30), 397 (12), 384 (27), 336 (60), 308 (8); NMR δ 4.05 (s, 3 H, OCH_3), 4.09 (s, 3 H, OCH_3), 4.16 (s, 3 H, OCH_3), 5.23 (s, 2 H, OCH_2), 7.20–7.59 (m, 5 H), 7.69 (dd, 1 H, $J_{10,11}$ = 10.0 Hz, $J_{8,10}$ = 3.0 Hz, C_{10}-H), 8.12 (d, 1 H, $J_{8,10}$ = 3.0 Hz, C_8-H), 8.19 (d, 1 H, $J_{4,5}$ = 6.0 Hz, C_4-H), 8.94 (d, 1 H, $J_{4,5}$ = 6.0 Hz, C_5-H), 9.02 (d, 1 H, $J_{10,11}$ = 10.0 Hz, C_{11}-H).

High-resolution mass spectrum calcd for $C_{26}H_{21}NO_5$: 427.1420. Found: 427.1413.

9-Hydroxy-1,2,3-trimethoxy-7*H*-dibenzo[*de,g*]quinolin-7-one (2). Benzyl ether **17** (18 mg, 0.042 mmol) was dissolved in 75 mL of 95% ethanol. Concentrated hydrochloric acid (1 mL) and 10% palladium on carbon (50 mg) were added, and the contents of the flask were hydrogenated at 45 psi in a Parr apparatus for 4 h. The catalyst was filtered off, the solvent evaporated, and water added to the residue. The solution was basified to pH 8–9 with 10% ammonium hydroxide and the product extracted into chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a residue which was chromatographed on a short silica column, eluting with purified ethyl acetate. Crystallization from acetone gave deep red needles of **2** (12 mg, 86%): mp 223–226 °C; IR (KBr) 1661 cm^{-1} (C=O). The infrared spectrum of this synthetic sample was identical in all respects with that of an authentic sample of the natural alkaloid subsessiline: *m/e* 337 (M^+, 100), 322 (68), 307 (27), 294 (18), 279 (30), 264 (35), 251 (16), 236 (33), 208 (18), 180 (13), 168.5 (9, double charged ion); NMR δ 4.05 (s, 3 H, OCH_3), 4.09 (s, 3 H, OCH_3), 4.15 (s, 3 H, OCH_3), 7.96 (d, 1 H, $J_{8,10}$ = 3.0 Hz, C_8-H), 8.17 (d, 1 H, $J_{4,5}$ = 5.5 Hz, C_4-H), 8.91 (d, 1 H, $J_{4,5}$ = 5.5 Hz, C_3-H), 8.97 (d, 1 H, $J_{10,11}$ = 10.0 Hz, C_{11}-H).

High-resolution mass spectrum calcd for $C_{19}H_{15}NO_5$: 337.0950. Found: 377.0954.

Acknowledgment. We thank the National Institutes of Health for a grant (CA-22337-01) in partial support of this work and Dr. C. E. Costello (Massachusetts Institute of Technology) for high-resolution mass spectral determinations. We also thank Dr. M. Hasegawa, Universidad Central de Venezuela, Caracas, for a generous gift of natural subsessiline.

Registry No.—**2,** 49620-02-2; **3,** 100-83-4; **4,** 68423-35-8; **5,** 59342-81-3; **6,** 42454-06-8; **7,** 58662-54-7; **8,** 68423-36-9; **9,** 68423-37-0; **10,** 23740-80-9; **11,** 68423-38-1; **12,** 68423-39-2; **13,** 58189-36-9; **14,** 22424-58-4; **15,** 68423-40-5; **16,** 68423-41-6; **17,** 68423-42-7; ethyl chloroformate, 541-41-3; benzyl chloride, 100-44-7.

References and Notes

(1) For the most recent compilation of all types of aporphines, see H. Guinaudeau, M. Leboeuf, and A. Cave, *Lloydia,* **38,** 275 (1975).
(2) M. Hasegawa, M. Sojo, A. Lira, and C. Marquez, *Acta Cient. Venez.,* **23,** 165 (1972); *Chem. Abstr.,* **79,** 42716 (1973).
(3) M. P. Cava and M. V. Lakshmikantham, *J. Org. Chem.,* **35,** 1867 (1970).
(4) K. N. F. Shaw, A. Gudmundson, and A. G. Morris, *Biochem. Prep.,* **9,** 12 (1962).
(5) For a comparative study of Reissert compound alkylations by these procedures, see J. W. Skiles and M. P. Cava, *Heterocycles,* **9,** 653 (1978).
(6) M. P. Cava and I. Noguchi, *J. Org. Chem.,* **38,** 60 (1973).
(7) H. Burton and J. L. Stoves, *J. Chem. Soc.,* 402 (1937).
(8) M. P. Cava, K. T. Buck, I. Noguchi, M. Srinivasan, and M. G. Rao, *Tetrahedron,* **31,** 1667 (1975).