Conversion of (—)-β-Hydrastine into (—)-Bicuculline and Related Phthalideisoquinolines

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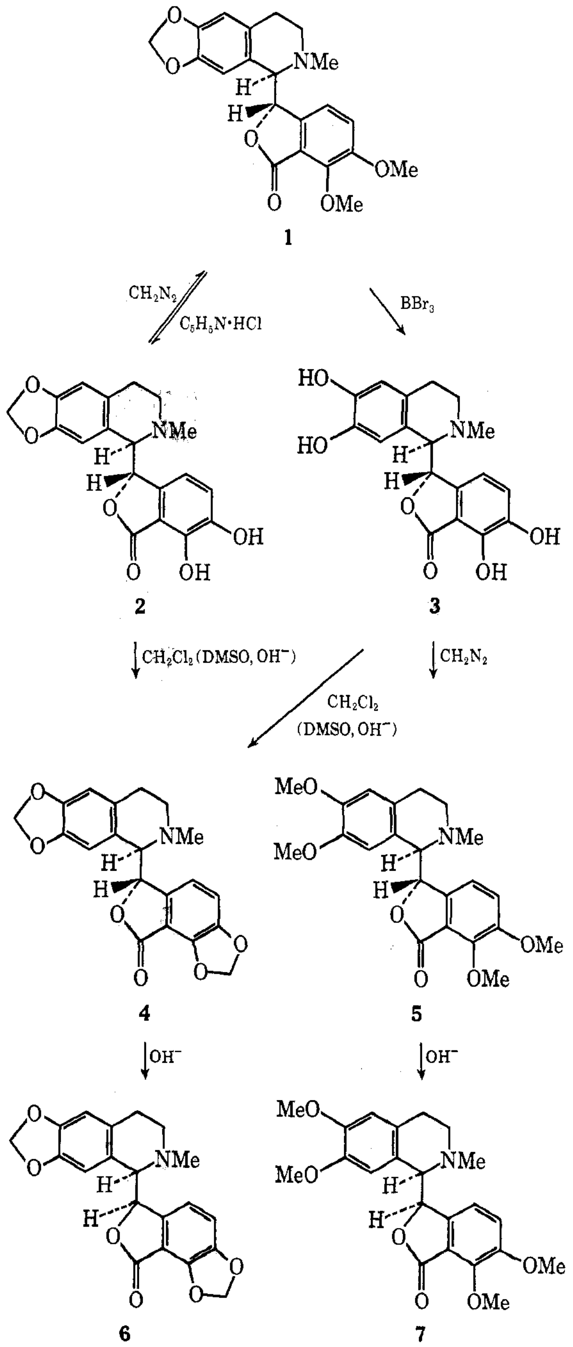
Commercially available (−)-β-hydrastine (**1**) was O-demethylated to the tetraphenol **3** followed by bis-O-methylenation or complete O-methylation to afford the rare phthalide alkaloid (−)-bicuculline (**4**) and the new phthalideisoquinoline (−)-cordrastine II (**5**), respectively. Alkaline isomerization provided the corresponding C-9 epimers capnoidine (**6**) and (−)-cordrastine I (**7**). An X-ray analysis of **4** HBr confirmed the assignments of absolute configuration.

In connection with our studies on the total synthesis of the benzazepine alkaloid rhoeadine,[1] a bismethylenedioxy-substituted phthalideisoquinoline was required as starting material. While the known[2] phthalide alkaloids (−)-bicuculline (**4**) and its epimer capnoidine (**6**) as well as the corresponding antipodes (+)-bicuculline and adlumidine contain such a substitution pattern, they are neither commercially available nor is their isomeric mixture, previously obtained by a multistep synthesis as *x*-bicuculline,[3] readily accessible. In contrast, we now report a facile and novel synthesis of the heretofore rare alkaloid (−)-bicuculline (**4**) based on O-dealkylation of commercially available (−)-β-hydrastine (**1**) followed by O-methylenation. Utilizing this approach, the tetramethoxy-substituted phthalideisoquinoline **5** was also prepared and the method was extended by isomerization of **4** and **5** to provide the C-9 epimers capnoidine (**6**) and **7**, respectively.

Treatment of (−)-β-hydrastine (**1**) with pyridine hydrochloride or boron tribromide in methylene chloride effected O-demethylation or complete deetherification to afford 30% of the diphenol **2** or 90% of the tetraphenol **3**, respectively. While diazomethane reconverted **2** into the starting material **1**, reaction of **2** or **3** in dimethyl sulfoxide with methylene chloride and 1 equiv of sodium hydroxide[4] provided in approximately 30% yield the same bismethylenedioxy-substituted phthalide **4**, identical in all respects with natural (−)-bicuculline.[2] Thus, the stereochemical assignment for the phenolic intermediates was secured.

As an extension of the utility of this approach, complete O-methylation of the tetraphenol **3** with diazomethane afforded the corresponding tetramethoxy-substituted phthalideisoquinoline **5**. In addition, treatment of **4** and **5** with alcoholic potassium hydroxide effected epimerization at the C-9 position to form the alkaloid capnoidine (**6**) and the related tetramethoxy derivative **7**, respectively.[4a] While the isomeric phthalides **5** and **7** are new, one of the racemates has been isolated as the alkaloid cordrastine[5] and the racemic diastereomers cordrastine I and cordrastine II have been obtained by synthesis.[6] By nmr and tlc comparison with the synthetic racemates,[7] **5** and **7** could be assigned as (−)-cordrastine II and (−)-cordrastine I, respectively.



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[1] W. Klötzer, S. Teitel, and A. Brossi, *Helv. Chim. Acta*, **54**, 2057 (1971).

[2] For leading references, see F. Šantavý in "The Alkaloids," Vol. XII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1970, p 396.

[3] P. W. G. Groenewoud and R. Robinson, *J. Chem. Soc.*, 199 (1936).

[4] W. Bonthrone and J. W. Cornforth, *J. Chem. Soc. C*, 1202 (1969).

[4a] NOTE ADDED IN PROOF.—Recently G. Gáal, P. Kerekes and B. Bognár, *J. Prakt. Chem.*, **313**, 935 (1971), reported the epimerization of (−)-α-narcotine at the C-1 position by successive treatment with cyanogen bromide and mineral acid. It should therefore be possible to prepare all four isomers of **4** and **5**.

[5] R. H. F. Manske, *Can. J. Res.*, **B16**, 81 (1938).

[6] R. D. Haworth and A. R. Pinder, *J. Chem. Soc.*, 1776 (1950).

[7] We are grateful to Professor R. D. Haworth, Sheffield University, England, for providing us with samples of racemic cordrastine I and cordrastine II.

Based on comparison of the nmr, ORD, and CD spectral data, (−)-β-hydrastine (**1**), (−)-bicuculline (**4**), and (−)-cordrastine II (**5**) all possess the 1*R*,9*S* configuration, while the epimers capnoidine (**6**) and (−)-cordrastine I (**7**) belong to the 1*R*,9*R* series. Unequivocal confirmation of the absolute configuration of these interrelated phthalides, previously assigned by other methods,[2] was obtained by an X-ray crystallographic analysis[8] of (−)-bicuculline hydrobromide (**4** HBr).

Experimental Section[9]

(+)-1-(*R*)-[6,7-Dihydroxy-3-(*S*)-phthalidlyl]-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (2).—A mixture of 5 g (12 mmol) of (−)-β-hydrastine hydrochloride (**1** HCl) and 15 g of pyridine hydrochloride was heated at 190° in a N_2 atmosphere for 30 min. The resulting solution was cooled to room temperature and partitioned between 150 ml of a 1:1 mixture of EtOAc and saturated $NaHCO_3$. The aqueous phase was separated and extracted with two 75-ml portions of EtOAc, and the combined organic extracts were evaporated. The residue (2 g) was crystallized from 50 ml of CH_2Cl_2 to give 1.5 g (35%) of **2**: mp 210–211°; R_f (system A) 0.29; $[\alpha]_D$ +140° (*c* 1, 1 *N* HCl); nmr δ 2.43 (s, 3, NCH_3), 2.1–2.9 (m, 4, CH_2CH_2), 3.96, 5.55 (2 d, 2, *J* = 4 Hz, 2 CH), 5.68 (s, 2, 2 OH), 5.92 (d, 2, OCH_2O), 6.50, 6.62 (2 s, 2, 2 aromatic), 6.83, 6.93 (2 d, 2, *J* = 8 Hz, 2 aromatic); uv max 296 nm (ε 6250), 318 (4900), 220 (3050) (infl), 240 (11,000); ORD (*c* 0.138, MeOH) $[\phi]_{600}$ −10°, $[\phi]_{589}$ −15°, $[\phi]_{340}$ −5850° (tr), $[\phi]_{303}$ +12,870° (pk), $[\phi]_{282}$ +4180° (tr), $[\phi]_{248}$ +18,000° (pk), $[\phi]_{239}$ +14,780° (tr), $[\phi]_{234}$ +16,710° (pk), $[\phi]_{210}$ −179,400° (tr); CD (*c* 0.0036 *M*, MeOH) $[\theta]_{380}$ 0, $[\theta]_{317}$ −12,170; $[\theta]_{293}$ +2070, $[\theta]_{284}$ 0, $[\theta]_{261}$ +8020, $[\theta]_{252}$ 0, $[\theta]_{223}$ +110,600, $[\theta]_{212}$ 0, $[\theta]_{204}$ −249,000.

Anal. Calcd for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.55; H, 5.03; N, 3.78.

Reconversion of Diphenol 2 into (−)-β-Hydrastine (1).—A mixture of 500 mg (1.4 mmol) of **2** in 30 ml of MeOH containing an excess of CH_2N_2 in Et_2O was stored at 4° for 2 hr and then at 25° for 18 hr. The solution was evaporated in a stream of N_2, and the residue was suspended in H_2O and extracted with CH_2Cl_2. The extract was acidified with ethanolic HCl and evaporated, and the residue was crystallized from a mixture of EtOH and Et_2O to give 400 mg (69%) of **1** HCl, mp 116–117°, $[\alpha]_D$ +121° (*c* 4, 1 *N* HCl), identical in mixture melting point, tlc, and optical rotation with authentic (−)-β-hydrastine hydrochloride.

(+)-1-(*R*)-[6,7-Dihydroxy-3-(*S*)-phthalidyl]-6,7-dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3 HCl).—To a solution of 20 g (48 mmol) of (−)-β-hydrastine hydrochloride (**1** HCl) in 300 ml of CH_2Cl_2 at −70° was added over 20 min a solution of 31 g (124 mmol) of BBr_3 in 250 ml of CH_2Cl_2. After stirring at room temperature for 17 hr, the reaction mixture was cooled to 4°, 300 ml of MeOH was added over 20 min, and then the mixture was evaporated. The residue was dissolved in 300 ml of H_2O and rendered neutral with saturated $NaHCO_3$, and the resulting precipitate was collected and dissolved in ethanolic HCl. The solution was evaporated and the residue was crystallized from a mixture of EtOH and Et_2O to give 16 g (90%) of **3** HCl: mp 205–206°; R_f (system A) 0.08; $[\alpha]_D$ +176.6° (*c* 1, MeOH); nmr δ 2.73 (s, 3, NCH_3), 2.6–4.0 (m, 4, CH_2CH_2), 4.96, 5.55 (2 s, 2, 2 CH), 6.27, 6.57 (2 s, 2, 2 aromatic), 7.08, 7.25 (2 d, 2, *J* = 8 Hz, 2 aromatic), 8.63, 9.04, 9.68, 9.98 (4 br, 4, 4 OH); uv max 292 nm (ε 4500), 321 (4500), 220 (27,500) (infl), 240 (10,000); ORD (*c* 0.344, MeOH) $[\phi]_{600}$ +470°, $[\phi]_{589}$ +500°, $[\phi]_{349}$ +1690° (tr), $[\phi]_{298}$ +18,780° (pk), $[\phi]_{281}$ +12,150° (tr), $[\phi]_{242}$ +55,240° (pk), $[\phi]_{210}$ −403,220° (tr); CD (*c* 0.0091 *M*, MeOH) $[\theta]_{370}$ 0, $[\theta]_{319}$ −5300, $[\theta]_{301}$ 0, $[\theta]_{290}$ +6960, $[\theta]_{271}$ +2100, $[\theta]_{226}$ +165,700, $[\theta]_{214}$ 0, $[\theta]_{207}$ −353,500.

Anal. Calcd for $C_{18}H_{17}NO_6 \cdot HCl$: C, 56.92; H, 4.78; N, 3.69. Found: C, 56.69; H, 5.13; N, 3.50.

(−)-2-Methyl-6,7-methylenedioxy-1-(*R*)-[6,7-methylenedioxy-3-(*S*)-phthalidyl]-1,2,3,4-tetrahydroisoquinoline [(−)-Bicuculline] (4). A. From 3.—A mixture of 10.4 g (27.4 mmol) of **3** HCl and 5.6 g (140 mmol) of powdered NaOH in 40 ml of CH_2Cl_2 and 140 ml of DMSO was stirred at 120° under a N_2 atmosphere for 1 hr, cooled, adjusted to pH 2 with 3 *N* HCl, and evaporated under reduced pressure. The residue was triturated with two 200-ml portions of CH_2Cl_2 and filtered, and the combined organic extracts were washed with 100-ml portions of saturated $NaHCO_3$ and evaporated. The residue (7 g) was dissolved in 100 ml of benzene and chromatographed over 35 g of silica gel. Elution with 500 ml of a 2:3 mixture of EtOAc and benzene followed by evaporation and crystallization from EtOH gave 3.4 g (34%) of **4**: mp 193–194°; $[\alpha]_D$ −120° (*c* 1, $CHCl_3$); $[\alpha]^{33}_D$ −128° (*c* 0.27, $CHCl_3$) [lit.[10] mp 193–195°, $[\alpha]^{33}_D$ −110° (*c* 0.27, $CHCl_3$); R_f (system B) 0.4; nmr ($CDCl_3$) δ 2.60 (s, 3, NCH_3), 2.0–3.0 (m, 4, CH_2CH_2), 4.09, 5.63 (2 d, 2, *J* = 4 Hz, 2 CH), 5.97, 6.20 (2, 2, 4, 2 OCH_2O), 6.25, 6.95 (2 d, 2, *J* = 8 Hz, 2 aromatic), 6.50, 6.64 (2 s, 2, 2 aromatic); uv max 220 nm (ε 29,300), 235 (11,700) (infl), 296 (6500), 320 (5500); ORD (*c* 0.184, 0.1 *N* HCl) $[\phi]_{650}$ +260°, $[\phi]_{589}$ +320°, $[\phi]_{348}$ +200° (tr), $[\phi]_{301}$ +9900° (pk), $[\phi]_{284}$ +4860° (tr), $[\phi]_{248}$ +26,500° (pk), $[\phi]_{242}$ +25,500° (tr), $[\phi]_{236}$ +29.500° (pk), $[\phi]_{209}$ −280,000° (tr); CD (*c* 0.005 *M*, 0.1 *N* HCl) $[\theta]_{365}$ 0, $[\theta]_{324}$ −3200, $[\theta]_{303}$ 0, $[\theta]_{294}$ +4600, $[\theta]_{273}$ +400, $[\theta]_{228}$ +106,000, $[\theta]_{213}$ 0, $[\theta]_{204}$ −332,000. ORD and CD mirror images of natural (+)-bicuculline[11] (antipode of **4**) were within experimental error.

Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.51; H, 4.87; N, 3.80.

An aliquot of **4** was converted into the hydrobromide with ethanolic HBr and crystallized from EtOH: mp 257–258°; $[\alpha]_D$ +96.9° (*c* 1, MeOH); nmr δ 2.97 (s, 3, NCH_3), 2.8–3.7 (m, 4, CH_2CH_2), 5.31, 5.70 (2 s, 2, 2 CH), 5.91, 5.98 (s, 2, OCH_2O), 6.25, 6.29 (s, 2, OCH_2O), 6.33, 6.84 (2 s, 2, 2 aromatic), 7.42 (s, 2, aromatic); uv max 222 nm (ε 27,600), 235 (11,900) (infl), 295 (6120), 322 (5540); ORD (*c* 0.448, MeOH) $[\phi]_{600}$ +390°, $[\phi]_{589}$ +409°, $[\phi]_{340}$ −1000° (tr), $[\phi]_{302}$ +13,500° (pk), $[\phi]_{281}$ +2750° (tr), $[\phi]_{244}$ +37,500° (pk), $[\phi]_{237}$ +35,000° (tr), $[\phi]_{233}$ +38,750° (pk), $[\phi]_{211}$ −269,960° (tr); CD (*c* 0.01 *M*, MeOH) $[\theta]_{380}$ 0, $[\theta]_{320}$ −5200, $[\theta]_{303}$ 0, $[\theta]_{294}$ +6300, $[\theta]_{275}$ 0, $[\theta]_{268}$ −1000, $[\theta]_{261}$ −200, $[\theta]_{255}$ −1100, $[\theta]_{252}$ 0, $[\theta]_{226}$ +136,000, $[\theta]_{214}$ 0; X-ray[8] orthorhombic, space group $P2_12_12_1$, $a = 8.720$, $b = 8.882$, $c = 25.645$ Å, $Z = 4$, $d_{obsd} = 1.48$ g cm^{-3}, μ (Cu Kα) = 34.4 cm^{-1}, $R = 3.7\%$ (all atoms except hydrogens anisotropic).

Anal. Calcd for $C_{20}H_{17}NO_6 \cdot HBr$: C, 53.59; H, 4.05; N, 3.13. Found: C, 53.62; H, 4.14; N, 3.05.

B. From 2.—A mixture of 3.5 g (20 mmol) of **2** and 0.9 g (42 mmol) of powdered NaOH in 10 ml of CH_2Cl_2 and 30 ml of DMSO was heated at 120° under N_2 for 1 hr and worked up by the procedure given above to yield 1.1 g (30%) of **4**, identical in mixture melting point, tlc, and optical rotation with **4** prepared *via* A.

(−)-2-Methyl-6,7-dimethoxy-1-(*R*)-[6,7-dimethoxy-3-(*S*)-phthalidyl]-1,2,3,4-tetrahydroisoquinoline [(−)-Cordrastine II] (5).—A mixture of 7 g (18.5 mmol) of **3** HCl in 50 ml of MeOH containing an excess of CH_2N_2 in Et_2O was stored at 4° for 4 hr and then at room temperature for 48 hr. The solution was evaporated at 40° in a stream of N_2, the residue was suspended in water and extracted with EtOAc, and the extract was chromatographed over 30 g of silica gel. Elution with 300 ml of EtOAc followed by evaporation gave 5.5 g of a residue which was dissolved in ethanolic HBr, evaporated, and crystallized from

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[8] We are indebted to our colleague Dr. J. F. Blount for the X-ray analysis; details will be published independently.

[9] Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. Thin layer chromatography employed silica gel G plates developed for 10 cm with either solvent system A (80 CH_3CN:20 NH_4OH), system B (1 EtOAc:1 benzene), or system C (EtOAc) and visualized with modified Dragendorff's reagent. Nmr spectra were obtained in DMSO-d_6, unless otherwise noted, on a Varian HA-100 instrument. Uv spectra were measured in 2-propanol with a Cary recording spectrophotometer, Model 14M. Optical rotations were measured with a Perkin-Elmer model at 25° unless otherwise indicated. Rotatory dispersion curves were determined at 23° with a Durrum-Jasco spectrophotometer, Model 5, using 1-cm, 0.1-cm, or 0.1-mm cells. Circular dichroism curves were measured on the same instrument and are expressed in molecular ellipticity units [θ]. Extracts of products were washed with water and dried over anhydrous sodium sulfate prior to evaporation. Reported yields are of isolated products homogeneous to tlc.

[10] M. S. Yunusov and S. Yu. Yunusov, *Chem. Natur. Compounds*, **4**, 54 (1968); *Chem. Abstr.*, **69**, 684a (1968).

[11] G. Snatzke, W. Wollenberg, J. Hrbek, Jr., F. Šantavý, K. Bláha, W. Klyne, and R. J. Swan, *Tetrahedron*, **25**, 5059 (1969).

EtOH to yield 5.2 g (59%) of **5** HBr: mp 212–213°; $[\alpha]_D$ +188° (*c* 1, MeOH); nmr δ 3.05 (s, 3, NCH_3), 2.8–3.8 (m, 4, CH_2CH_2), 2.68 (s, 3, OCH_3), 3.71 (s, 6, 2 OCH_3), 3.87 (s, 3, OCH_3), 5.32, 5.40 (2 s, 2, 2 CH), 6.39, 6.84 (2 s, 2, 2 arom), 7.66, 7.81 (2 d, 2, *J* = 8 Hz, 2 aromatic); uv max 220 nm (ϵ 31,500) (infl), 235 (17,900) (infl), 289 (4550), 311 (3950).

Anal. Calcd for $C_{22}H_{25}NO_6 \cdot HBr$: C, 55.01; H, 5.46; N, 2.92. Found: C, 54.69; H, 6.01; N, 2.56.

Neutralization of the above hydrobromide and crystallization of the resulting free base from a mixture of ether and petroleum ether (bp 30–60°) afforded **5**: mp 90°; $[\alpha]_D$ −10° (*c* 1, $CHCl_3$); R_f (system C) 0.09; nmr δ 2.47 (s, 3, NCH_3), 2.1–2.9 (m, 4, CH_2CH_2), 3.46, 3.69 (2 s, 6, 2 OCH_3), 3.79 (s, 6, 2 OCH_3), 4.04, 5.75 (2 d, 2, *J* = 3.5 Hz, 2 CH), 6.31 (s, 1, aromatic), 6.59 (d, 1, *J* = 8 Hz, aromatic), 6.65, 7.30 (2 s, 2, 2 aromatic); uv max 220 nm (ϵ 22,600) (infl), 235 (11,850) (infl), 290 (4170), 310 (3380); ORD (*c* 0.415, MeOH) $[\phi]_{700}$ +209°, $[\phi]_{589}$ +740°, $[\phi]_{334}$ −910° (tr), $[\phi]_{296}$ +11,060° (pk), $[\phi]_{285}$ +9370° (tr), $[\phi]_{245}$ +49,610° (pk), $[\phi]_{209}$ −245,660° (tr); CD (*c* 0.01 *M*, MeOH) $[\theta]_{360}$ 0, $[\theta]_{360}$ 0, $[\theta]_{317}$ −7400, $[\theta]_{292}$ 0, $[\theta]_{289}$ +480, $[\theta]_{285}$ 0, $[\theta]_{272}$ −2500, $[\theta]_{261}$ 0, $[\theta]_{222}$ +94,200, $[\theta]_{210}$ 0, $[\theta]_{203}$ −168,270; identical within experimental error in tlc and nmr which we obtained with racemic cordrastine II[7] (racemate of **5**).

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.14; H, 6.23; N, 3.45.

(−)-2-Methyl-6,7-methylenedioxy-1-(*R*)-[6,7-methylenedioxy-3-(*R*)-phthalidyl]-1,2,3,4-tetrahydroisoquinoline (Capnoidine) (6).—A solution of 3 g (0.82 mmol) of **4** and 3 g (54 mmol) of KOH in 50 ml of MeOH was refluxed for 72 hr, acidified with 6 *N* HCl, and evaporated. The residue was dissolved in 5% $NaHCO_3$ and extracted with Me_2Cl_2, and the extract was evaporated. The residue was crystallized from 50 ml of a 9:1 mixture of benzene and EtOAc to give 2 g (66%) of **6**: mp 239–240° (lit.[12] mp 236°); $[\alpha]_D$ −114° (*c* 1, $CHCl_3$) [lit.[13] $[\alpha]_D$ −113.2° (*c* 2, $CHCl_3$)]; R_f (system B) 0.78; nmr ($CDCl_3$) δ 2.49 (s, 3, NCH_3), 2.3–3.2 (m, 4, CH_2CH_2), 3.98, 5.60, (2 d, 2, *J* = 3.5 Hz, 2 CH), 5.82, 6.17 (2 s, 4, 2 OCH_2O), 6.37, 6.64 (2 s, 2, 2 aromatic), 6.89, 7.11 (AB, 2, *J* = 8 Hz, aromatic); uv max 221 nm (*c* 28,100), 235 (12,200) (infl), 2.96 (6050), 322 (5300); ORD (*c* 0.177, 0.1 *N* HCl) $[\phi]_{600}$ −55°, $[\phi]_{589}$ −57°, $[\phi]_{348}$ +2755° (pk), $[\phi]_{300}$ −5510° (tr), $[\phi]_{287}$ −4580° (pk), $[\phi]_{275}$ −4990° (tr), $[\phi]_{260}$ −3220° (pk), $[\phi]_{233}$ −72,780° (tr), $[\phi]_{213}$ +127,400° (pk); CD (*c* 0.001 *M*, 0.1 *N* HCl) $[\theta]_{400}$ 0, $[\theta]_{324}$ +6146, $[\theta]_{293}$ +1560, $[\theta]_{250}$ +19,380, $[\theta]_{241}$ 0, $[\theta]_{224}$ −120,800, $[\theta]_{213}$ 0, $[\theta]_{206}$ +106,250; identical within experimental error in ORD and CD with natural capnoidine.[11]

Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.59; H, 4.82; N, 3.77.

Evaporation of the mother liquors followed by crystallization from 20 ml of ethanol afforded 1 g (33%) of unreacted **4**. Treatment of **6** with KOH in MeOH effected epimerization to give a 9:1 mixture of **6** and **4** as visualized by tlc.

(−)-2-Methyl-6,7-dimethoxy-1-(*R*)-[6,7,dimethoxy-3-(*R*)-phthalidyl]-1,2,3,4-tetrahydroisoquinoline [(−)-Cordrastine I] (7).—A solution of 6 g (12.5 mmol) of **5** HBr and 6 g (107 mmol) of KOH in 120 ml of MeOH was refluxed for 72 hr and worked up by the procedure in the preceding example to yield a reaction product which upon crystallization from EtOH afforded 3 g (60%) of **7**: mp 189–190°; R_f (system C) 0.58; $[\alpha]_D$ −99° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 2.61 (s, 3, NCH_3), 2.2–3.2 (n, 4, CH_2CH_2), 3.69 (s, 3, OCH_3), 3.77 (s, 6, 2 OCH_3), 3.86 (s, 3, OCH_3), 4.02, 5.57 (2 d, 2, *J* = 3.5 Hz, 2 CH), 6.33, 6.66 (2 s, 2, 2 aromatic), 6.97, 7.28 (2 d, 2, *J* = 8 Hz, 2 aromatic); uv max 220 nm (ϵ 32,000) (infl), 290 (4800), 310 (3720); ORD (*c* 0.367, 0.1 *N* HCl) $[\phi]_{700}$ −72°, $[\phi]_{589}$ −86°, $[\phi]_{328}$ +4620° (pk), $[\phi]_{292}$ −9800° (tr), $[\phi]_{264}$ −3670° (pk), $[\phi]_{251}$ −6670° (tr), $[\phi]_{245}$ −5170° (pk); $[\phi]_{227}$ −99,300° (tr); CD (*c* 0.009 *M*, 0.1 *N*HCl) $[\theta]_{260}$ 0, $[\theta]_{310}$ +11,300, $[\theta]_{284}$ +870, $[\theta]_{238}$ +39,130, $[\theta]_{231}$ 0, $[\theta]_{216}$ −160,870, $[\theta]_{208}$ 0; identical within experimental error in tlc and nmr which we obtained with racemic cordrastine I[7] (racemate of **7**).

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.18; H, 6.30; N, 3.51.

The above mother liquors were adjusted to pH 2 with ethanolic HBr and evaporated, and the residue was crystallized from EtOH to yield 1.7 g (28% of unreacted **5** HBr.

Registry No.—**1** HCl, 5936-28-7; **2**, 34408-04-3; **3** HCl, 34408-05-4; **4**, 19730-80-4; **4** HBr, 34408-06-5; **5**, 34408-07-6; **5** HBr, 34417-89-5; **6**, 25344-52-9; **7**, 34408-08-7.

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(12) R. H. F. Manske, *Can. J. Res.*, **14B**, 347 (1936).

(13) R. H. F. Manske, *J. Amer. Chem. Soc.*, **72**, 3207 (1950).

Opium Alkaloids. XIII.[1,2a] Isolation of 16-Hydroxythebaine

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A new hydrophenanthrene alkaloid has been isolated from opium and characterized as 16-hydroxythebaine by means of uv, ir, nmr, and mass spectrometry.

The hydrophenanthrene alkaloids of opium have been studied extensively, and their biosynthesis in the living plant has been established in considerable detail. Investigation of the minor alkaloid constituents of opium has led to the isolation of a new alkaloid of this group. It was isolated from the nonphenolic alkaloid fraction of opium and purified by preparative thin-layer chromatography (tlc) on silica gel and by column chromatography on neutral aluminum oxide.

Structural Studies. Gas Chromatography.—When subjected to gas chromatographic analysis (glc), the new alkaloid had the same retention time as thebaine on a nonpolar column (2% silicone rubber, SE-30, 200°, 8 min). However, treatment with bistrimethylsilylacetamide (BSA) resulted in a slight but noticeable shortening of the retention time indicating the presence of an active hydrogen. On a polar cyanosilicone column (2% XE-60, 210°) the effect of silylation was more pronounced, the retention time shifting from 22 to 10 min while that of thebaine remained unchanged.

Mass Spectrometry.—The mass spectrum displayed a molecular ion peak at *m/e* 327 shown by accurate

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(1) See E. Brochmann-Hanssen, *J. Pharm. Sci.*, in press, for paper XII in this series.

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