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, $[\theta]_{350}$ 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_2-CH_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.

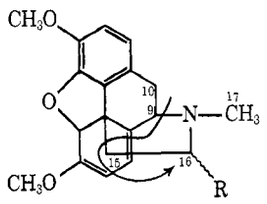
(1) See E. Brochmann-Hanssen, *J. Pharm. Sci.*, in press, for paper XII in this series.

(2) (a) Supported by Research Grant No. MH-03487 from the National Institute of Mental Health, Bethesda, Md. (b) To whom inquiries should be directed.

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

mass measurements[3,4] to correspond to $[C_{19}H_{21}NO_4]^+$. The fragmentation pattern was very similar to that reported for thebaine[5] which has the empirical formula $C_{19}H_{21}NO_3$. This strongly suggested that the new compound might be an oxygenated thebaine derivative. The nature of the oxygen function as a free hydroxyl group was indicated by a peak at *m/e* 309 corresponding to $C_{19}H_{19}NO_3$ (M − H_2O). This was further substantiated by an increase in the molecular ion of one mass unit on deuteration with CH_3OD while the *m/e* 309 fragment remained unchanged (M − HOD). Silylation gave a mono-TMS derivative (M^+ = 399, corresponding to $C_{22}H_{29}NO_4Si$) in which the actual silylation of the hydroxyl function can be deduced from the observation of an abundant M − Me_3SiOH fragment at *m/e* 309 of proper composition. The most prominent fragment of the spectrum (*m/e* 254) has the composition $C_{16}H_{14}O_3$, reflecting the loss of a C_3H_7NO moiety comprising the hydroxyl substituent. This may also be concluded from the fact that the peak at *m/e* 254 remained unshifted in the spectrum of the deuterated compound. The positions of attachment of the hydroxyl group, therefore, appeared to be limited to C-15, C-16, and C-17 (I). Comparable elimination of a C_3/N unit under loss, gain, or retention of hydrogen (M − C_3H_6N, M − C_3H_8N, and M − C_3H_7N, in decreasing importance) is highly characteristic of the fragmentation behavior of thebaine and represents the most prominent feature of the upper mass range of its spectrum.



I

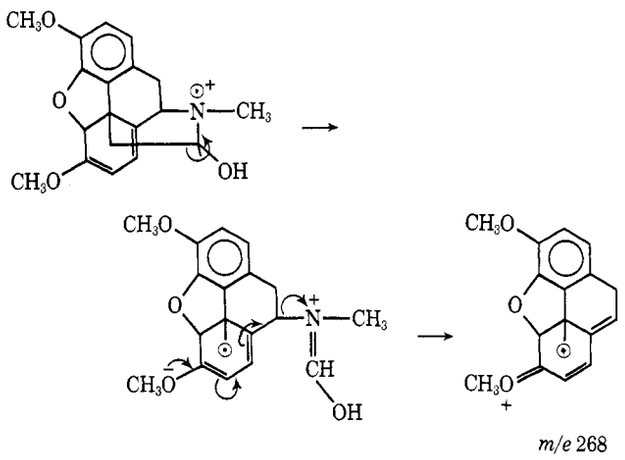
Analysis of the less abundant fragments M − C_2/N and C_2/N under high resolution conditions permitted distinction between the two likely sites of attachment, C-15 and C-16, in favor of the latter. Attachment to C-17 (=N−$^{17}CH_2OH$) could largely be disregarded on grounds of chemical instability. While thebaine displays an appreciable peak at *m/e* 268 which consists, contrary to earlier observations, of the two components M − C_2H_5N and M − C_2H_3O in a ratio of approximately 2:1, hydroxythebaine formed a corresponding M − C_2H_5NO species of even higher abundance. This demonstrated loss of the nitrogen atom together with the hydroxyl group and the two α-carbon atoms, C-16 and C-17, and established the former as the most likely site of attachment. In thebaine, generation of an unstabilized primary radical (C-15) makes initial α cleavage of the C-15/C-16 bond less favorable in comparison to 9,10 cleavage, but should gain additional driving force upon donor substitution at C-16

(3) Complete real-time high-resolution spectra were obtained at a resolving power of approximately 20,000 by scanning an MS-902 mass spectrometer on line with an SDS Sigma computer.

(4) The authors wish to thank Dr. A. L. Burlingame of the Space Sciences Laboratory of the University of California, Berkeley, for access to his high-resolution mass spectrometry facilities, and Mr. B. R. Simoneit of the same laboratory for assistance in the precise mass measurements.

(5) D. M. S. Wheeler, T. H. Kinstle, and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **89**, 4494 (1967).

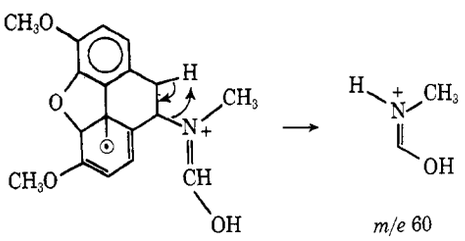
SCHEME I



(Scheme I). This type of cleavage generates a suitable leaving group for subsequent heterolytic dissociation of an allylic immonium ion, shown recently to represent a favorable mode of fragmentation in comparable benzylic heterolysis.[6]

Inspection of the C_2/N ions gave additional support for the presence of a hydroxyl group at the 16 position. The *m/e* 44 fragment (C_2H_6N) of thebaine has its analog in a less abundant, but nevertheless highly characteristic C_2H_6NO fragment at *m/e* 60 (Scheme II).

SCHEME II



The fragmentation of the 16-TMSO derivative exhibited similar features, *e.g.*, loss of a $C_2H_4NOSiMe_3$ moiety from the molecular ion (*m/e* 399 → *m/e* 268) and formation of a $C_2H_5NOSiMe_3$ species (*m/e* 132). This is in perfect analogy to loss of C_2H_5NO and formation of a C_2H_6NO fragment in the case of 16-hydroxythebaine.

Uv, Ir, and Nmr Spectroscopy.—The uv spectrum of the isolated substance in ethanol gave maxima at 225 and 285 mμ and was very similar to the spectrum of thebaine.[7] Similarity with thebaine is also apparent in the ir spectra of the compound taken under various conditions.[8] Characteristic differences are mainly observed in the carbonyl region, *i.e.*, in a band at 1735 cm^{-1}, absent in thebaine[9] and strongly dependent in its intensity on the pH of the medium. It is of low intensity in liquid films deposited on KBr and in $CHCl_3$ solution, however, very intense after addition of traces of NaOH to the latter. This band is likely to be due to the carbonyl function of an "open" amino aldehyde tautomer which exists in equilibrium with the cyclic α-

(6) W. J. Richter and W. Vetter, *Org. Mass Spectrom.*, **2**, 781 (1969).

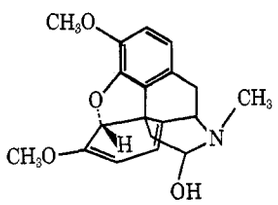
(7) A. W. Sangster and K. L. Stuart, *Chem. Rev.*, **65**, 69 (1965).

(8) The authors are indebted for these measurements to Mr. K. O. Alt, Ciba-Geiby AG, CH-4002 Basle, Switzerland.

(9) Sadtler Standard Spectra, Midget Edition, Spectrum Number 4104, edited by Sadtler Research Laboratories, Inc., Philadelphia, Pa. 19104.

hydroxyamine form. The nmr spectrum[10] in deuteriochloroform with internal TMS standard also showed distinct similarities to that of thebaine: two methoxyl singlets at 3.86 and 3.62 (thebaine, 3.84 and 3.59) and a *N*-methyl group at 3.40 ppm (thebaine, 2.46). The spectrum further showed a one-proton singlet (C-5) at 5.41 (thebaine, 5.29) and two doublets (J = 6–7 cps) representing the C-7 and C-8 protons, resonating at 5.82 and 5.11 (thebaine, 5.54 and 5.02), and two aromatic protons in an AB quartet at 6.65 and 6.68 ppm (thebaine, 6.61 and 6.64). The strong downfield shift of the *N*-methyl protons indicated the presence of an electron-withdrawing group on an adjacent carbon atom.

It seems reasonable that the 16-hydroxy function may exist in solution in both epimeric forms interconvertible *via* the amino aldehyde.[11] However, the axial orientation of the hydroxy group in a half-chair conformation of the piperidine ring (II) may be considered the most prominent molecular species based on the downfield shift of the protons at C-5, C-7, and C-8.



II

Alkaloids which contain a hydroxyl group in the α position to the heterocyclic nitrogen are not uncommon, but have not been found previously among the hydrophenanthrenes. Thebaine is a very reactive molecule, and one cannot exclude the possibility that 16-hydroxythebaine may be an artifact produced during the drying or storage of opium or during the isolation and purification of the alkaloids. So far, extensive studies of the chemical reactions of thebaine have not revealed a product of this nature. *In vitro* oxidation of codeine introduces a hydroxyl function in the 10 position.[12] On the other hand, the biosynthesis postulated for several opium alkaloids involve oxidation at a carbon atom adjacent to the nitrogen, *e.g.*, biosynthesis of chelidonine, narcotine, porphyroxine, or protopine. It is, therefore, conceivable that the hydroxyl group is introduced at the reticuline stage and that 3-hydroxyreticuline may undergo biotransformation in the normal way to 16-hydroxythebaine. This view gains support from the fact that (+)-reticuline produced in the biosynthetic sequence is racemized in the opium poppy by an oxidation–reduction system.[13]

(10) Japan Electronic Optics Laboratory Model JNM 4H-100.

(11) R. W. King, C. F. Murphy, and W. C. Wildman, *J. Amer. Chem. Soc.*, **87**, 4912 (1965).

(12) H. Rapoport and G. W. Stevenson, *ibid.*, **76**, 1796 (1954).

Experimental Section

Isolation.—Four pounds of powdered opium of Indian origin were extracted and a preliminary separation of alkaloid groups was carried out as described in a previous communication.[14] A chloroform solution of the nonphenolic fraction was concentrated under reduced pressure. Addition of methanol gave a heavy precipitate containing mainly codeine and cryptopine. The filtrate was evaporated to dryness and the residue was extracted with ether. The ether solution was concentrated and subjected to preparative tlc on silica gel with chloroform–methanol (9:1) (double development). The alkaloid band having the lowest R_f value (*ca.* 0.05) was scraped off and extracted with methanol. The methanol solution, which contained several alkaloids as indicated by glc and analytical tlc, was concentrated and chromatographed on a column of neutral alumina (Woelm, activity IV) with benzene and ethanol. The polarity of the eluent was increased gradually during the elution by increasing the concentration of ethanol from 0 to 50%. The progress of the elution was monitored by glc and micro tlc. After the elution of 13-oxycryptopine[15] a new alkaloid appeared in the eluate. The fractions containing this alkaloid were combined and evaporated to dryness under reduced pressure. The yellowish-brown residue (29 mg) was crystallized from a mixture of acetone and petroleum ether (bp 30–60°), yielding pale yellow crystalline prisms which melted at 126–128° (capillary) and 118–119° (micro mp, K.). The crystalline compound exhibited single, well-defined spots in three different tlc systems, *e.g.*, silica gel with chloroform–methanol (9:1) and benzene–ethanol (4:1), alumina with benzene–ethanol (4:1).

Registry No.—II, 34388-67-5.

(13) A. R. Battersby, D. M. Foulkes, and R. Binks, *J. Chem. Soc.*, 3323 (1965).

(14) E. Brochmann-Hanssen, B. Nielsen, and K. Hirai, *J. Pharm. Sci.*, **56**, 754 (1967).

(15) E. Brochmann-Hanssen, A. Y. Leung, K. Hirai, and G. Zanati, *Planta Med.*, **18**, 366 (9970).

The Hydroboration of Dihydrothujopsene

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The hydroboration of dihydrothujopsene (**2**) at room temperature affords as the major component the abnormal hydroboration addition product, tertiary alcohol **7**, and a minor product, diol **8**, derived from the normal hydroboration addition orientation.

Although a number[1] of recent publications have dealt with the intriguing chemistry of the sesquiterpene hydrocarbon (−)-thujopsene (**1**) there has appeared no chemistry pertaining to dihydrothujopsene[2] (**2**), derived from **1** by catalytic 1,4 reduction.

During the course of some systematic investigations on the chemistry of thujopsene-derived hydrocarbons, we examined the hydroboration of dihydrothujopsene (**2**), expecting to obtain the secondary alcohol mixture **3** and **4** for eventual oxidation to the corresponding ketones. Although two products in a 77:23 ratio were indeed isolated in an overall yield of 84%, neither of these afforded the spectral or chemical characteristics compatible with secondary alcohols **3** and **4**.

The major component of the hydroboration reaction

(1) See H. U. Daeniker, A. R. Hochstetler, K. Kaiser, and G. C. Kitchens, *J. Org. Chem.*, **37**, 1 (1972), and references cited therein.

(2) T. Norin, *Acta Chem. Scand.*, **15**, 1676 (1961).