13β-Hydroxystylopine. Structure and Synthesis

Peter W. Jeffs*[1] and Jeffery D. Scharver

Paul M. Gross Laboratory, Duke University, Durham, North Carolina 27706

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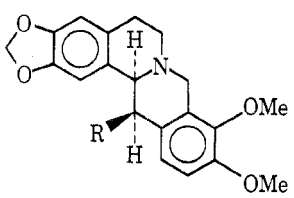
The isolation of 13β-hydroxystylopine (**2**, R = OH) is described and the elucidation of its structure by spectral methods is confirmed by a synthesis of the alkaloid.

Despite the large number of alkaloids belonging to the protoberberine group, most of which differ from each other in the number and placement of various oxygen functions on the two aromatic rings, ophiocarpine (**1**, R = OH) is the only alkaloid of this group containing a 13-hydroxyl group that has been reported.[2] Since 13-oxygenated protoberberines are established as the biosynthetic precursors of the phthalide–isoquinoline alkaloids[3] and are potential intermediates in the formation of other alkaloid families, such as the rhoeadines,[4] it is somewhat surprising to find that 13-hydroxylated protoberberines are not of more widespread occurrence.

In connection with a study of the biosynthesis of ophiocarpine, we have reinvestigated the alkaloids of *Corydalis ophiocarpa*, one of the two plants in which this alkaloid is reported to occur.[5]

Chromatography of the crude alkaloid fraction over alumina in benzene–ethyl acetate gave (−)-tetrahydroberberine (**1**, R = H), (−)-stylopine (**2**, R = H), and a fraction



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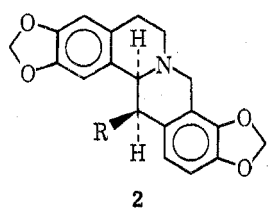

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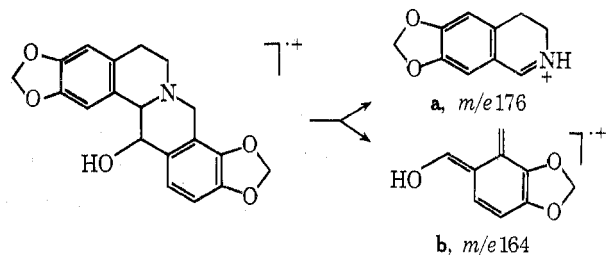
eluted with benzene–ethyl acetate and ethyl acetate:ethyl acetate–methanol (9:1) which contained a mixture of three components. Preparative layer chromatography of the mixture on silica gel impregnated with 5% K_2CO_3 afforded (−)-13β-hydroxystylopine (**2**, R = OH), which crystallized as colorless prisms from ethanol, mp 214°, $[\alpha]_{589}$ −259°. The molecular formula $C_{19}H_{17}NO_5$ for this base was derived initially by high-resolution mass spectral analysis and was subsequently supported by the results of combustion analysis. Classification of the new alkaloid as a member of the protoberberine series was readily apparent from examination of its ^1H nmr and mass spectral features and elucidation of its structure relied on many parallel comparisons which could be made with its companion alkaloid, ophiocarpine.

The 100-MHz ^1H nmr spectrum (Figure 1) contained four proton signals in the aromatic region as two singlets at δ 6.80 and 6.02 and a pair of doublets at 6.95 and 6.79 (J = 8.0 Hz) and established the substitution pattern on rings A and D. These signals are accompanied by a two-proton singlet at δ 6.00 and a two-proton "quartet" at δ 5.94 which we assigned to two methylenedioxy groups in which the hydrogens of one of these groups exhibit chemical-shift nonequivalence. These observations and the general appearance of the spectrum suggested that the alkaloid was a protoberberine base related to stylopine. Further evidence in support of this contention was the occurrence of the C-8 methylene group as an AB system at δ 4.07 and 3.53 (J = 16 Hz). This significant difference in chemical shift is indicative of a 9,10-substituted protoberberine in which the presence of a 9-oxygen function enhances the nonequivalence of the C-8 methylene hydrogens by selective deshielding of the more proximate quasiequatorial C-8 β hydrogen.[6]

Placement of the fifth oxygen function as a hydroxyl group at the C-13 position was suggested by the occurrence of a broadened singlet at δ 4.80 ($W_{1/2}$ = 8.0 Hz) in the nmr spectrum of the alkaloid which sharpened upon addition of D_2O ($W_{1/2}$ = 4.0 Hz). Support for this assignment was provided by the mass spectrum which displayed prominent ions at *m/e* 176 (**a**) and *m/e* 164 (**b**) resulting from separate cleavage pathways leading to the characteristic retro-Diels–Alder fragmentation of ring C of the protoberberine system. Confirmation of the presence of a hydroxyl group in

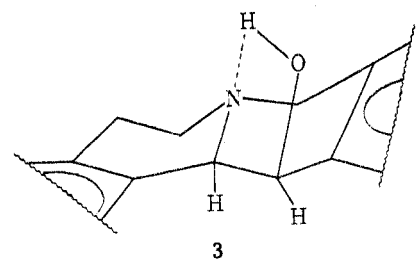


a, *m/e* 176

b, *m/e* 164

the alkaloid was provided by the formation of an *O*-acetyl derivative ($\nu_{C=O}$ 1730 cm^{-1}).

The infrared spectrum of the alkaloid exhibited a broad hydroxyl absorption at 3500 cm^{-1} which proved to be concentration independent in $CHCl_3$ solution over the range 10^{-3}–10^{-4} M and was thus in keeping with an intramolecular OH–H hydrogen bond.[7] The infrared spectrum also showed multiple absorption bands (Bohlmann bands) in the region 2700–2800 cm^{-1} and indicated the predominant conformation of the alkaloid was represented by a *trans*-quinolizidine structure.[8] On the basis of a *trans*-quinolizidine structure, the existence of an intramolecular hydrogen-bonded hydroxyl implies that the 13-hydroxyl is trans to H-14 as indicated in the partial structure **3**. The oppo-



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site stereochemistry at C-13 cannot lead to an intramolecular hydrogen bond between a hydroxyl at this position and the nitrogen. The dihedral angle between H-13 and H-14 in the partial structure **3** is *ca.* 60° and it is known in related systems to give rise to $J_{13,14}$ = 2–4 Hz.[9] While the broad singlet of the H-13 resonance observed in the spectrum of the alkaloid is in conformity with this stereochemical assignment, the spectrum (Figure 2) of its *O*-acetyl derivative

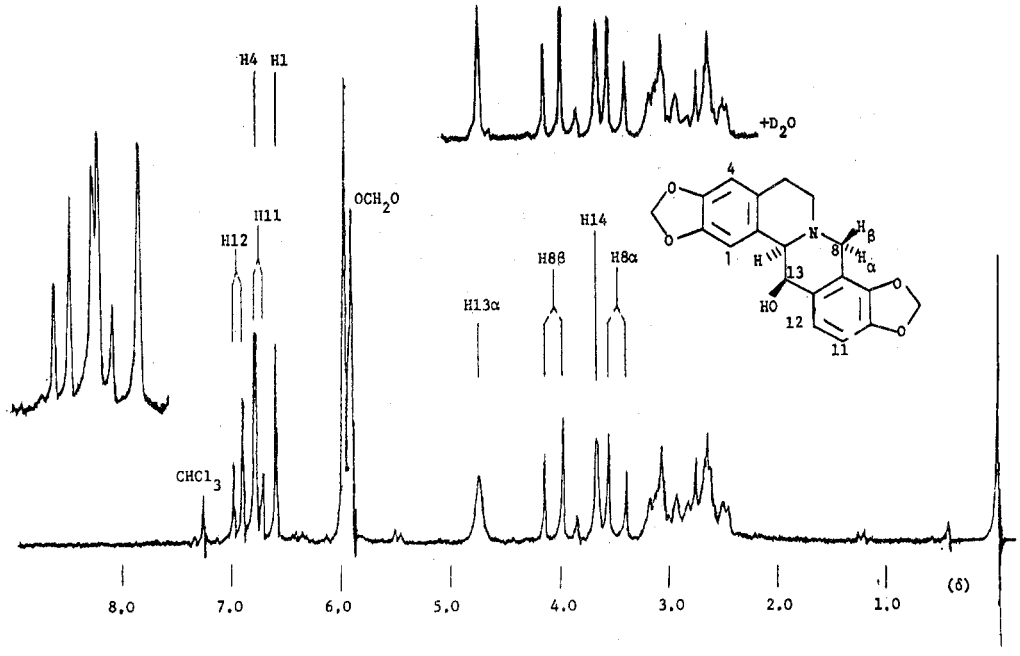

Figure 1. ^{1}H nmr spectrum of 13β-hydroxystylopine.

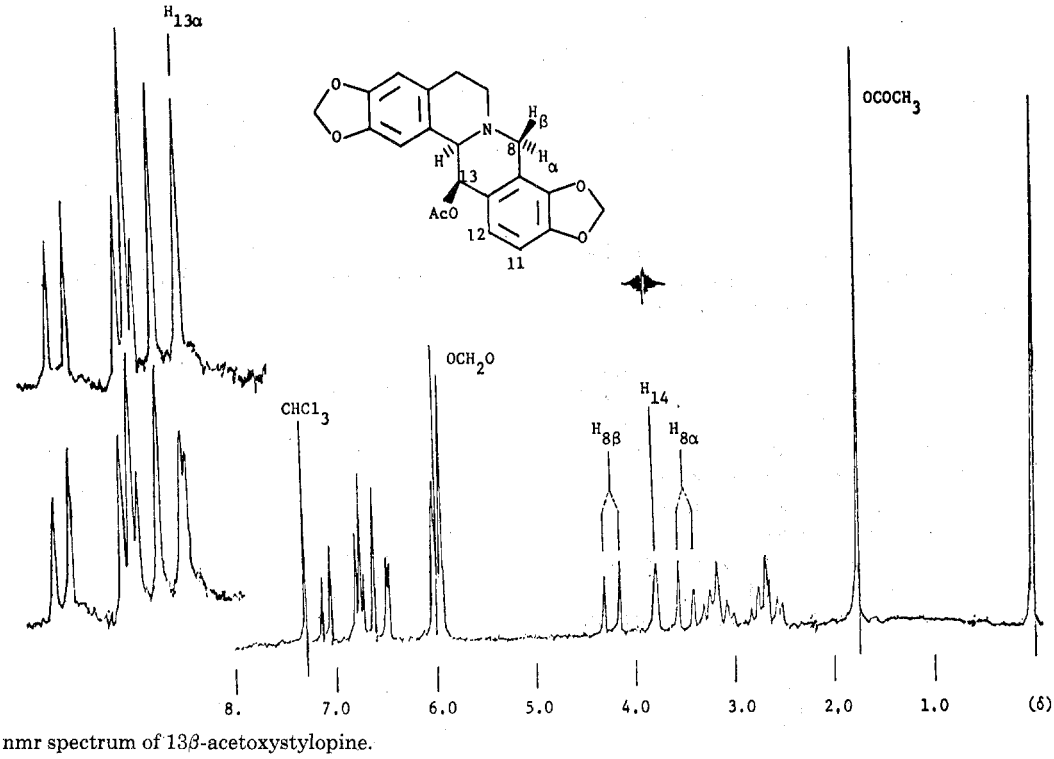

Figure 2. ^{1}H nmr spectrum of 13β-acetoxystylopine.

2 (R = OAc) reveals this more clearly in that the H-13 signal appears as a doublet at δ 6.46 (J = 3.0 Hz). Confirmation of the assignment of the latter signal was obtained by a spin-decoupling experiment in which irradiation of the H-14 signal at δ 3.78 resulted in collapse of the H-13 resonance to a singlet (Figure 2). A somewhat distinctive feature of the spectrum of the *O*-acetyl compound was the occurrence of the acetate methyl resonance at abnormally high field (δ 1.76). A similar situation is observed in the spectrum of *O*-acetylophiocarpine in which the acetate methyl shift is at δ 1.78 whereas the acetate methyl shift in *O*-acetyl-13-epiophiocarpine appears at a more typical value of δ 2.23. It has been pointed out by Ohta and coworkers[10] that the acetyl group in *O*-acetylophiocarpine is shielded by ring D and a similar situation obviously obtains in the analogous 13β-acetoxystylopine.

With the foregoing spectral evidence supporting the structure of the alkaloid as 13β-hydroxystylopine it remained to establish its absolute configuration. Tetrahydroberberines belonging to the 14*R* series exhibit a negative ORD spectrum from 600 to 240 nm.[11] Before applying this method to 13β-hydroxystylopine it was necessary to establish what effect the introduction of a 13β-hydroxyl group in this ring system would have on the ORD spectrum. Examination of the ORD spectrum of (−)-ophiocarpine showed a plain negative dispersion curve from 600 to 250 nm and indicated that when the new chiral center at C-13 is a β-hydroxyl the sign of curve is not affected. Consequently the

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EXPERIMENTAL

General Methods

Melting points were determined on a Thomas-Hoover Mel-Temp apparatus and are uncorrected. Infrared spectra were determined on Perkin-Elmer models 237 and 621 recording spectrophotometers. Nuclear magnetic resonance spectra were determined at 60 MHz on Varian A-60 and T-60 instruments, at 90 MHz on the Bruker HFX-10, and at 100 MHz on the JEOL MH-100 spectrometer. Chemical shifts are reported in δ-units relative to internal TMS. Ultraviolet spectra were recorded on Beckman DB-G and Cary Model 14 recording spectrophotometers. The ORD spectra were obtained on a Durrum-Jasco ORD-UV/5.

Low resolution mass spectra were recorded on a DuPont 21-490 and an AEI MS 902 instruments. High resolution spectra were obtained on the MS-902 at the Research Triangle Institute Center for Mass Spectrometry.

Elemental analyses were performed by MHW Laboratories, Garden City, Michigan.

Chromatography was routinely performed on neutral Woelm Aluminum Oxide, grade III, or W. R. Grace silica gel unless otherwise indicated. Thin layer (0.25 mm) and preparative layer (1 mm) chromatography using aluminum oxide, silica gel or silica gel-5% potassium carbonate was used. Various solvent systems and multi-development techniques are noted. Visualization was achieved by ultraviolet light and by spraying with iodoplatinic acid or ceric ammonium sulfate in sulfuric acid.

All solvents were routinely redistilled prior to use.

Isolation of the Alkaloids from Corydalis Ophiocarpa plants.

Corydalis ophiocarpa plants were grown in the Duke University Phytotron from seeds obtained from the Ipswich Seed Co., Great Britain. Top growth from the plants was periodically trimmed and dried. The dried material ca. 9 Kg was thoroughly ground in a Waring blender with 95% ethanol and filtered. The filter cake was extracted with ethanol in a Soxhlet. The combined extracts were concentrated in vacuo, diluted with a large volume of hot water, and acidified with concentrated hydrochloric acid to a Congo Red endpoint. The acidic extract was allowed to stand at room temperature for 2 days and

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filtered through Celite. The filtrate was washed twice with ether and basified with concentrated ammonium hydroxide producing a flocculent precipitate. This aqueous portion was extracted several times with chloroform and emulsified material was readily separated by vacuum filtration through a layer of Celite. The combined organic extracts were washed twice with water, dried over magnesium sulfate, and solvent removed in vacuo to give 21.4 gm (0.23%) of crude alkaloids as a dark brown foam.

Purification by Column and Preparative Layer Chromatography

The crude alkaloids (12 g) in chloroform were evaporated over alumina (100 g) and thoroughly dried under high vacuum. The alkaloid containing alumina was then placed on a wet-packed column of alumina (1.5 kg) in benzene and eluted successively with the linear gradients: benzene - EtOAc (4 l), EtOAc-EtOAc/MeOH (9:1, 2 l) EtOAc/MeOH (9:1)-EtOAc/MeOH (4:1, 2 l). A total of 450 fractions of 20 ml were collected and every tenth fraction was examined by tlc and pooled according to the results as follows: Fr. 1-50 (trace), Fr. 51-89 unknown base (113 mg), Fr. 90-114 (trace), Fr. 115-120, (-)-stylopine (233 mg), Fr. 121-134, mixture of (+)-stylopine and (-)-tetrahydroberberine (1.185 g), Fr. 135-239, mixture of (-)-ophiocarpine, protopine and (-)-13β-hydroxystylopine (7.0 g), Fr. 240-450, unknown alkaloids (1.02 g). Preparative layer chromatography (plc) of Fr. 121-134 on silica using a $CHCl_3$-EtOAc (9:1) and triple development gave 300 mg pure (-)-stylopine mp 195-197 (lit.[20] mp 202°) and 1.19 g (-)-tetrahydroberberine, mp 131-132° (lit.[21] mp 135°). Full characterization by nmr, ms, and ir supported the identification of these alkaloids.

A 300 mg sample of the mixture of alkaloids contained in Fr. 135-239 was separated by plc on SiO_2-5% K_2CO_3 by triple development with benzene - EtOAc (4:1) giving 125 mg (-)-ophiocarpine, mp 187-188 (lit.[5] mp 188°), 81 mg protopine, mp 202-204 (lit.[14] 207-208°), both of which were fully characterized by their nmr, ms and ir spectral properties, and 73 mg of a new base, (-)-13β-hydroxystylopine (2, R=OH), mp 213-215°C, $[\alpha]_D$ - 259° (c 0.1, $CHCl_3$); R_f 0.72; ir $\lambda_{max}^{CHCl_3}$ 3500 cm^{-1} (w, OH) (concentration independent over the range 10^{-3} to 10^{-2} M), 2800-2700 cm^{-1} (Bohlmann bands, trans-quinolizidine); mass spectrum m/e (rel intensity) 339 (9), 176 (100), 164 (22); Calcd for $C_{19}H_{17}NO_5$, 339.1106; Found: 339.1113; nmr (100 MHz) ($CDCl_3$) δ 6.95 (d, 1, J=8 Hz), (C-12 H), 6.80 (s, 1, C-4 H), 6.79 (d, 1, J=8 Hz, C-11 H), 6.62 (s, 1, C-1 H), 5.90 (s, 2, OCH_2O), 5.94 (m, 2, OCH_2O), 4.76 (bs, 1, $W_{1/2}$=8 Hz, C-13H), addition of D_2O

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sharpened this to a singlet with $W_{1/2}$=4 Hz, 4.07 (d, 1, J=16 Hz, C-8βH, 3.72 (s, 1, C-14H, unaffected by D_2O), 3.53 (d, 1, J=16 Hz, C-8αH); ORD (c 0.1 95% EtOH) $[\alpha]_{350}$ - 1980°, $[\alpha]_{300}$ - 2400° (trough), $[\alpha]_{292}$ - 2340° (peak), $[\alpha]_{260}$ - 6100°, $[\alpha]_{240}$ - 12,100° (trough), $[\alpha]_{233}$ - 11,900° (peak), $[\alpha]_{226}$ - 13, 300°.

Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.04; N, 4.12. Found: C, 67.23; H, 5.04; N, 3.84.

(-)-13-Hydroxystylopine Acetate (2, R=OAc). 70.0 mg (0.2 mmole) of the base was dissolved in dry pyridine (1 ml) under nitrogen and freshly distilled acetic anhydride (2 ml) was added in one portion. A solid slowly formed and after 4 hours it was removed by filtration, washed with cold water, and air dried to give 41.0 mg. The filtrate was diluted with water (10 ml) and basified with satd. Na_2CO_3 until CO_2 evolution had ceased. This was washed with $CHCl_3$ (2 x 20 ml), the combined organic layers were washed with H_2O (2 x 30 ml), satd. NaCl (1 x 50 ml), dried (Na_2SO_4), and solvent removed in vacuo to give a yellow oil containing pyridine. The tlc (SiO_2, $CHCl_3$-EtOAc 9:1, 2x) indicated that the above solid and yellow oil were indentical, R_f 0.75. The yellow oil was dissolved in $CHCl_3$ and passed through a short column of alumina. The acetate was immediately eluted and this was combined with the above solid to give 69.0 mg (88%) of the acetate. Recrystallization from CH_2Cl_2-pet. ether gave fine needles; mp 237-239°C (sealed tube); ir $\lambda_{max}^{CHCl_3}$ 1730 cm^{-1} (C=O), 1200 cm^{-1} (COC); nmr (100 MHz) ($CDCl_3$) δ 7.09 (d, 1, J=8 Hz, C-11H), 6.76 (d, 1, J=8 Hz, C-12H), 6.74 (s, 1, C-4H), 6.60 (s, 1, C-1H), 6.46 (d, 1, J=3 Hz, C-13H) irradiation at 3.78 collapsed this to a singlet, 6.00 (q, 2, J=1.5 Hz, OCH_2O), 5.92 (s, 2, OCH_2O), 4.24 (d, 1, J=16 Hz, C-8βH), 3.78 (bs, 1, C-14H), 3.52 (d, 1, J=16 Hz, C-8αH), ca. 3.20 (m, 2, C-5H or C-6H), 2.68 (m, 2, C-5H or C-6H), 1.76 (s, 3, acetate CH_3).

Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.14; H, 5.02; N, 3.67. Found: C, 66.19; H, 4.95; N, 3.45.

Dihydrocoptisine-N-methe chloride (9). The following is a modification of the method of Haworth and Perkin.[16] Protopine (2.83 mmole) was refluxed for 20 min under a dry N₂ atmosphere in freshly distilled phosphoryl chloride (5 ml). Solvent was removed in vacuo and the residue recrystallized from water to give a yellow solid. This was filtered, washed with a small amount of 10% HCl, and air dried. Recrystallization from MeCN-EtOAc gave 660 mg (63%) of dihydrocoptisine -N-methochloride (9) as yellow crystals: mp 193-195°C (lit.[16] 215°C); uv λ_{max}

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(95% EtOH) 373 nm (ε 21,900), 356 (ε 23,500), 343 sh (ε 18,000), 305 (ε 6950), 255 (ε 6860); (lit.[20] 375 (ε 21,400), 357 (ε 24,000), 343 sh (ε 18,299), 306 (ε 7590), 255 (ε 6910).

Dihydrocoptisine (7). 111.3 mg, (0.3 mmole) prepared from protopine was placed in a sublimation apparatus and the system evacuated to 10^{-3} mm. This was placed in a metal bath at 270°C for one minute and a yellow solid immediately condensed on the cooler parts of the system. After cooling to room temperature in vacuo the product was dissolved in warm benzene, insoluble material removed by filtration, and the filtrate stripped in vacuo. This was repeated an additional two times and the benzene soluble portions were combined. The product was chromatographed on alumina (Woelm, II, neut.) in benzene and eluted with benzene-ethyl acetate (9:1). The eluent was collected under N_2 and solvent was removed in vacuo to give 179.0 mg (64%) of dihydrocoptisine (7) as a yellow solid: mp 175-179°C (lit.[13] 194-196°C); R_f 0.84 (SiO_2, $CHCl_3$-EtOAc 1:1); nmr (60 MHz) ($CHCl_3$) δ 7.20 (s, 1, C-1H), 6.67 (d, 1, J=8 Hz, C-12H), 6.61 (s, 1, C-4H), 6.52 (d, 1, J=8 Hz, C-11H), 6.02 (s, 1, C-13H), 5.97 (s, 2, OCH_2O), 5.95 (s, 2, OCH_2O), 4.28 (s, 2, C-8H), 3.04 (m, 4, C-5H and C-6H).

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13-Hydroxy-2,3,9,10-bismethylenedioxy-5,6-dihydro-dibenzo[a,g]quinolizine (13-Hydroxy-coptisine) (6). A standard solution of m-chloroperbenzoic acid was prepared by dissolving 192.7 mg (1.11 mmole) in CH_2Cl_2 (25 ml) under N_2 and the solution cooled to -78°C. The peracid was slowly added dropwise from a buretta and progress of the reaction was monitored by tlc. Dihydrocoptisine could not be detected after the addition of 1.2 equivalents of peracid. The reaction mixture was warmed to room temperature, washed with satd. NaCl (30 ml), dried ($MgSO_4$), and solvent removed in vacuo to give a yellow-orange solid. Recrystallization from 95% EtOH containing several drops of 1% HCl gave 159.4 mg (78%) of the phenol as small orange needles: mp 285°C; uv λ_{max}(95% EtOH) 457 (ε 8,493), 358 (20,692), 345 (19,879), 288 infl (10,451), 237 (28,614).

Anal. Calcd for $C_{19}H_{14}NO_5Cl$: C, 61.44; H, 3.79; N, 3.77. Found: C, 61.21; H, 3.84; N, 3.12.

(±)-13β-Hydroxystylopine (2, R=OH). The phenol (6) (74.2 mg, 0.2 mmole) was dissolved in 60 ml of EtOH-H_2O (5:1) at room temperature and $NaBH_4$ (30 mg) was added under N_2. After 1 hr an additional 30 mg of borohydride was added and the mixture was stirred overnight before carefully acidifying with 10% HCl.

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The residue obtained upon distillation of the solvent was diluted with H_2O (100 ml), washed with benzene (50 ml), and the acidic extract was basified with 6N KOH (pH 9). The precipitated solid was taken up in $CHCl_3$ (2 x 60 ml), the combined organic extracts were washed with H_2O (60 ml), NaCl soln. (60 ml), dried ($MgSO_4$), and solvent removed in vacuo to give 47 mg (69%) of a light yellow foam. Recrystallization from 95% EtOH gave (±)-13β-Hydroxystylopine as fine white needles, mp 219-221° (dec), with chromatographic (R_f 0.58, SiO_2-5% K_2CO_3, $CHCl_3$-EtOAc 1:1 1x); R_f 0.47, SiO_2-5% K_2CO_3, C_6H_6-EtOAc 4:1 2x) and spectral properties (ms, nmr) identical with naturally occurring material.

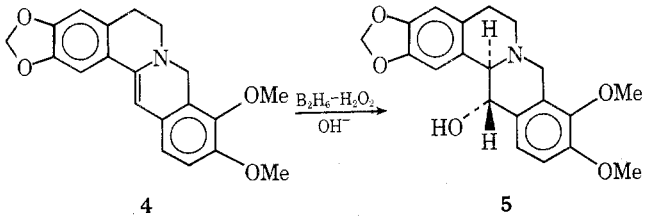
Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.04; N, 4.12. Found: C, 67.20; H, 5.03; N, 3.94.

(±)-13β-Acetoxystylopine

(±)-13β-Hydroxystylopine (24.5 mg, 0.07 mmole) was dissolved in dry pyridine (1 ml) and freshly distilled acetic anhydride (2 ml) and stirred under N_2 for 4 hrs. Work-up in the usual manner gave 27.4 mg (99%) of the acetate as a yellow oil. Recrystallization from CH_2Cl_2-pet. ether gave small plates, mp 242-243° (dec), which proved indistinguishable chromatographically (R_f 0.75, SiO_2, $CHCl_3$-EtOAc 9:1v/v, 2x) from (-)-13β-acetoxystylopine.

plain negative dispersion curve subsequently determined for 13β-hydroxystylopine served to establish its absolute stereochemistry as 13*R*,14*R* as depicted in structure **2** (R = OH).

Final verification of the structure of 13β-hydroxystylopine has been achieved by a stereoselective synthesis from protopine. Although there have been several synthetic approaches described to ophiocarpine which are potentially adaptable to the synthesis of 13β-hydroxystylopine they suffer from certain disadvantages. The procedure of Govindachari[12] is both lengthy and nonstereoselective while Elliott's[13] method of hydroboration–oxidation of the enamine **4** provides 13-epiophiocarpine (**5**) as the major product rather than ophiocarpine. The most successful route em-



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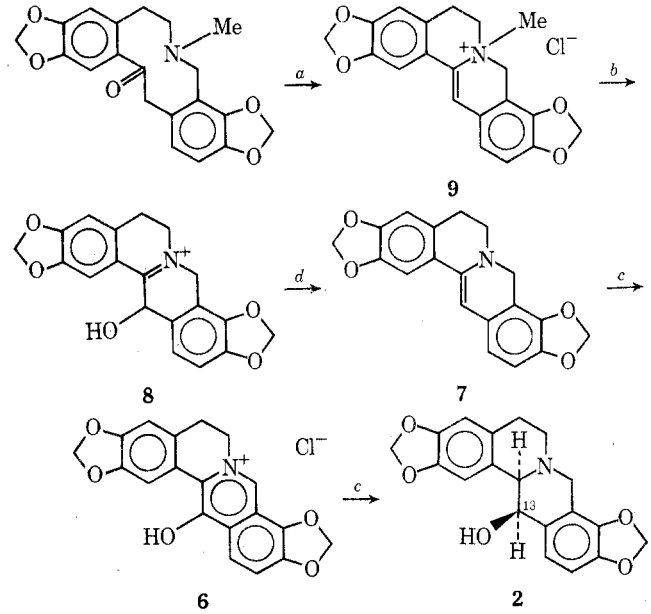
ploys the phenol–betaine, 13-hydroxyberberinium chloride (*cf.* **6**), which is obtained from berberine as first described by Pyman.[14] Reduction of 13-hydroxyberberinium chloride with sodium borohydride is reported[15] to proceed in a highly stereoselective manner to afford (±)-ophiocarpine.

It appeared that it might be possible to devise a more convenient route to the analogous phenol–betaine **6** required for the synthesis of 13β-hydroxystylopine than by employing the original procedure of Pyman. Our approach was based upon the rationale that the enamine **7** should

Scheme I
Synthesis of (±)-13β-Hydroxystylopine



[a] $POCl_3$. [b] Δ *in vacuo*. [c] *m*-Chloroperbenzoic acid. [d] O_2. [e] $NaBH_2$.

react with an electrophilic oxygen, such as a peracid, to afford the hydroxylated iminium salt **8**, which should undergo a facile oxidation to the required phenol–betaine **6** (see Scheme I).

Dihydrocoptisine (**7**) required for the synthesis was obtained by the procedure of Haworth and Perkin[16] by treat-

ment of protopine with $POCl_3$ followed by pyrolysis of the resulting salt **9** *in vacuo*.[17] Addition of 1.2 equiv of *m*-chloroperbenzoic acid to dihydrocoptisine at −78° led to rapid oxidation as evidenced by the disappearance of starting material when monitored by tlc.[18] The stoichiometry suggests that the iminium salt **8** is formed initially in this reaction. However, after allowing to come to room temperature, the product isolated in 78% yield after crystallization is 13-hydroxycoptisine chloride (**6**) as yellow-orange crystals, mp 285°. The latter is presumably formed by a highly efficient air oxidation of **8**. Reduction of **6** with sodium borohydride in aqueous ethanol gave (±-13β-hydroxystylopine, mp 219–220°, identical in its chromatographic and spectral properties with the natural alkaloid.

Careful examination of the borohydride reduction failed to show the presence of any of the 13α-hydroxy epimer of **2** (R = OH) in this reaction. The high stereoselectivity of this reduction is presumably a simple consequence of steric factors governing "approach control" of the borohydride. Alternatively, similar arguments can be made assuming a product-like transition state where, in the case of the 13α-hydroxy isomer, it is destabilized by nonbonded interactions of the C-13α hydroxyl with the C-1 hydrogen. Furthermore, if a product-like transition state is involved, the 13β-hydroxy system may gain additional stabilization by the development of an intramolecular hydrogen bond (*cf.* **3**) with the incipient electron pair on nitrogen.

Acknowledgments. We are indebted to the Duke University Research Council and the National Science Foundation (GP 9436) for grants in support of this work. Dr. David Rosenthal and Mr. Fred Williams, Research Triangle Mass Spectrometry Center, are thanked for providing the high-resolution mass spectral data. The Duke University Phytotron Facility is supported by National Science Foundation Grants GB 19634 and GB 28950 and we gladly acknowledge the use of this facility.

Registry No.—(−)-**2** (R = OH), 53777-76-7; (−)-**2** (R = OAc), 53777-77-8; (±)-**2** (R = OH), 53833-90-2; (±)-**2** (R = OAc), 53798-26-8; **6**, 53798-64-4; **7**, 53777-78-9; **8**, 53798-65-5; **9**, 53777-79-0; protopine, 130-86-9; phosphoryl chloride, 10025-87-3; *m*-chloroperbenzoic acid, 937-14-4.

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References and Notes

(1) This work was supported through a Career Development Award (GM 42342) and a research grant from the National Science Foundation (GP-9436).
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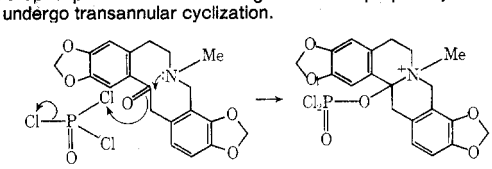
(17) It would seem that the conversion of protopine to **9** proceeds *via* the dichlorophosphate ester **i** reflecting the known propensity of this system to undergo transannular cyclization.



i

(18) The study of the oxidation of enamines with peracids appears not to have been investigated.[19] Preliminary experiments on the peracid oxidation of simple enamines have indicated that the conversion $COCH_2$ to COCHOH may be accomplished through this reaction (E. J. Rauckman, unpublished observation).
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