Acknowledgment. We are grateful to Dr. Catherine E. Costello for mass spectra analyses carried out at the National Institutes of Health sponsored Mass Spectrometry Facilities at the Massachusetts Institute of Technology (Grant No. RR00317), Professor K. Biemann, Principal Investigator. The authors thank Dr. A. Redfield for his help with the NMR experiments.

Registry No. 8, 500-22-1; 11, 71718-88-2; 12, 71718-89-3; 13, 71718-90-6; 13 picrate, 71718-91-7; 14, 71718-92-8; 15, 71749-89-8; 16, 71771-91-0; 17, 71718-93-9; 18, 71718-94-0; 19, 71718-95-1; 20, 71718-96-2; 20 dipicrate, 71718-97-3; 21, 71718-98-4; 22, 71718-99-5; 23, 71719-00-1; 23 picrate, 71785-25-6; 24, 71719-01-2; 25, 71719-02-3; 26, 71719-03-4; 27, 71719-04-5; 28, 4591-55-3; 29, 20826-04-4; 30, 29681-44-5; 31, 71719-05-6; 32, 64319-85-3; 33, 71719-06-7; 34, 71719-07-8; 35, 71719-08-9; 36, 71719-09-0; 37, 71719-10-3; 38, 71719-11-4; benzylamine, 100-46-9; succinic anhydride, 108-30-5; hexanoic anhydride, 2051-49-2; 1-(trimethylsilyl)pyrrolidin-2-one, 14468-90-7; benzyl chloride, 100-44-7; 1-methyl-2-pyrrolidinone, 872-50-4.

Conversion of Berberine into Phthalideisoquinolines[1]

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Ferricyanide oxidation of berberine (1) yields the dimer oxybis(berberine) whose breakdown with methanolic hydrogen chloride gives 8-methoxyberberinephenolbetaine (12). Hydration of 12 in wet ether furnishes enaminol 14 which can be N-methylated to dehydrohydrastine methyl ester (15). $NaBH_4$ reduction of 15 leads to a 1:2 mixture of (±)-α-hydrastine (9) and (±)-β-hydrastine (6), thus achieving the first conversion of 1 to the hydrastines. Whereas $NaBH_4$ reduction of 14·HCl gives mostly β-norhydrastine (5) together with a little α-norhydrastine (8), similar reduction of *N*-*n*-propyldehydronorhydrastine methyl ester (17) hydroiodide provides only *N*-*n*-propyl-α-norhydrastine (11). Diisobutylaluminum hydride reduction of 5 leads to (±)-epiophiocarpine (22), and the diastereoisomeric (±)-ophiocarpine (23) is formed by $NaBH_4$ reduction of betaine 12. Hydration of 12 in wet THF generates methyl isoanhydroberberilate (26), while methyl anhydroberberilate (32) is obtained through acetic anhydride treatment of betaine 12 to furnish 13-acetoxyoxoberberine (30), followed by reaction with methanolic KOH.

Berberine is the best known, oldest, and most available of the protoberberine alkaloids, having been first isolated in 1826,[2] while its structural elucidation dates to the first decade of this century.[3,4] The protoberberines themselves occupy a prominent position in the biogenetic lineage of other groups of isoquinoline alkaloids, including the phthalideisoquinolines, spirobenzylisoquinolines, rhoeadines, and protopines.[5,6] A biogenetic relationship between protoberberines and phthalideisoquinolines was first suggested by Perkin and Robinson in 1910.[4,7] Their hypothesis has been supported and refined by radio tracer incorporation studies in recent years, involving in particular the feeding of labeled (−)-scoulerine (3).[8] The rational conclusion was thus drawn that it is tetrahydroprotoberberines rather than berberinium salts that act as biogenetic precursors for the phthalideisoquinoline alkaloids.[8]

Interestingly enough, however, at the inception of our studies on berberine (1), the chemical conversion of this alkaloid or of its tetrahydro derivative canadine (2) to its phthalideisoquinoline analogue β-hydrastine (6) still remained to be achieved. Key requirements for such a transformation are the selective oxidation of the protoberberine skeleton at carbons 8 and 13, and the cleavage of ring C with accompanying N-methylation, since *N*-norphthalideisoquinolines are unknown in nature.

Because introduction of an oxygen substituent at position 8 of berberine (1) is trivially accomplished with aqueous alkali, our initial effort was directed toward an alkaline reagent for the selective oxygenation of position 13, necessary for the conversion to the phthalideisoquinoline alkaloid β-hydrastine (6). Since even dilute alkaline permanganate treatment results in drastic oxidation of the berberine system, the use of the mild, alkali-stable one-electron oxidant potassium ferricyanide was investigated. Indeed, on our very first attempt, using potassium ferricyanide followed by aqueous sodium hydroxide, colorless plates of the hitherto unknown dimer oxybis(berberine) were obtained. Although the exact structure of this dimer is rather complex and remains to be elucidated, it is clear from its reactions that it is formed from the condensation of 1 mol of a berberine derivative that has been oxidized at C-8 and C-13 with 1 mol of unoxidized berberine. Significantly, however, both the IR and ^{13}C NMR spectra of oxybis(berberine) show no evidence of carbonyl groups.[9]

When a slurry of oxybis(berberine) in methanol was treated with 10% methanolic hydrogen chloride, immediate breakdown of the dimer took place with formation of a red coloration. Reaction workup gave the new compound 8-methoxyberberinephenolbetaine (12) as fine orange needles, together with an equivalent amount of berberine (1) chloride.

It was immediately recognized that the phenolbetaine 12 possesses the requisite oxygen function at C-13 as well as a potential carboxylic acid at C-8 for transformation to β-hydrastine (6). The unmasking of the C-8 carboxyl was achieved by simple hydration whereby a stirring solution

(1) Parts of this work were published in communication form: J. L. Moniot and M. Shamma, *J. Am. Chem. Soc.*, **98**, 6714 (1976); J. L. Moniot, A. H. Abd el Rahman, and M. Shamma, *Tetrahedron Lett.*, 3787 (1977).

(2) M. Chevalier and G. Pelletan, *J. Chim. Med., Pharm., Toxicol.*, **2**, 314 (1826).

(3) J. Gadamer, *Chem.-Ztg.*, **26**, 291 (1902).

(4) W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **97**, 305 (1910).

(5) M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972, pp 360, 381, 400, 345.

(6) M. Shamma and J. L. Moniot, "Isoquinoline Alkaloids Research 1972–1977", Plenum Press, New York, 1978, pp 307, 325, 337, 299.

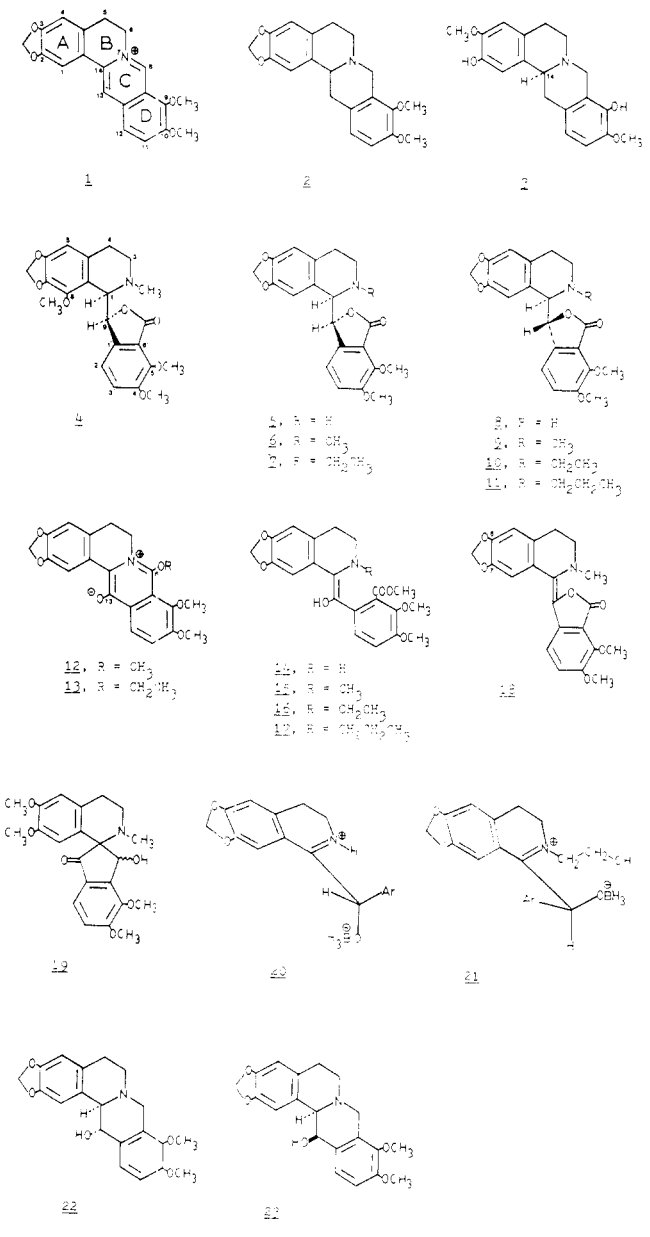
(7) R. Robinson, "Structural Relations of Natural Products", Clarendon Press, Oxford, 1955, p 88.

(8) A. R. Battersby, M. Hirst, D. J. McCaldin, R. Southgate, and J. Staunton, *J. Chem. Soc. C*, 2163 (1968).

(9) An X-ray analysis of oxybis(berberine) is presently being attempted. It should be stated that this dimer is not an absolute requirement for the preparation of 8-methoxyberberinephenolbetaine (12) since subsequent to our initial communication[1] 12 was prepared through photoirradiation of berberine in methanol: see ref 13 below.

0022-3263/79/1944-4337$01.00/0

Chart I



of **12** in water-saturated ether at room temperature slowly decolorized to furnish in 80% yield the hydrochloride salt of dehydronorhydrastine methyl ester (**14**). N-Alkylation of the free-base **14** with methyl iodide in refluxing acetonitrile afforded dehydrohydrastine methyl ester (**15**), whose sodium borohydride reduction followed by acid workup provided a separable 1:2 mixture of (±)-α-hydrastine (**9**) and (±)-β-hydrastine (**6**) in 90% overall yield, spectrally identical with semisynthetic (−)-α-hydrastine and natural (−)-β-hydrastine, respectively.[10] The first laboratory conversion of berberine (**1**) to the hydrastines had thus been achieved.

Alternatively, treatment of dehydrohydrastine methyl ester (**15**) with methanol containing some hydrochloric acid provided dehydrohydrastine (**18**)[10a] in excellent yield. It has previously been shown that diisobutylaluminum hydride reduction of the 6,7-dimethoxy analogue of **18**, namely, dehydrocordrastine, furnishes an equimolar mixture of the spirobenzylisoquinolines **19**,[11] so that our present preparation of dehydrohydrastine (**18**) may be considered a potential avenue for the conversion of berberine (**1**) to its corresponding spirobenzylisoquinoline base.

When dehydronorhydrastine methyl ester (**14**) hydrochloride was added to a stirred solution of sodium borohydride in methanol, the product was a separable mixture consisting of 93% β-norhydrastine (**5**) and 7% α-norhydrastine (**8**). This small yield of the α isomer is to be compared with the 32% yield of α-hydrastine (**9**) obtained from analogous reduction of dehydrohydrastine methyl ester (**15**) hydroiodide. It was subsequently established that the relative yields of the α isomers augment consistently with increasing size of the N substituent on the norhydrastine methyl ester, so that reduction of *N*-ethyldehydronorhydrastine methyl ester (**16**) hydroiodide led to a 55:45 mixture of *N*-ethyl-α-norhydrastine (**10**) and *N*-ethyl-β-norhydrastine (**7**), while only *N*-*n*-propyl-α-norhydrastine (**11**) could be obtained from the reduction of *N*-*n*-propyldehydronorhydrastine methyl ester (**17**) hydroiodide. These stereochemical results are consistent with the thesis that reduction of intermediate **20** which is favored in the N–H series leads to mostly β-norhydrastine (**5**), while reduction of intermediate **21** which is favored in the *N*-*n*-propyl case leads to the α isomer **11**. In each case, hydride addition to the iminium double bond is through a cyclic mechanism involving initial formation of a borate complex, **20** or **21**.

In line with the above stereochemical assignments, β-norhydrastine (**5**) upon reduction with diisobutylaluminum hydride yielded the tetrahydroprotoberberine epiophiocarpine (**22**) as the racemate.[12,13] Epiophiocarpine (**22**) is not a natural product, even in an optically active form. Its diastereomer, ophiocarpine (**23**), is a known and well-characterized alkaloid which, in our hands, could be obtained preferentially and in high yield as the racemate[12,13] by direct sodium borohydride reduction of 8-methoxyberberinephenolbetaine (**12**).

Another interesting facet of the chemistry of 8-methoxyberberinephenolbetaine (**12**) is its hydration. It has been mentioned above that when this compound is stirred in wet ether, a solvent in which it is only slightly soluble, the product is dehydronorhydrastine methyl ester (**14**). If, however, wet THF is used for this purpose, a medium in which **12** is appreciably soluble, the reaction takes a different and unusual course and generates methyl isoanhydroberberilate (**26**) in 71% yield. Attempted reduction of this imidic methyl ester with sodium borohydride in ethanol resulted only in solvolysis with formation of noroxyhydrastinine (**28**) and 1-(carboethoxy)-2-(carbomethoxy)-3,4-dimethoxybenzene (**29**). In like fashion, 8-ethoxyberberinephenolbetaine (**13**), derived from cleavage of oxybis(berberine) in ethanolic hydrogen chloride, upon treatment with wet THF supplied the corresponding imidic ethyl ester, ethyl isoanhydroberberilate (**27**).[14] These transformations indicate that the ester carbonyls in **26** and **27** are derived from the alkoxylated C-8 carbons of phenolbetaines **12** and **13**, respectively.

The unusual migration involved in going from **12** to **26** can be rationalized in terms of the mechanism indicated in Scheme I, in which **12** is first hydrated and air oxidized to the peroxide **24**. Subsequent formation of aziridine **25**,

(10) (a) R. D. Haworth and A. R. Pinder, *J. Chem. Soc.*, 1776 (1950); (b) R. D. Haworth, A. R. Pinder, and R. Robinson, *Nature (London)*, **165**, 529 (1950); (c) W. H. Perkin, Jr., J. N. Rây, and R. Robinson, *J. Chem. Soc.*, **127**, 740 (1925).

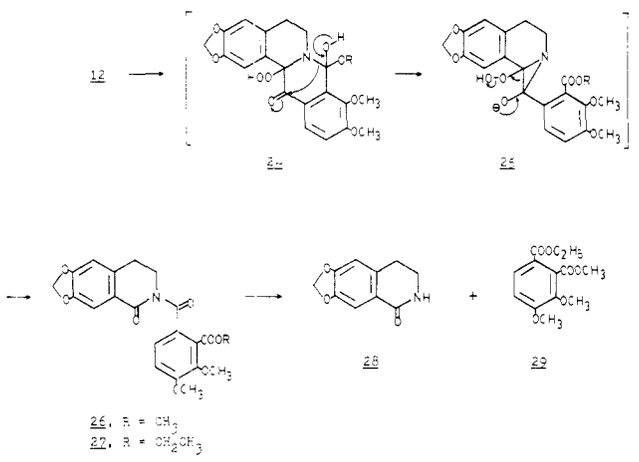
(11) H. L. Holland, D. B. MacLean, R. G. A. Rodrigo, and R. H. F. Manske, *Tetrahedron Lett.*, 4323 (1975).

(12) I. W. Elliott, Jr., *J. Heterocycl. Chem.*, **4**, 639 (1967).

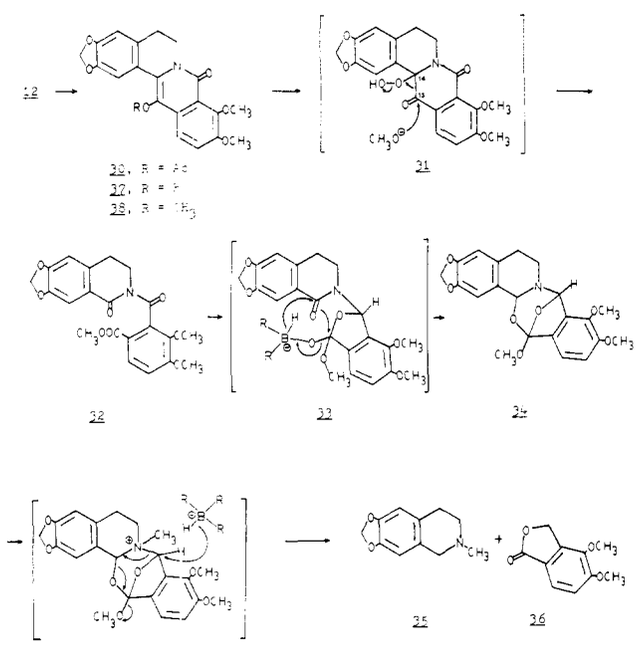
(13) M. Hanaoka, C. Mukai, and Y. Arata, *Heterocycles*, **6**, 895 (1977).

(14) Significantly, solvolysis of ethyl isoanhydroberberilate (**27**) in methanol furnished the known 1-(carbomethoxy)-2-(carboethoxy)-3,4-dimethoxybenzene first prepared by A. Kirpal, *Monatsh. Chem.*, **35**, 677 (1914).

Scheme I



Scheme II



followed by loss of hydroxide anion, would then lead to the product. A parallel mechanism can be invoked for the conversion of **13** to **27**.

The structural isomer of methyl isoanhydroberberilate (**26**), namely, methyl anhydroberberilate (**32**),[15] was readily obtained from 8-methoxyberberinephenolbetaine (**12**) through reaction with acetic anhydride in pyridine which furnished 13-acetoxyoxoberberine (**30**) in 95% yield, followed by treatment with methanolic potassium hydroxide (Scheme II).

Worthy of note is the difference between the two key intermediates **24** and **31**, both of which incorporate an α-hydroperoxy ketone moiety. The hydroxyl group at C-8 in species **24** furnishes the required source of electrons for the rearrangement to take place. On the other hand, **31** is a lactam which undergoes preferential nucleophilic attack at C-13 by methoxide anion, with subsequent cleavage of the C-13 to C-14 bond to give rise to methyl anhydroberberilate (**32**).

Sodium borohydride reduction of **32** unexpectedly furnished in 52% yield the methyl orthoester **34** which shows no carbonyl band in the IR region and may be formed through intramolecular participation of the hydridoborate **33**. N-Methylation of the methyl orthoester **34** succeeded by reduction with sodium borohydride supplied the known compounds hydrohydrastinine (**35**)[15] and pseudomeconine (**36**).[14]

Cleavage of the dimer oxybis(berberine) by acetic anhydride in pyridine, or dimethyl sulfate in benzene, with a view toward obtaining variants of the betaine **12** led instead to the pyridinones 13-acetoxyoxoberberine (**30**) and 13-methoxyoxoberberine (**38**), respectively. Similarly, separate treatments of phenolbetaine **21** with dilute aqueous acid, acetic anhydride, or methyl iodide in THF generated pyridinones **37**, **30**, and **38**, respectively. Apparently, when the electrons of the C-13 oxygen anion of the betaine are not readily available, hydrolysis of the C-8 imidate function to the pyridinone occurs.

During the course of the structural elucidation of many of these new compounds, the most powerful structural probe was found to be carbon-13 NMR spectroscopy. In the present study, a number of highly substituted carbons were encountered and the full ^{13}C NMR assignments have been published for several of these highly functionalized alkaloid derivatives.[17]

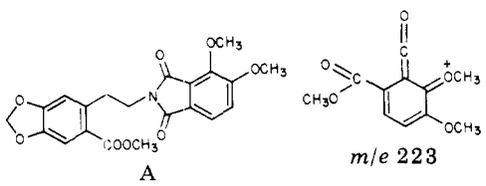
Experimental Section

Standard Experimental Procedures. Melting points are uncorrected. ^1H NMR spectra were recorded at 60 MHz on a Varian A-60A with Me_4Si as an internal standard. ^{13}C NMR chemical shifts were determined in $CDCl_3$ solution by using pulsed Fourier transform techniques on either a Varian CFT-20 or a JEOL JNM PS-100-FT spectrometer operating at 25.03 MHz. Mass spectra were determined at 70 eV on an AEI MS-902 double-focusing spectrometer. All TLC was on Merck 254 precoated silica gel plates. Spots were visualized under UV light and by spraying with chloroplatinate or chromatropic acid spray reagents. Combustion analyses were by Midwest Microlab, Inc.

Oxybis(berberine). A saturated solution of berberine (1) chloride (200 g, 0.54 mol) in water at 60 °C was treated with powdered potassium ferricyanide until precipitation was complete. The resultant slurry was allowed to stand at room temperature and the supernatant liquid decanted. The remaining thick greenish yellow slurry was treated with an aqueous saturated solution of sodium hydroxide until a permanent color change to yellow-tan had occurred. After 2–6 min of stirring, the slurry was rapidly extracted with ether. Both layers clarified, and the organic ether layer was filtered rapidly through anhydrous potassium carbonate. Oxybis(berberine) was allowed to crystallize at room temperature; crystallization was complete in 48 h. Following the collection of the crystals, the ether mother liquors which contained berberine pseudobase were concentrated and acidified to recover unreacted berberine.

The crystals of oxybis(berberine) were washed successively with water, methanol, and ether and then air-dried at room temperature. Recrystallization from pyridine–ether (1:2) afforded 120 g (59%) of fine white plates: mp 215–216 °C; ^1H NMR (pyridine-d_5) δ 2.00–3.40 (m, 8 H), 3.47 (s, 3 H), 3.57 (s, 3 H), 3.88 (s,

(15) W. H. Perkin, Jr., *J. Chem. Soc.*, **57**, 992 (1890). In this paper, which was written almost 90 years ago, Perkin assigned to methyl anhydroberberilate the isomeric structure A.



A

m/e 223

However, in our hands, the mass spectrum with a base peak at *m/e* 223 ($C_{11}H_{11}O_5$) supports expression **32**.

(16) D. B. Clayson, *J. Chem. Soc.*, 2016 (1949).

(17) The ^{13}C NMR assignments for compounds **1**, **14**, **26**, **28**, **30**, **32**, **37**, and **38** have been summarized in diagrams 356, 416, 317, 315, 398, 316, 296, and 397, respectively, in M. Shamma and D. M. Hindenlang, "Carbon-13 NMR Shift Assignments of Amines and Alkaloids", Plenum Press, New York, 1979.

3 H), 3.93 (s, 3 H), 4.58 (m, 1 H), 5.28 (s, 1 H), 5.60 (s, 2 H), 5.67 (m, 1 H), 5.75 (m, AB q, 2 H), 6.27, 6.44, 6.48, 6.58, 6.63, 6.78 (8 H), 7.68 (s, 1 H); ^{13}C NMR ($CDCl_3$) eight oxygen-substituted aromatic carbons at 142.3, 145.2, 145.3, 146.3, 146.5, 146.8, 151.4, and 151.7 ppm, eight carbon-substituted aromatic carbons at 123.9, 128.5, 128.9, 129.1, 131.2, 131.5, 132.5, and 133.6 ppm, eight protonated aromatic carbons at 107.1, 110.6, 107.2, 107.3, 107.7, 111.9, 121.1, and 123.9 ppm, two methylenedioxy carbons at 100.5 and 100.8 ppm, three nonprotonated aliphatic carbons at 78.8, 80.9, and 95.5 ppm, three monoprotonated aliphatic carbons at 57.6, 80.3, and 94.8 ppm, four methoxylated carbons at 55.6, 55.6, 61.2, and 61.6 ppm, four methylene carbons at 28.0, 28.2, 39.0, and 45.3 ppm, for an apparent total of 40 carbons.

Oxybis(berberine) crystallizes from pyridine–ether as monoclinic plates in the space group $P2_1/c$ with cell dimensions a = 16.12 Å, b = 11.19 Å, c = 16.91 Å, and β = 118°05′.

Typical combustion analytical values are: C, 66.13 ± 0.21; H, 55.15 ± 0.25; N, 3.90 ± 0.10; residual oxygen. The compound does not lend itself to mass spectral analysis due to low volatility and thermal decomposition.

The following alternate preparation results in a somewhat lower yield of oxybis(berberine). Berberine chloride (373 g, 1 mol) was placed in hot tap water (3 L) and stirred for 3 h. The slurry was treated with a hot aqueous solution of potassium ferricyanide (329 g, 1.1 mol) and the resultant slurry was further diluted with 6 L of hot tap water. Slow stirring was continued for 24 h. The yellow-tan slurry was treated with an aqueous saturated solution of potassium hydroxide (~7:1 berberine/ferricyanide to potassium hydroxide solution or ~3500 mL of slurry to 500 mL of aqueous base), and the whole was stirred vigorously for 5 min. A subtle color change to pink occurred which lasted for only 5 s. The mixture then faded to a dull tan, with a layer of foam at the top. The mixture was quickly extracted with ether. The emulsion layer that had formed was also collected for later use. The clear red ether layer was filtered rapidly through anhydrous potassium carbonate, and the oxybis(berberine) was allowed to crystallize at room temperature for 72 h. The ether mother liquors were decanted, concentrated, and acidified to recover unreacted berberine. The solid oxybis(berberine) was freed from the flask walls with methanol (50 mL), collected on a filter, washed with ether, and air-dried to yield 32 g (8.6%) of yellow-tan oxybis(berberine).

The above emulsion layer was allowed to air-dry to a solid plug. The solid was washed with water and methanol, vacuum filtered to dryness, and treated with pyridine (200 mL) at 50 °C. The solution was filtered to remove a black, gelatinous substance which had formed. Ether (1 L) was added to the warm pyridine solution, causing the precipitation of a gummy material which was filtered off and discarded. The pyridine solution was treated with ether (4 L), and oxybis(berberine) crystallized out completely in 48 h. The mother liquors were decanted and discarded. The solid oxybis(berberine) was freed from the flask walls with methanol, filtered, washed with ether, and dried at room temperature to afford 12 g as a yellow-tan powder.

8-Methoxyberberinephenolbetaine (12). A slurry of oxybis(berberine) (0.5 g, 0.7 mmol) in methanol (50 mL) was treated with 10% methanolic anhydrous hydrogen chloride (20 mL) at room temperature. A red color developed immediately, and upon standing a yellow crystalline mass formed. The entire mixture was partitioned between ether and 2% NH_4OH (100 mL), and the organic layer was separated and filtered through anhydrous potassium carbonate. Residual emulsions were further extracted with chloroform. The organic layers were combined, the solvent was removed, and the residue crystallized upon addition of chloroform–ether to give 0.25 g (0.65 mmol, 93%) of **12** as fine orange needles: mp 175–176 °C; λ_{max}^{EtOH} 230, 262 (sh), 313, 359, 374, 455 nm (log ϵ 4.50, 4.11, 4.09, 3.81, 3.80, 3.83); ^1H NMR ($CDCl_3$) δ 2.90 (t, 2 H), 3.86 (s, 3 H), 3.98 (s, 6 H), 4.58 (t, 2 H), 5.86 (s, 2 H), 6.51 (s, 1 H), 7.35 (d, 1 H), 8.28 (d, 1 H), 8.80 (s, 1 H).

Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.14; H, 4.99. Found: C, 65.92; H, 5.02.

The alkaline aqueous layer was reacidified and extracted with ether to yield berberine chloride (0.2 g, 0.54 mmol).

Dehydronorhydrastine Methyl Ester (14). A saturated ether solution of **12** was stirred at room temperature with a few milliliters of water for 48–72 h in sunlight until the color disappeared. The ether solution was dried and concentrated, and dry HCl gas was passed through. The precipitated HCl salt of **14** (80%) was filtered and recrystallized from methanol–ether as light yellow plates: mp 144–145 °C; $\nu_{max}^{CHCl_3}$ 1670 and 1730 cm^{-1}.

The oily free base **14** exhibits the following data: λ_{max}^{EtOH} 210, 228, 280, 308 nm (log ϵ 4.50, 4.37, 4.20, 4.19); ^1H NMR ($CDCl_3$) δ 2.73, 3.81 (2 t, 2 × 2H, CH_2CH_2), 3.84, 3.92, 3.96 (3 s, 3 × 3 H, $3OCH_3$), 5.98 (s, 2 H, OCH_2O), 6.70, 7.03 (3 s, 2 × 1 H, C-5 and C-8 H), 7.04 (AB q, 2 H, J = 9 Hz, ics = 10 Hz, C-2′ and C-3′ H).

Anal. Calcd for $C_{21}H_{21}NO_7 \cdot CH_3OH$: C, 53.90; H, 4.73. Found: C, 53.73; H, 4.67.

Dehydrohydrastine Methyl Ester (15). The HCl salt of **14** (0.6 g, 1.2 mmol) was stirred in 50 mL of water, and the solution was neutralized with aqueous $NaHCO_3$ and extracted with chloroform. The organic layer was filtered through anhydrous sodium sulfate and the solvent removed to leave an oil. A solution of this oil (0.49 g, 1.2 mmol) in acetonitrile (100 mL) and methyl iodide (6 mL) was refluxed for 8 h, the mixture was cooled, and the solvent was evaporated to leave crude **15** as the orange-yellow HI salt, mp 167–168 °C (MeOH) (0.5 g, 68%).

Anal. Calcd for $C_{22}H_{23}NO_7HI$: C, 48.41; H, 4.46; I, 23.44. Found: C, 48.84; H, 4.23; I, 23.08.

Treatment of the salt with aqueous $NaHCO_3$, followed by chloroform extraction, yielded free base **15**: mp 125–127 °C (MeOH); $\nu_{max}^{CHCl_3}$ 1670, 1735 cm^{-1}; λ_{max}^{EtOH} 258, 298, 302, 387 nm (log ϵ 4.61, 4.70, 4.68, 3.92); ^1H NMR ($CDCl_3$) δ 2.22 (s, 3 H, NCH_3), 2.5–3.4 (m, 4 H, CH_2CH_2), 3.45 (s, 1 H, C-1 H), 3.81, 3.83, 3.97 (3 s, 3 × 3 H, $3OCH_3$), 5.83 (s, 2 H, OCH_2O), 6.32, 6.60 (2 s, 2 × 1 H, C-5 and C-8 H), 7.30 (AB q, 2 H, J = 9 Hz, ics = 74 Hz, C-2′ and C-3′ H).

(±)-β-Hydrastine (6) and (±)-α-Hydrastine (9). A solution of **15**·HI (0.08 g, 1.5 mmol) in ethanol (50 mL) was reduced with excess sodium borohydride. The mixture was acidified with aqueous hydrochloric acid and allowed to stand for 3 h. After neutralization with solid sodium bicarbonate, the solution was partitioned with chloroform, and the organic layer was dried and filtered. Evaporation of the solvent left a residue which crystallized from methanol. Column chromatography on silica gel using chloroform–methanol mixtures afforded **9** (0.18 g, 32%), mp 162–163 °C (MeOH), and **6** (0.36 g, 62%), mp 207–208 °C (MeOH), spectrally identical with semisynthetic and authentic samples of (−)-α-hydrastine and (−)-β-hydrastine, respectively.

(±)-*N*-Ethyl-β-norhydrastine (7) and (±)-*N*-Ethyl-α-norhydrastine (10). A solution of **14** free base (0.4 g, 1 mmol) in acetonitrile (30 mL) was treated with ethyl iodide (2.5 mL), and the solution was refluxed under nitrogen overnight. Following removal of the solvent, the solid quaternary salt was immediately taken up in methanol and treated with excess sodium borohydride. The mixture was poured into water, the pH adjusted to 2, and the solution allowed to stand 1 h. Adjustment to pH 7 and extraction with chloroform, followed by evaporation of the organic layer, gave an oil which was chromatographed on silica gel with chloroform–methanol mixtures to give **10** (0.20 g): mp 196–197 °C (MeOH–ether); $\nu_{max}^{CHCl_3}$ 1775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, 3 H, J = 7 Hz, CH_3CH_2), 2.3–3.1 (m, 6 H, CH_2 × 3), 3.78 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.22 (d, 1 H, J = 2.5 Hz, H-1), 5.51 (d, 1 H, J = 2.5 Hz, H-9), 5.70 (q, 2 H, J = 1.5 Hz, OCH_2O), 6.25 (s, 1 H, H-8), 6.53 (s, 1 H, H-5), 6.95, 7.20 (AB q, 2 H, J = 8.5 Hz, ring D aromatic H).

High-resolution mass spectrum: calcd for $C_{22}H_{23}NO_6$, 397.1519; found, 397.1508.

A second product was **7** (0.16 g): mp 166–167 °C (MeOH); $\nu_{max}^{CHCl_3}$ 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 7 Hz, CH_3CH_2), 2.3–3.1 (m, 6 H, CH_2 × 3), 3.85 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 4.32 (d, 1 H, J = 4 Hz, H-1), 5.42 (d, 1 H, J = 4 Hz, H-9), 5.81 (s, 2 H, OCH_2O), 6.41 (s, 1 H, H-8), 6.60 (s, 1 H, H-5), 6.50, 7.08 (AB q, 2 H, J = 8.5 Hz, ring D aromatic H).

High-resolution mass spectrum: calcd for $C_{22}H_{23}NO_6$, 397.1519; found, 397.1501.

(±)-*N*-*n*-Propylnorhydrastine (11). This compound was obtained through alkylation of **14** free base with *n*-propyl iodide followed by reduction with sodium borohydride in methanol in a manner parallel to that described above. Compound **11**·HCl: mp 184–186 °C (MeOH); $\nu_{max}^{CHCl_3}$ free base 1770 cm^{-1}; ^1H NMR ($CDCl_3$) 0.83 (t, 2 H, J = 7 Hz, $CH_3CH_2CH_2$), 1.41 (m, 2 H,

$CH_3CH_2CH_2N$), 2.50 (m, 4 H, 2 × CH_2N), 2.8–3.3 (m, 2 H, benzylic CH_2), 3.82 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 4.08 (d, 1 H, J = 3 Hz, H-1), 5.49 (d, 1 H, J = 3 Hz, H-9), 5.78 (q, 2 H, J = 1 Hz, OCH_2O), 6.40 (s, 1 H, H-8), 6.68 (s, 1 H, H-5), 7.04, 7.27 (AB q, 2 H, J = 8.5 Hz, ring D aromatic H).

High-resolution mass spectrum: calcd for $C_{23}H_{25}NO_6$, 411.1675; found, 411.1662.

(±)-β-Norhydrastine (5) and (±)-α-Norhydrastine (8). To a stirred solution of $NaBH_4$ (excess) in methanol (70 mL) was added portionwise 14·HCl (0.54 g). The mixture was poured into water, adjusted to pH 5 and then to pH 7, and extracted with chloroform. The chloroform extracts were chromatographed over silica gel with methanol–chloroform mixtures to afford 0.42 g (93%) of **5** as fine white needles: mp 156–158 °C ($CHCl_3$), mp 169–170 °C (ether); $\nu_{max}^{CHCl_3}$ 1765, 3400 cm^{-1}; m/e 369 (M^+, 10), 193 (30), 176 (100); ^1H NMR δ 2.53 (t, 2 H, J = 4 Hz, H-4), 2.79 (t, 2 H, J = 4 Hz, H-3), 3.09 (s, 1 H, NH), 3.87 (s, 3 H, OCH_3), 4.08 (s, 3 H, OCH_3), 4.68 (d, 1 H, J = 3.5 Hz, H-1), 5.74 (d, 1 H, J = 3.5 Hz, H-9), 5.96 (s, 2 H, OCH_2O), 6.62 (s, 2 H, H-5 and H-8), 6.38, 7.05 (AB q, 2 H, J = 8.5 Hz, ring D aromatic H).

High-resolution mass spectrum: calcd for $C_{20}H_{19}NO_6$, 369.1207; found, 369.1202.

A minor product was **8**: 0.02 g (4%); mp of the HCl salt 187–188 °C (ether–MeOH); $\nu_{max}^{CHCl_3}$ (free base) 1765, 3350 cm^{-1}; mass spectrum of free base m/e 369 M^+ (5), 193 (10), 176 (base), 164 (10), 149 (20).

High-resolution mass spectrum: calcd for $C_{20}H_{19}NO_6$, 369.1207; found, 369.1207.

Dehydrohydrastine (18). A solution of **15**·HI (0.2 g, 0.38 mmol) in methanol (30 mL) was treated with 1 mL of concentrated HCl, and the mixture was stirred for 18 h and diluted with 300 mL of water. The pH was adjusted to 7 with sodium bicarbonate, and the mixture was extracted with chloroform. The organic layer was dried, filtered, and evaporated. The residue crystallized from methanol to yield 0.137 g (96%) of dark orange needles of **18**: mp 203–204 °C [lit.[10a] mp 204–205 °C]; $\nu_{max}^{CHCl_3}$ 1595, 1665, 1740 cm^{-1}; m/e 381 (M^+, 10), 352 (15), 336 (100), 223 (10), 208 (8), 190 (70), 142 (70).

Dehydronorhydrastine Ethyl Ester (14 Ethyl Ester). A filtered solution of **13** (0.4 g, 1.01 mmol) in 8 L of ether containing 30 mL of water was stirred in light and air until colorless (24 h). The solution was dried and reduced to 200 mL and then treated with hydrogen chloride gas. The bright yellow precipitate of the HCl salt was collected and recrystallized to afford 0.312 g (68.7%): mp 142–143 °C (MeOH–ether); $\nu_{max}^{CHCl_3}$ 1670, 1730 cm^{-1}. The oily free base exhibited λ_{max}^{EtOH} 210, 230, 282, and 309 nm (log ε 4.46, 4.35, 4.21, and 4.20).

High-resolution mass spectrum: calcd for $C_{22}H_{23}NO_7$, 413.1486; found, 413.1452.

(±)-Epiophiocarpine (22). To a stirred solution of **5** (0.11 g, 0.3 mmol) in dry THF at −20 °C was added 0.7 mL of a solution of Dibal (20% in hexane), and after stirring at −20 °C for 1 h, the mixture was allowed to come to room temperature. Dilute H_2SO_4 and ice were added, the pH was adjusted to 7, and the mixture was extracted with chloroform. The organic layer was dried and evaporated. The residue was purified by preparative TLC on silica gel plates to afford 0.053 g (50%) of **22** as very light yellow bars from methanol, mp 169–170 °C.[12,13]

(±)-Ophiocarpine (23). To a stirred solution of 0.5 g of $NaBH_4$ in methanol (60 mL) was added 0.32 g (0.85 mmol) of **12**, and the mixture was stirred overnight. The organic layer, following partition with water and chloroform, was dried and evaporated. The residue afforded 0.26 g (87%) of fine white needles, mp 224–225 °C (MeOH–$CHCl_3$), spectrally identical with a sample of ophiocarpine.

The minor component present in the mother liquor was purified by preparative TLC on silica gel and afforded 0.033 g (11%) of **23**, mp 169–170 °C (ether).[12,13]

Overnight acetylation of **23** with acetic anhydride in pyridine at room temperature led to (±)-ophiocarpine acetate, mp 173–174 °C (MeOH).

Methyl Isoanhydroberberilate (26). A solution of **12** (1.03 g, 2.71 mmol) in THF (1 L) was treated with water (15 mL), and the solution was stirred in light and air for 24 h whereupon the original orange color had faded to a pale yellow. Chloroform extraction, followed by drying and evaporation, left an oil which was taken up in ether (200 mL). The solution was dried, and dry hydrogen chloride gas was passed through. Following filtration and solvent evaporation, the oily residue crystallized from methanol as white needles: mp 143–144 °C; 0.82 g (71%); $\nu_{max}^{CHCl_3}$ 1685, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.00 (t, 2 H, J = 7 Hz, H-4), 3.71 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.04 (t, H, J = 7 Hz, H-3), 5.98 (s, 2 H, OCH_2O), 6.67 (s, 1 H, H-5), 7.43 (w, 1 H, H-8), 6.91, 7.19 (AB q, 2 H, J = 8.5 Hz, H-5′ and 6′); m/e 413 (M^+, 50), 382 (90), 364 (5), 354 (40), 223 (base), 193 (5), 191 (30), 177 (20).

High-resolution mass spectrum: calcd for $C_{21}H_{19}NO_8$, 413.1105; found, 413.1097.

Conversion of Methyl Isoanhydroberberilate (26) to 1-(Carboethoxy)-2-(carbomethoxy)-3,4-dimethoxybenzene (29). To a stirred slurry of **26** (0.41 g, 0.98 mmol) in ethanol was added excess sodium borohydride (0.5 g) portionwise, and the mixture was allowed to stir for 4 h. Extraction with chloroform, followed by TLC on silica gel, afforded diester **29** (0.16 g, 60%) as an oil: $\nu_{max}^{CHCl_3}$ 1710, 1730 cm^{-1}; λ_{max}^{EtOH} 258, 288 nm (log ε 3.82, 3.62); ^1H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7 Hz, OCH_2CH_3), 3.85 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 4.33 (q, 2 H, J = 7 Hz, OCH_2CH_3), 6.92, 7.80 (AB q, 2 H, J = 8.5 Hz, H-5 and H-6, respectively); m/e 268 M^+ (base), 237 (20), 223 (90), 208 (80), 191 (50).

High-resolution mass spectrum: calcd for $C_{13}H_{16}O_6$, 268.0945; found, 268.0941.

The other product of the reaction was noroxyhydrastinine (**28**) which crystallized as soft needles from ether, mp 180–181 °C (lit.[4] mp 179–180 °C).

Conversion of Ethyl Isoanhydroberberilate (27) to 1-(Carbomethoxy)-2-(carboethoxy)-3,4-dimethoxybenzene. To a stirred slurry of **27** (0.4 g, 0.97 mmol) in methanol was added excess sodium borohydride (0.5 g) portionwise, and the mixture was stirred for 4 h. Workup as above provided the known noroxyhydrastinine (**28**) (0.09 g, 49%), mp 180–181 °C [lit.[15] mp 180 °C], and also the known 1-(carbomethoxy)-2-(carboethoxy)-3,4-dimethoxybenzene (0.13 g, 50%) as colorless plates from methanol: mp 86–87 °C [lit.[14] mp 88 °C (ether–H_2O)]; $\nu_{max}^{CHCl_3}$ 1710, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (t, 3 H, J = 7 Hz, OCH_2CH_3), 3.81 (s, 6 H, 2 × OCH_3), 4.43 (q, 2 H, J = 7 Hz, OCH_2CH_3), 6.87, 7.71 (AB q, 2 H, J = 8.5 Hz, H-5 and H-6, respectively); m/e 268 M^+ (65), 237 (10), 223 (base), 209 (50), 191 (55), 179 (30), 165 (45).

High-resolution mass spectrum: calcd for $C_{13}H_{16}O_6$, 268.0945; found, 268.0965.

8-Ethoxyberberinephenolbetaine (13). Treatment of 1 g (1.34 mmol) of oxybis(berberine) in ethanol (120 mL) with ethanolic hydrogen chloride by the procedure followed to obtain **12** furnished 0.43 g (82%) of **13**, mp 187–188 °C (ether–$CHCl_3$), as orange needles.

High-resolution mass spectrum: calcd for $C_{22}H_{21}NO_6$, 395.1364; found, 395.1358.

Ethyl Isoanhydroberberilate (27). A solution of **13** (0.34 g, 0.86 mmol) in THF (500 mL) was treated with water (15 mL) and stirred in light and air for 18 h. The colorless solution was worked up as above to afford after two recrystallizations from ethanol 0.273 g (74%) of colorless plates: mp 141–142 °C; $\nu_{max}^{CHCl_3}$ 1690, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 7 Hz, CH_3CH_2O), 2.98 (t, 2 H, J = 7 Hz, H-4), 3.88 (s, 6 H, 2 × OCH_3), 4.00 (t, 2 H, J = 7 Hz, H-3), 4.18 (q, 2 H, J = 7 Hz, CH_3CH_2O), 5.94 (s, 2 H, OCH_2O), 6.67 (s, 1 H, H-5), 7.38 (s, 1 H, H-8), 6.88, 7.16 (AB q, 2 H, J = 8.5 Hz, H-5′ and H-6′).

High-resolution mass spectrum: calcd for $C_{22}H_{21}NO_8$, 427.1261; found, 427.1247.

Methyl Anhydroberberilate (32). A solution of **30** (0.1 g, 0.25 mmol) in methanol (60 mL) was treated with a saturated methanolic potassium hydroxide solution (15 mL), and 10 min after the generation of a deep yellow coloration, the mixture was poured into water and extracted with chloroform. The organic layer was dried and evaporated to leave a residue which crystallized from methanol (0.04 g, 40%), mp 185–186 °C (MeOH), identical with an authentic sample of methyl anhydroberberilate:[15] $\nu_{max}^{CHCl_3}$ 1685, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.00 (t, 2 H, J = 7 Hz, H-4), 4.32 (t, 2 H, J = 7 Hz, H-3), 3.75, 3.78, 3.89 (3 s, 3 × 3 H, 3 × OCH_3), 5.94 (s, 2 H, OCH_2O), 6.64 (s, 1 H, H-5), 7.34 (s, 1 H, H-8), 6.89, 7.78 (AB q, 2 H, J = 8.5 Hz, H-4′ and H-5′); m/e 413 (M^+, 50) 382 (10), 364 (4), 354 (40), 338 (5), 223 (base),

193 (40), 191 (40), 190 (30), 177 (40).

High-resolution mass spectrum: calcd for $C_{21}H_{19}NO_8$, 413.1109; found, 413.1108.

Anal. Calcd for $C_{21}H_{19}NO_8$: C, 61.02; H, 4.63; N, 3.39. Found: C, 60.92; H, 4.65; N, 3.37.

Ortho Ester 34. To a stirred slurry of **32** (0.3 g, 0.72 mmol) in methanol was added sodium borohydride (0.6 g) over 1 h. The resulting solution was stirred for 18 h and then poured into water and extracted with chloroform. The organic layer was dried and the solvent evaporated. The residue crystallized from ether to give 0.15 g (52%) of colorless rosettes: mp 175–176 °C (ether); $\nu_{max}^{CHCl_3}$ 1380, 1430, 1470 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.10 (t, 2 H, J = 7 Hz, benzylic CH_2), 3.98 (t, 2 H, J = 7 Hz, CH_2N), 3.68 (s, 3 H, OCH_3 ortho ester), 3.77 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3) 4.91 (s) and 5.03 (s, 2 × 1 H, carbinolamine H), 5.93 (s, 2 H, OCH_2O), 6.93 (s, 1 H, ArH), 7.22 (s, 1 H, ArH), 7.13, 7.55 (AB q, 2 H, J = 8.5 Hz, ArH); m/e 399 (M^+, 5), 368 (70), 367 (40), 219 (5), 205 (10), 194 (60), 193 (base), 164 (20), 147 (30).

High-resolution mass spectrum: calcd for $C_{21}H_{21}NO_7$, 399.1312; found, 399.1298.

Anal. Calcd for $C_{21}H_{21}NO_7 \cdot H_2O$: C, 60.43; H, 5.51; N, 3.36. Found: C, 60.65; H, 5.68; N, 3.47.

Hydrohydrastinine (35) and Pseudomeconine (36). A stirred slurry of **34** (0.13 g, 0.33 mmol) in acetonitrile (10 mL) was treated with methyl iodide (1 mL) and the solution was refluxed for 12 h. The resulting red solution was evaporated to a gum which was dissolved in methanol and immediately treated with sodium borohydride (0.2 g) for 4 h. The colorless reaction mixture was diluted with water (300 mL) and extracted with chloroform. The organic layer was dried and the solvent evaporated. The residue was chromatographed on silica gel plates with 5% methanol in chloroform to give two major components. The first (higher R_f) was extremely soluble in organic solvents but crystallized from water to afford 36 mg (56%) of fine needles: mp 124–126 °C; $\nu_{max}^{CHCl_3}$ 1775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.31 (s, 2 H, CH_2), 3.95 (s, 6 H, 2 × OCH_3), 7.08, 7.60 (AB q, 2 H, J = 8.5 Hz, aromatic H); identical with pseudomeconine (lit.[14] mp 124 °C).

The second component was obtained as a light tan oil which was treated with methanolic hydrogen bromide and crystallized upon addition of ether to yield 16 mg of light tan plates, mp 274–275 °C [lit.[15] hydrohydrastinine hydrobromide melting point 276–278 °C].

High-resolution mass spectrum of the free base: calcd for $C_{11}H_{13}NO_2$, 191.0943; found, 191.0940.

13-Acetoxyoxoberberine (30). (a) From 8-Methoxyberberinephenolbetaine (12). To a solution of **12** (1.139 g, 3 mmol) in pyridine (10 mL) was added acetic anhydride (5 mL), and the mixture was allowed to stand overnight at room temperature. Removal of the solvent gave a residue which crystallized from methanol. Recrystallization from chloroform afforded 1.11 g (92%) of yellow prisms, mp 237–238 °C.

(b) From Oxybis(berberine). To a stirred and filtered solution of the dimer (1.5 g, 2 mmol) in pyridine (50 mL) was added acetic anhydride (15 mL), and the mixture was refluxed for 8 h, cooled, and allowed to stand overnight. Removal of the solvent left a dark brown residue which crystallized from methanol to yield 0.6 g (1.5 mmol, 72%) of light yellow prisms: mp 176 °C (MeOH) or 237 °C ($CHCl_3$); $\nu_{max}^{CHCl_3}$ 1610, 1658, 1775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3 H, CH_3CO), 2.6–3.6 (m, 4 H, CH_2CH_2), 3.92 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 6.00 (s, 2 H, OCH_2O), 6.70 (s, 1 H, H-4), 7.29 (AB q, 2 H, H-11 and H-12), 7.47 (s, 1 H, H-1); m/e 409 (40), 367 (90), 366 (base), 352 (40). The compound shows a characteristic blue-white fluorescence under 254-nm light.

Anal. Calcd for $C_{22}H_{19}NO_7 \cdot {}^1/_2CH_3OH$: C, 63.52; H, 4.94; N, 3.29. Found: C, 63.23; H, 4.78; N, 3.24.

13-Hydroxyoxoberberine (37). A slurry of **12** (0.5 g, 1.3 mmol) in 6 N hydrochloric acid (30 mL) was stirred at 50 °C for 2 h and at room temperature for 1 h until the original yellow-orange color had faded to a pale tan-yellow. The solid was collected and washed with water and with cold methanol. Recrystallization afforded 0.35 g (73%) of **37**: mp 216–217 °C (MeOH); $\nu_{max}^{CHCl_3}$ 1655, 3300 cm^{-1}; ^{1}H NMR (TFA) δ 3.11 (t, 2 H, J = 7 Hz, H-5), 4.18 (s, 3 H, OCH_3), 4.46 (s, 3 H, OCH_3), 4.63 (t, 2 H, J = 7 Hz, H-6), 6.03 (s, 2 H, OCH_2O), 6.90 (s, 1 H, H-4), 7.75 (s, 1 H, H-1), 7.92, 8.27 (AB q, 2 H, J = 8.5 Hz, H-11 and H-12).

High-resolution mass spectrum: calcd for $C_{20}H_{17}NO_6$, 367.1052; found, 367.1046.

13-Methoxyoxoberberine (38). To a stirred solution of betaine **12** (1.5 g, 3.9 mmol) in refluxing THF was added methyl iodide (6 mL), and refluxing was continued for 4 h, whereupon the initial red color changed to yellow-orange. The residue, after removal of the solvent, crystallized from methanol (1.3 g, 85%) as light tan prisms: mp 194–195 °C; $\nu_{max}^{CHCl_3}$ 1600, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.82 (t, 2 H, J = 7 Hz, H-5), 3.55 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 4.23 (t, 2 H, J = 7 Hz, H-6), 5.93 (s, 2 H, OCH_2O), 6.68 (s, 1 H, H-4), 7.48 (AB q, 2 H, J = 9 Hz, ics = 16 Hz, H-11 and H-12), 7.90 (s, 1 H, H-1).

High-resolution mass spectrum: calcd for $C_{21}H_{19}NO_6$, 381.1207; found, 381.1204.

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Registry No. 1 chloride, 633-65-8; (±)-**5**, 66408-36-4; (±)-**6**, 60594-55-0; (±)-**7**, 71734-43-5; (±)-**8**, 68780-76-7; (±)-**8** HCl, 71734-44-6; (±)-**9**, 60827-73-8; (±)-**10**, 71734-45-7; **11**, 71734-46-8; **11**·HCl, 71734-47-9; **12**, 61138-60-1; **13**, 71734-48-0; (±)-**14**, 71734-49-1; (±)-**14**·HCl, 71734-50-4; (±)-14 ethyl ester, 71734-51-5; (±)-14 ethyl ester HCl, 71734-52-6; (±)-**15**, 71734-53-7; (±)-**15**·HI, 71734-54-8; (±)-**18**, 71734-55-9; (±)-**22**, 18090-57-8; (±)-**23**, 18090-55-6; (±)-**23** acetate, 18090-56-7; **26**, 65628-84-4; **27**, 66054-86-2; **28**, 21796-14-5; **29**, 66054-85-1; **30**, 66054-87-3; **32**, 66054-88-4; **34**, 66054-89-5; **35**, 494-55-3; **35**·HBr, 5985-05-7; **36**, 4741-58-6; **37**, 66408-27-3; **38**, 56470-41-8; 1-(carbomethoxy)-2-(carboethoxy)-3,4-dimethoxybenzene, 71734-56-0; oxybis(berberine), 66419-60-1; ethyl iodide, 75-03-6; *n*-propyl iodide, 107-08-4.