Chemistry of 8,13-Dioxoberbines

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Pyridine hydrochloride in pyridine breakdown of the dimer oxybis(berberine) followed by aqueous workup yields 8,13-dioxo-14-hydroxycanadine (**3**), as well as berberine (**1**). α-Keto carbinolamide **3** is converted to **5** with methanolic hydrogen chloride via salt **4**. If **4** is allowed to stand in concentrated hydrochloric acid, dimer **6** is generated. In hot 25% H_2SO_4, iminium salt **4** is first hydrolyzed to **13** which cyclizes to γ-lactol **14**. Compound **14** is readily converted stereospecifically through N-methylation and borohydride reduction to (±)-β-hydrastine (**17**). Ammonium hydroxide treatment of **3** provides α-keto carbinolamide **7**. In >28% H_2SO_4, **7** gives the blue-black iminium salt **9** which can be quenched in methanol to **10**. Strong alkali cleaves **3** to anhydroberberilic acid (**11**). When oxybis(berberine) is cleaved in a mixture of dry hydrogen chloride, pyridine, and methanol, 13-hydroxyoxoberberine (**21**) is obtained, as well as berberine (**1**). Alternatively, if oxybis(berberine) is treated with pyridine containing pyridine hydrochloride and the mixture is allowed to stand for several hours before methanol workup, **1**, **5**, and the previously unknown keto ester **22** are obtained. The probable initial products in the acid breakdown of oxybis(berberine) are, in all cases, 8,13-dihydroxyberberine (**23**) and berberine (**1**).

A continuing investigation of the chemical reactivity of oxybis(berberine), the crystalline ferricyanide oxidation dimer of berberine (**1**), has unveiled some unusual and interesting chemical transformations.[1] It has previously been shown that methanolic hydrogen chloride cleaves oxybis(berberine) to 8-methoxyberberinephenolbetaine (**2a**) and berberine (**1**) chloride.[2] Furthermore, analogous treatment of oxybis(berberine) with ethanolic hydrogen chloride afforded in an equimolar ratio 8-ethoxyberberinephenolbetaine (**2b**) and berberine chloride.[2] Clearly, the alcoholic medium behaves in a nucleophilic manner at some stage in the cleavage reaction.

When the acid-catalyzed breakdown was studied in the initial absence of nucleophiles, several novel products were obtained, their number and nature being intimately associated with the timing and amounts of nucleophile added at a later stage. The nonnucleophilic acidic medium pyridine hydrochloride in pyridine effects the decomposition of oxybis(berberine) to yield crystalline berberine chloride and a red solution which when quenched with aqueous acid provides the new highly oxidized compound 8,13-dioxo-14-hydroxycanadine (**3**), $\nu_{max}^{CHCl_3}$ 1665 and 1725 cm^{-1}. Compound **3** incorporates a nonenolizable ketone linked to a tertiary carbinol center α to an amidic nitrogen, an unusual juxtaposition of functionalities best described as a homoannular α-keto carbinolamide. As might be expected, both acid and base pH modifications result in cleavage or rearrangement of the α-keto carbinolamide grouping.

Treatment of **3** with anhydrous methanolic hydrogen chloride causes the elimination of the C-14 tertiary hydroxyl group to give the transient iminium salt **4** which is reversibly solvated by the methanol present. Evaporation of the solvent generates in quantitative yield the crystalline aliphatic methyl ether derivative 8,13-dioxo-14-methoxycanadine (**5**), $\nu_{max}^{CHCl_3}$ 1665 and 1725 cm^{-1}.

When a concentrated solution of the deep violet iminium salt **4**, arising from **3**, **5**, or oxybis(berberine), is allowed to stand in concentrated hydrochloric acid, some 8,13-dioxo-14-hydroxycanadine (**3**) present serves as the nucleophile to quench the iminium salt, thus generating the new crystalline dimer **6**, $\nu_{max}^{CHCl_3}$ 1650, 1660, and 1710 (br) cm^{-1}. Subsequent treatment of either 8,13-dioxo-14-methoxycanadine (**5**) or the dimer **6** with concentrated hydrochloric acid, dilution with water, and extraction with chloroform regenerate 8,13-dioxo-14-hydroxycanadine (**3**), again through the intermediacy of **4**.

In contrast, a skeletal rearrangement occurs upon treatment of a chloroform solution of **3** with ammonium hydroxide to produce the isomeric crystalline aporhoeadane **7**, $\nu_{max}^{CHCl_3}$ 1700 and 1720 cm^{-1}, which incorporates a heteroannular α-keto carbinolamide grouping.[3] Most probably, after the abstraction of the acidic carbinol hydrogen, ring cleavage occurs to the intermediate **8**. On recyclization, the former C-13 carbonyl is more proximate to the nitrogen than the former C-14 center, thus resulting in a quantitative carbinol–carbonyl transposition with the generation of **7**.

As in the case of the homoannular α-keto carbinolamide **3**, the angular C-2 hydroxyl in **7** can be exchanged under acidic conditions. However, the blue-black iminium cation **9** requires very acidic conditions, i.e., >28% sulfuric acid, before it is formed in appreciable concentration. Addition of methanol quenches the iminium salt **9** with formation of the trimethoxylated aporhoeadane **10**, $\nu_{max}^{CHCl_3}$ 1695 and 1710 cm^{-1}.

Treatment of **3** at room temperature with strong alkaline conditions results in oxidative rupture of the C-13 to C-14 bond to supply Perkin's anhydroberberilic acid (**11**), as well as its hydrolysis product noroxyhydrastinine (**12**).[4] The heteroannular α-keto carbinolamide **7**, however, is more stable than its structural isomer **3** and does not undergo facile base-mediated oxidative cleavage or rearrangement. The further chemistry of the heteroannular α-keto carbinolamides **7** and **10** will be discussed in a subsequent paper.

As seen above, the α-keto carbinolamides **3**, **5**, and **6**, under acid conditions, are in equilibrium with the iminium salt **4**. If the equilibrium could be strongly shifted toward the iminium salt, then a hydrolysis of the N-7 to C-8 amide bond to afford secoberbines might be effected. Indeed, when a deep violet solution of salt **4**, derived from **3** or **5**, in 25% sulfuric acid was heated at 70 °C for 2 h, hydrolysis occurred to give the water-soluble yellow iminium keto acid **13** which was not isolated. Neutralization and extraction supplied the recyclized γ-lactol **14**, $\nu_{max}^{CHCl_3}$ 1675, 1773, and 3200 cm^{-1}, in 90% overall yield from **3**.

N-Methylation of **14** with methyl iodide in acetonitrile at room temperature for 4 h gives rise to the methiodide

(1) Parts of this work were published in communication form: M. Shamma, J. L. Moniot, and D. M. Hindenlang, *Tetrahedron Lett.*, 4273 (1977); M. Shamma, D. M. Hindenlang, T. T. Wu, and J. L. Moniot, *ibid.*, 4285 (1977).

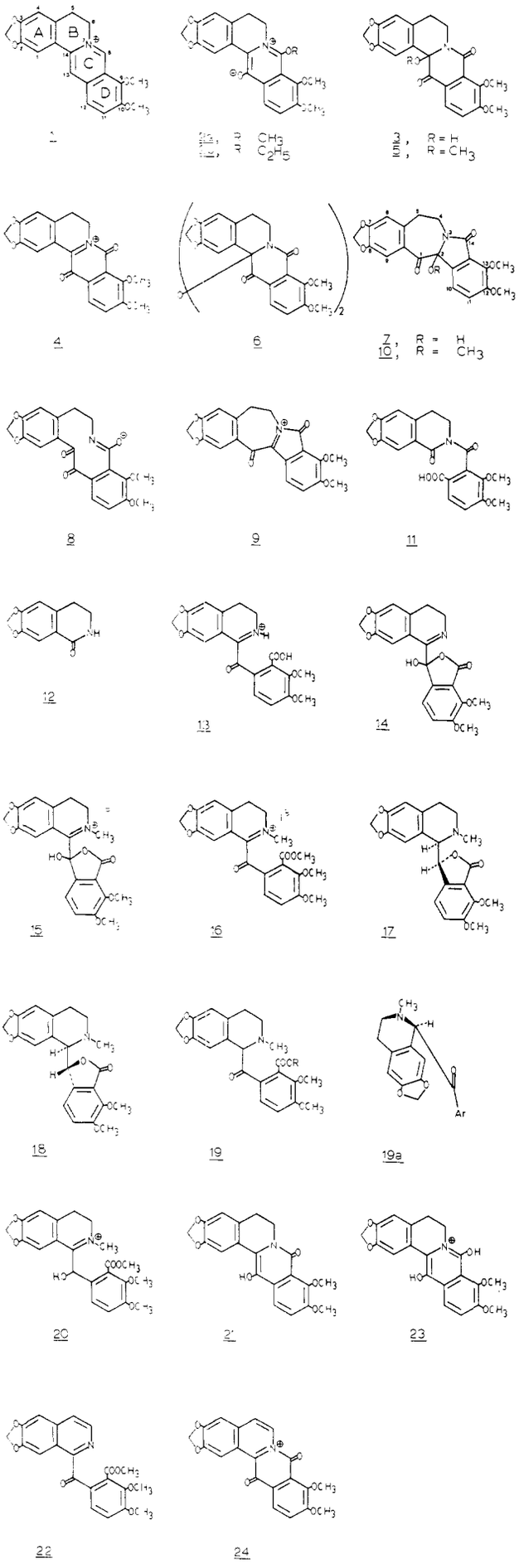
(2) J. L. Moniot and M. Shamma, *J. Org. Chem.*, preceding paper in this issue.

(3) The term aporhoeadane refers to the isoindolo[2,3-c][3]benzazepine skeleton present in **7** and **9**.

(4) W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **97**, 305 (1910); W. H. Perkin, *ibid.*, **57**, 992 (1890).

0022-3263/79/1944-4343$01.00/0

Chart I



salt **15**. If the methylation reaction is carried out under more stringent conditions, i.e., for 24 h or under reflux for 4 h, only the iminium keto methyl ester **16**, $\nu_{max}^{CHCl_3}$ 1670 and 1740 cm^{-1}, is isolated. Sodium borohydride in methanol reduction of either iminium salts **15** or **16** proceeds in a stereospecific manner to form (±)-β-hydrastine (**17**) in 85% overall yield from **3**, accompanied by only a possible trace (<1%) of the racemate of the less common base α-hydrastine (**18**).

The high degree of specificity observed in the above reductions can be rationalized on the premise that the iminium double bond is attacked first to furnish species **19** which exists in the preferred conformation **19a**. Application of Cram's rule, with approach of the borohydride anion from the less hindered side of the ketone, leads to the product stereochemistry observed. This stereospecific reduction stands in contrast to that for dehydrohydrastine methyl ester hydroiodide (**20**) which proceeds to **17** and **18** with only marginal specificity in favor of the β isomer **17**.[2] In this case, **20** incorporates a hydroxyl group adjacent to the iminium double bond, which can complex with the borohydride anion and allow for neighboring-group participation during the reduction.

To summarize the reactivity of the novel homoannular α-keto carbinolamides **3** and **5**, it can be stated that treatment with acid allows nucleophile exchange at C-14, via iminium salt **4**, while heating in strong acid solution further hydrolyzes the N-7 to C-8 bond. Reaction of the homoannular α-keto carbinolamide **3** with concentrated base in air effects oxidative scission of the C-13 to C-14 bond, whereas treatment with weak base nonoxidatively ruptures the N-7 to C-14 bond allowing for a carbinol–carbonyl rearrangement to the isomeric heteroannular α-keto carbinolamide **7**.

It will be noted that α-keto carbinolamides **3** and **5** are at a higher oxidation level than phenolbetaines **2a** and **2b** obtained by cleavage of oxybis(berberine) in alcoholic hydrogen chloride. This indicates that, in the poorly nucleophilic solvent pyridine, air oxidation rapidly follows breakdown of the dimer. When the cleavage of the dimer is performed in the presence of a mixture of dry hydrogen chloride, pyridine, and methanol, the major product is 13-hydroxyoxoberberine (**21**), $\nu_{max}^{CHCl_3}$ 1655 and 3300 cm^{-1}, previously isolated as the hydrolysis product of 8-methoxyberberinephenolbetaine (**2a**).[2] Compound **21** can also be obtained by sodium borohydride reduction of **5**, followed by loss of methanol.

We have determined that even subtle variations in the pyridine acidic breakdown of oxybis(berberine) can significantly affect product distribution. When the reaction mixture of oxybis(berberine) in pyridine containing pyridine hydrochloride is allowed to stand for several hours before the addition of a nucleophile (in this instance a small amount of methanol), workup produces an approximately 1:1 separable mixture of the homoannular α-keto carbinolamide **5** and the previously unknown keto ester **22**, $\nu_{max}^{CHCl_3}$ 1667 and 1738 cm^{-1}.

The above variety of acidic cleavage products from oxybis(berberine) provides further mechanistic insight into the chemistry of these novel oxidized berbinoid systems. We propose that the probable initial product of the acid decomposition of oxybis(berberine), in addition to berberine chloride (**1**), is 8,13-dihydroxyberberine (**23**). This reactive intermediate can explain both the dimer breakdown with methanolic hydrogen chloride to give rise to 8-methoxyberberinephenolbetaine (**2a**) and the alternate cleavages with pyridine hydrochloride in pyridine to the various further oxidized derivatives **3**, **5**, **21**, and **22**.

In methanolic hydrogen chloride, methanol solvates the initial dihydroxy intermediate **23** at C-8, and subsequent dehydration then readily leads to the isolable 8-methoxyberberinephenolbetaine (**2a**). 13-Hydroxyoxoberberine (**21**) is formed from **23** under conditions of in situ dry hydrogen chloride, pyridine, and methanol. The initial presence of a large quantity of methanol during the breakdown of the dimer precludes further oxidation of **23**, so that deprotonation of the intermediate yields pyridinone **21**.

In the absence of a good nucleophile, the hydroquinone-like **23** undergoes air oxidation mediated by pyridine, so that the product from the cleavage of the dimer with pyridine hydrochloride in pyridine is the quinone-like iminium salt **4**. In aqueous solution, **4** is quenched to the isolable 8,13-dioxo-14-hydroxycanadine (**3**) or, in methanol, to the analogous methyl ether **5**.

Finally, in the case where the pyridinic red dimer cleavage solution is allowed to stand at room temperature, some of the iminium salt **4** undergoes further pyridine-mediated air oxidation to the transient ring B aromatic iminium salt **24**. This highly conjugated salt can undergo nucleophilic attack at C-8 by the small amount of methanol subsequently added, causing opening of ring C to furnish imino keto ester **22**. Under these conditions some unoxidized iminium salt **4** is also quenched by the methanol to give the α-keto carbinolamide **5**.

To our knowledge, **3**, **5**, **6**, **7**, and **10** are the first berbinoidal α-keto carbinolamides reported in the literature. It is apparent that this complex grouping is stabilized by the presence of the aromatic rings A and D in each of these species.

During the course of the structural elucidation of many of these novel compounds, the most powerful structural probe was found to be carbon-13 NMR spectroscopy. In the present study, a number of very highly substituted carbons were encountered and the full ^{13}C NMR assignments have now been published for several of these highly functionalized alkaloidal derivatives.[5]

Experimental Section

General Experimental Procedures. These have been described in the previous paper.[2]

8,13-Dioxo-14-hydroxycanadine (3). (a) From Oxybis(berberine). A filtered solution of 0.5 g (0.7 mmol) of oxybis(berberine) in pyridine (50 mL) was treated with 1 g of pyridine hydrochloride, and the solution was stirred at room temperature for 2 h. The crystalline precipitate of berberine chloride was filtered off, and the filtrate was allowed to stand until no further crystallization took place. After a second filtration, about 50 mL of a red pyridine solution was obtained, as well as an accumulated total of 0.2 g (0.5 mmol) (79%) of berberine chloride.

The red filtrate was poured onto 200 g of ice and 20% hydrochloric acid (50 mL). The resulting mixture was further diluted with 200 mL of cold water and extracted with chloroform. The organic layer was dried and the solvent evaporated. The residue was purified by column chromatography on silica gel, using chloroform as the eluent. Crystallization from ether gave 0.15 g (0.4 mmol, 58%) of colorless rosettes of needles: mp 134 °C; ^1H NMR ($CDCl_3$) 2.6–3.0 (m, 2 H, H-5), 3.88 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.4–5.0 (m, 2 H, H-6), 5.88 (s, 2 H, OCH_2O), 6.53 (s, 1 H, H-4), 6.93 (s, 1 H, H-1), 7.10, 7.74 (AB q, 2 H, J = 8.5 Hz, H-11 and H-12).

High-resolution mass spectrum: calcd for $C_{20}H_{17}NO_7$, 383.1004; found, 383.1017.

The compound decomposes slowly on standing.

(5) The ^{13}C NMR spectra for **1**, **5**, **7**, **10**, **12**, **14**, **16**, and **21**, have been summarized in diagrams 356, 389, 399, 400, 315, 415, 417, and 396 respectively, in M. Shamma and D. M. Hindenlang, "Carbon-13 NMR Shift Assignments of Amines and Alkaloids", Plenum Press, New York, 1979.

(b) From 8,13-Dioxo-14-methoxycanadine (5). A deep violet mixture of **5** (0.2 g, 0.5 mmol) in 30 mL of hydrochloric acid was poured onto 2 L of water. Following chloroform extraction, the organic layer was dried, filtered, and evaporated to leave a residue which crystallized from ether to supply 0.14 g (0.36 mmol, 73%) of **3**, mp 134 °C.

14-Bis(8,13-dioxo-14-canadinyl) Ether (6). (a) From 3 or 5. A stirred deep violet solution formed by dissolving **3** or **5** (0.7 g, 1.8 mmol) in concentrated hydrochloric acid (12 N, 100 mL) was slowly heated with water until the mixture was no longer intensely violet and a tan precipitate had formed. The strongly acidic solution was extracted with chloroform, and the organic layer was dried and evaporated to a gum. Column chromatography on silica gel with chloroform–methanol mixtures afforded two major components, viz., **3** (0.293 g) and **6** which crystallized from chloroform (0.24 g, 31%) as pale tan prisms: mp 154–155 °C (MeOH); ^1H NMR ($CDCl_3$) δ 2.5–3.5 (br m, 4 H, H-5), 4.2–5.0 (br m, 4 H, H-6), 3.87, 3.89, 3.93 (s, 3 H, 3 H, and 6 H, 4 × OCH_3), 5.84, 5.93 (2 s, 2 H, 2 H, 2 × OCH_2O), 6.49, 6.60, 6.94, 7.00 (4 s, 4 H, 4 × ArH, ring A), 7.07 and 7.72 (AB q, 2 H, J = 8.5 Hz, 2 × ArH ring D), and 7.09 and 7.72 (AB q, 2 H, J = 8.5 Hz, 2 × ArH ring D).

High-resolution mass spectrum: calcd for $C_{40}H_{32}N_2O_{13}$, 748.1901; found, 748.1925.

(b) From Oxybis(berberine). Oxybis(berberine) (1.0 g, 1.4 mmol) was added to a stirred saturated solution of pyridine hydrochloride in pyridine (100 mL). The reaction shortly provided a yellow precipitate of berberine chloride which after 2 h was removed by filtration. The filtrate was poured onto concentrated hydrochloric acid (100 mL), and the mixture was cooled in ice to provide a deep violet solution. Water was added dropwise while the solution faded in color and provided a tan precipitate which was extracted with chloroform. Evaporation of the organic layer after drying left an oil which was purified by silica gel column chromatography ($CHCl_3$) or by TLC with MeOH–$CHCl_3$ (3:97) as a band of R_f 0.23; off-white needles (210 mg, 20%); mp 154–155 °C dec ($CHCl_3$ or ether).

8,13-Dioxo-14-methoxycanadine (5). (a) From Oxybis(berberine). The above red pyridine filtrate obtained through the decomposition of oxybis(berberine) was diluted with 200 mL of methanol, and the solvent was removed in vacuo at below 40 °C. Reevaporation with two other aliquots of 200 mL each of methanol left a dark brown residue which was rapidly passed through a short silica gel column (3% methanol in chloroform as eluent) to supply 0.23 g (0.58 mmol) of a colorless oil. Crystallization from ether or from methanolic hydrogen chloride furnished 0.18 g (0.45 mmol) (67%) of colorless rosettes of fine needles: mp 126 °C; ^1H NMR ($CDCl_3$) δ 2.80 (m, 2 H, H-5), 3.17 (s, 3 H, C-14 OCH_3), 3.95 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 5.00 (m, 2 H, H-6), 5.92 (s, 2 H, OCH_2O), 6.62 (s, 1 H, H-4), 6.98 (s, 1 H, H-1), 7.11, 7.74 (AB q, 2 H, J = 8 Hz, H-11 and H-12). Compound **5** characteristically turns deep violet upon exposure to mineral acid.

High-resolution mass spectrum: calcd for $C_{21}H_{19}NO_7$, 397.1160; found, 397.1196.

Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47, H, 4.82. Found: C, 63.40; H, 4.92.

(b) From 8,13-Dioxo-14-hydroxycanadine (3). A solution of **3** (0.2 g, 0.52 mmol) in methanol (100 mL) was treated with 10% methanolic hydrogen chloride (10 mL), and the mixture was stirred for 6 h. Evaporation of the solvent left a residue which readily crystallized from ether to afford 0.2 g of **5** (96%) as fine needles, mp 126 °C.

(c) From 14-Bis(8,13-dioxo)canadinyl Ether (6). The dimeric ether (52 mg, 0.07 mmol) was dissolved in 10% methanolic hydrogen chloride (50 mL). The solution was stirred for 1 h, diluted with water, and extracted with chloroform. The organic layer was washed with water, dried, and evaporated to a dark oil. This material was purified by preparative TLC on silica gel, using MeOH–$CHCl_3$ (3:97), as a band of R_f 0.85: 42 mg (75%), mp 125–126 °C (ether).

1,14-Dioxo-2-hydroxy-7,8-(methylenedioxy)-12,13-dimethoxyaporhoeadane (7). A solution of **3** (0.31 g, 0.81 mmol) in chloroform (200 mL) was vigorously shaken with 10% ammonium hydroxide (200 mL) for 20 min. The organic layer was dried, filtered, and evaporated. The residue was purified by silica gel

preparative TLC to supply after crystallization from methanol 0.28 g (0.73 mmol, 90%) of colorless prisms: mp 155 °C; $\nu_{max}^{CHCl_3}$ 1270, 1370, 1490, 1500, 1620, 1700, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.6–4.15 (br m, 4 H, CH_2CH_2), 3.80 s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 5.00 (br s, 1 H, OH), 5.91 (s, 2 H, OCH_2O), 6.63 (s, 1 H, aromatic H), 6.73 (s, 1 H, aromatic H), 6.94, 7.42 (AB q, 2 H, J = 8 Hz, aromatic H).

High-resolution mass spectrum: calcd for $C_{20}H_{17}NO_7$, 383.1004; found, 383.1022.

Anal. Calcd for $C_{20}H_{17}NO_7$: C, 62.66; H, 4.44. Found: C, 62.56; H, 4.34.

1,14-Dioxo-2-methoxy-7,8-(methylenedioxy)-12,13-dimethoxyaporhoeadane (10). A solution of aporhoeadane **7** (0.34 g, 0.88 mmol) in methanolic hydrogen chloride (10%, 60 mL) was stirred overnight, and upon evaporation of the solvent, the residue was crystallized to afford 0.31 g (0.78 mmol, 88%) of **10** as dense, colorless prisms: mp 147–148 °C (MeOH); λ_{max}^{MeOH} 278 (sh), 316 nm (log ϵ 3.88, 4.01).

High-resolution mass spectrum: calcd for $C_{21}H_{19}NO_7$, 397.1160; found, 397.1174.

Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.78. Found: C, 63.26; H, 4.81.

Anhydroberberilic Acid (11) and Noroxyhydrastinine (12). A solution of **3** (0.4 g, 1 mmol) in methanol was treated with 100 mL of 10% aqueous sodium hydroxide and then stirred in air for 3 h. The mixture was poured into water (1 L) and extracted with chloroform. The organic layer was dried and evaporated, and the residue was purified by preparative TLC over silica gel to afford as the major component 0.13 g of **12** as soft needles from ether, mp 180–181 °C [lit.[4] mp 179–180 °C].

The aqueous alkaline layer from the above was acidified with glacial acetic acid and extracted with chloroform. The organic layer was dried, filtered, and evaporated to yield a crystalline mass. Recrystallization afforded 0.11 g of **11** identical with a sample of authentic anhydroberberilic acid:[4] mp 123–124 °C (MeOH); $\nu_{max}^{CHCl_3}$ 1690, 1700 cm^{-1}; m/e 399, 383, 366, 354, 223, 208, 101 (base), 162.

9-Hydroxy-1,2-dehydronorhydrastine (14). Compound **5** (397 mg, 1 mmol) was dissolved in stirring 25% aqueous sulfuric acid (50 mL), instantly producing a deep violet color. Heating at 70 °C for 2 h caused the solution to slowly turn dark red and then lighten to a stable deep yellow. The reaction mixture was cooled, diluted with water (100 mL), and carefully basified to pH 8 with powdered potassium hydroxide, using saturated aqueous ammonium chloride (25 mL) as a buffer. The colorless solution was extracted with chloroform to remove nonacidic products. The aqueous layer was acidified with concentrated sulfuric acid to pH 6.8, thus restoring the yellow color to the solution which was extracted with chloroform, so removing the color. This sequence was repeated three times. The combined organic layers were dried and evaporated to a yellow oil. This was purified by TLC on silica gel, using MeOH–$CHCl_3$ (20:80), to furnish a band of R_f 0.25 which led to off-white needles (345 mg, 90%): mp 154–155 °C (ether); λ_{max}^{EtOH} 238, 290, 300 (sh) nm (log ϵ 3.95, 3.75, 3.74); ^{1}H NMR ($CDCl_3$) δ 2.70 (br t, 2 H, J = 7.5 Hz, $ArCH_2$), 3.82 (br t, 2 H, J = 7.5 Hz, CH_2N), 3.94 (s, 3 H, OCH_3), 4.16 (s, 3 H, OCH_3), 5.90 (s, 2 H, OCH_2O), 6.34 (s, 1 H, H-5), 6.68 (s, 1 H, H-8), 7.07, 7.19 (AB q, 2 H, J = 8.5 Hz, ring D aromatic H).

High-resolution mass spectrum: calcd for $C_{20}H_{16}NO_7$, 382.0924 $(M - H)^+$, found, 382.0903.

Anal. Calcd for $C_{20}H_{17}NO_7 \cdot {}^1/_2H_2O$: C, 61.22; H, 4.63. Found: C, 61.39; H, 4.85. The same product, **14**, was obtained in similar yields by analogous treatment of **3**.

9-Oxo-1,2-dehydrohydrastine Methyl Ester Iodide (16). Lactol **14** (383 mg, 1 mmol), acetonitrile (70 mL), and methyl iodide (4.56 g, 32 mmol) were refluxed for 4 h or stirred for 24 h at room temperature. The mixture was evaporated to a yellow residue which was purified by TLC on silica gel, using MeOH–$CHCl_3$ (15:85), as a band of R_f 0.5 to afford bright yellow needles of **16** (528 mg, 98%): mp 141–142 °C (CH_3CN); λ_{max}^{EtOH} 240 (sh), 257 (sh), 310, 388 nm (log ϵ 4.31, 4.23, 4.19, and 3.87); ^{1}H NMR ($CDCl_3$) δ 2.5–3.5 (br m, 2 H, $ArCH_2$), 3.83 (s, 3 H, NCH_3), 3.91 (s, 3 H, $ArOCH_3$), 4.01 (s, 6 H, $ArOCH_3$ and $COOCH_3$), 4.2–5.0 (br m, 2 H, CH_2N), 6.12 (s, 2 H, OCH_2O), 6.79 (s, 1 H, H-5), 6.88 (s, 1 H, H-8), 7.29, 8.49 (AB q, 2 H, J = 8.5 Hz, ring D aromatic H).

High-resolution mass spectrum: calcd for $C_{21}H_{19}NO_6$, 381.1211 $(M - OCH_3)^+$; found, 381.1216.

Anal. Calcd for $C_{22}H_{22}NO_7I \cdot {}^1/_2H_2O$: C, 48.18; H, 4.23. Found: C, 48.23; H, 4.35.

Shorter term reaction, 4 h at room temperature, afforded 9-hydroxy-1,2-dehydrohydrastine methiodide (**15**): mp 178–180 °C dec (CH_3CN); m/e 398 (0.1) (M^+), 381 (0.1), 207 (10), 190 (10), 142 (base).

(±)-β-Hydrastine (17). Salt **16** (270 mg, 0.5 mmol) was suspended in methanol (50 mL) and sodium borohydride (380 mg, 10 mmol) was added in portions. The mixture was stirred for 1 h, diluted with water, carefully acidified to pH 4 by dropwise addition of concentrated sulfuric acid, returned to near-neutral pH with saturated aqueous sodium bicarbonate, and then extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride solution, dried, and evaporated to a colorless oil which crystallized to give **17** (186 mg, 97%): mp 207–208 °C ($CHCl_3$); $\nu_{max}^{CHCl_3}$ 1762 cm^{-1}; λ_{max}^{EtOH} 298 nm (log ϵ 3.90).

Analogous treatment of salt **15** also provided only (±)-β-hydrastine (**17**) in a similar yield.

13-Hydroxyoxyberberine (21). (a) From Oxybis(berberine). To a stirred slurry of the dimer (0.5 g, 1.3 mmol) in pyridine (50 mL) was added 20 mL of anhydrous methanolic hydrogen chloride, and the mixture was stirred at room temperature for 6 h, during which time crystallization ceased. The crystals were filtered and washed successively with cold methanol, chloroform, methanol, and water. The light tan crystals were taken up in a hot chloroform–methanol mixture, and, on cooling, the mixture afforded 0.35 g (0.95 mmol, 73%) of **20**: mp 216–217 °C (MeOH); $\nu_{max}^{CHCl_3}$ 1655, 3300 cm^{-1}.[2]

(b) From 8,13-Dioxo-14-methoxycanadine (5). A solution of **5** (0.17 g, 0.44 mmol) in methanol (40 mL) was treated with excess sodium borohydride for 12 h. The mixture was diluted with water and extracted with chloroform. The organic layer was dried and soon began to develop a red coloration. The solvent was evaporated, and methanol was added. Light tan crystals formed (0.11 g, 68%), mp 216–217 °C (MeOH).[2]

2′-(Carbomethoxy)-α-oxo-1,2,3,4-didehydronorromneine (22). Oxybis(berberine) (1.0 g, 1.4 mmol) was added to a stirred saturated solution of pyridine hydrochloride in pyridine (100 mL). A yellow precipitate of berberine (**1**) chloride started appearing. The mixture was stirred 4 h until precipitation had ceased. Salt **1** was removed by filtration, and 10% methanolic hydrogen chloride (10 mL) was added to the filtrate which was stirred for an additional 2 h. The mixture was then diluted into a large volume of water (600 mL) and repeatedly extracted with ether. The combined ether layers were washed with water, dried, and evaporated to a red oil. Purification by TLC on silica gel, using MeOH–$CHCl_3$ (3:97), produced a yellow band, R_f 0.65, which crystallized as off-white needles (216 mg, 39%): mp 170–171 °C (ether); ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3 H, $COOCH_3$), 3.82 (s, 6 H, 2 × $ArOCH_3$), 5.95 (s, 2 H, OCH_2O), 6.72, 7.23 (AB q, 2 H, J = 8.5 Hz, ring D aromatic H), 6.99 (s, 1 H, ring A aromatic H), 7.38, 8.18 (AB q, 2 H, J = 6 Hz, ring B aromatic H), 7.53 (s, 1 H, ring A aromatic H).

High-resolution mass spectrum: calcd for $C_{21}H_{17}NO_7$, 395.1004; found, 395.0996.

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Registry No. 1 chloride, 633-65-8; (±)-**3**, 71766-69-3; (±)-**5**, 71733-96-5; **6**, 66408-28-4; (±)-**7**, 71700-15-7; (±)-**10**, 71700-16-8; **11**, 66408-33-1; **12**, 21796-14-5; (±)-**14**, 66408-34-2; (±)-**15**, 71733-97-6; **16**, 66408-37-5; (±)-**17**, 60594-55-0; **21**, 66408-27-3; **22**, 71733-98-7; methyl iodide, 74-88-4; oxybis(berberine), 66419-60-1.