Chemistry of Highly Oxidized Aporhoeadanes

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Highly oxidized aporhoeadane **5**, an unusual isoindolobenzazepine, was prepared from 8-methoxyberberinephenolbetaine (**7**) via α-keto carbinolamide **8**. Acid treatment of aporhoeadane **5** effected reversible nucleophilic exchange by way of iminium salt **11** to methoxy analogue **6** or to acetoxy derivative **12**. Zinc in HCl–HOAc reduction of **5** provided enaminol **10** and the known lactam **9**, thus proving the aporhoeadane skeleton of **5**. $NaBH_4$ reduction of **5** led predominantly to trans diol **13**, while similar treatment of **6** provided cis hydroxy ether **15** as the major product. These products were methylated to give diethers **17** and **18**, respectively. Solvolytic ring contraction in strong acid, reduction, and methylation of **5** afforded (±)-β-hydrastine methiodide (**21**). Alternatively, rupture of ring C of aporhoeadane **5** with strong base via a Haller–Bauer-type cleavage provided imidol **26**. Strong-acid treatment of **26** or of its dimethyl derivative **27** produced *C*-noroxyberbine **30** through Friedel–Crafts alkylation at the substituted carbon, followed by decarboxylation.

Treatment of a norrhoeadine (papaverrubine) base with mineral acid leads to the formation of a red quaternary isoindolobenzazepine,[1] e.g., **1**, which has been reduced catalytically to **2** and subsequently oxygenated to the benzazepine lactam **3**.[2] The designation aporhoeadane has been applied to the ring system present in **1–3**, connoting the close chemical kinship of the isoindolobenzazepines with the naturally occurring rhoeadine and papaverrubine alkaloids.[3] The isoindolobenzazepine **4**, commonly referred to as Schöpf's base VI, has been prepared from commercially available (−)-β-hydrastine[4,5] or by zinc in acetic acid reduction of berberinephenolbetaine.[6,7] The degradative chemistry of **4** and its interconversion to the protopine base α-allocryptopine has been described.[8]

We report here the first systematic study of the chemistry of highly oxygenated aporhoeadanes **5** and **6**, also derived from a berberinephenolbetaine via ring expansion. It has been shown that 8-methoxyberberinephenolbetaine (**7**) on dilute-acid solvolysis affords 13-hydroxyoxoberberine which undergoes facile oxidation to the homoannular α-keto carbinolamide **8**.[9] It has been further demonstrated that ammonium hydroxide treatment of **8** quantitatively produces the isomeric heteroannular α-ketocarbinolamide **5**.[10] Zinc in HCl–HOAc reduction of **5** gave, as the major product, the known lactam **9**,[4] $\nu_{max}^{CHCl_3}$ 1490 and 1690 cm^{-1}, thus confirming the aporhoeadane skeleton of **5**. A minor product from this same reduction was the crystalline enaminol **10**, $\nu_{max}^{CHCl_3}$ 1600 and 3400 cm^{-1}.

Reaction of **5** with 28% sulfuric acid results in generation of the blue-black iminium salt **11** which when quenched with methanol decolorizes and provides the analogous trimethoxylated aporhoeadane **6**, the results of a net nucleophilic exchange at C-2.[10] Similarly, reaction of **5** with acetic anhydride in pyridine at room temperature led to the crystalline acetate **12**, $\nu_{max}^{CHCl_3}$ 1695 and 1718 cm^{-1}. Since the acetylating conditions are mild and the reacting alcohol group is tertiary, this transformation most probably proceeds through the intermediacy of iminium salt **11** which must readily add acetate anion.

The natural rhoeadine bases possess asymmetric centers at C-1 and C-2 and occur with both the cis and trans relative stereochemistry. The use of sodium borohydride to reduce the keto functions of α-keto carbinolamides **5** and **6** presently led to the preparation of a parallel series of asymmetrically substituted aporhoeadanes. Following sodium borohydride reduction of **5**, the major product, obtained after dilution with water, extraction with chloroform, and evaporation of the organic solvent, was the diol **13** which was assigned the trans C-1,2 stereochemistry. However, acidification of the aqueous mother liquors from the reduction mixture, followed by chloroform extraction and evaporation, led to another diol, **14**. This minor product was ascribed the cis C-1,2 relative stereochemistry. The genesis of diol **13** must involve initial complexation of the borohydride anion with the angular C-2 hydroxyl of **5**, followed by hydride addition to the C-1 carbonyl, via intramolecular participation, from the side cis to the angular alcohol. The fact that diol **14** required the presence of acid in its workup suggested that it was strongly chelated as a cyclic borate ester following its formation from the α-keto carbinolamide **5**, thus implying a cis stereochemistry for its 1,2-glycol system.

Of greater importance in settling the stereochemical problem was the study of the sodium borohydride reduction of the trimethoxylated α-keto carbinolamide **6**. This reaction gave two crystalline products, namely, the cis hydroxy ether **15** as the major product, formed by hydride attack of **6** from the less sterically hindered side trans to the angular methoxyl substituent, while the alternate trans analogue **16** was isolated in a much smaller amount. The trans glycol **13** and the trans hydroxy ether **16** were interrelated by O-methylation using methyl iodide and sodium hydride in THF–DMF to supply the identical trans tetramethoxy ether **17**. O-Methylation of the cis hydroxy ether **15**, on the other hand, supplied the cis tetramethoxy ether **18**, different from its diastereomer **17**.

The ^1H NMR spectra of hydroxy ethers **15** and **16** were also diagnostic. In the trans compound **16**, H-1 is nearly in the same plane as, and proximate to, ring A, so that it suffers a downfield shift to δ 5.00. The corresponding proton in the cis analogue **15**, in contrast, appears at δ 4.75.

(1) This reaction is the basis of a color test widely used in the analysis of samples seized from the illicit opium trade since papaverrubines are always present in opium samples.

(2) M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972, p 408.

(3) M. Shamma and J. L. Moniot, "Isoquinoline Alkaloid Research 1972–1977", Plenum Press, New York, 1978, p 300.

(4) S. Teitel, W. Klötzer, J. Borgese, and A. Brossi, *Can J. Chem.*, **50**, 2022 (1972).

(5) For the preparation of an analogue of 4 from narceine, see J. Trojánek, Z. Koblicová, Z. Veselý, V. Suchan, and J. Holubek, *Collect. Czech. Chem. Commun.* **40**, 681 (1975).

(6) H. O. Bernhard and V. Snieckus, *Tetrahedron Lett.*, 4867 (1971).

(7) C. Schöpf and M. Schweikert, *Chem. Ber.*, **98**, 2566 (1965).

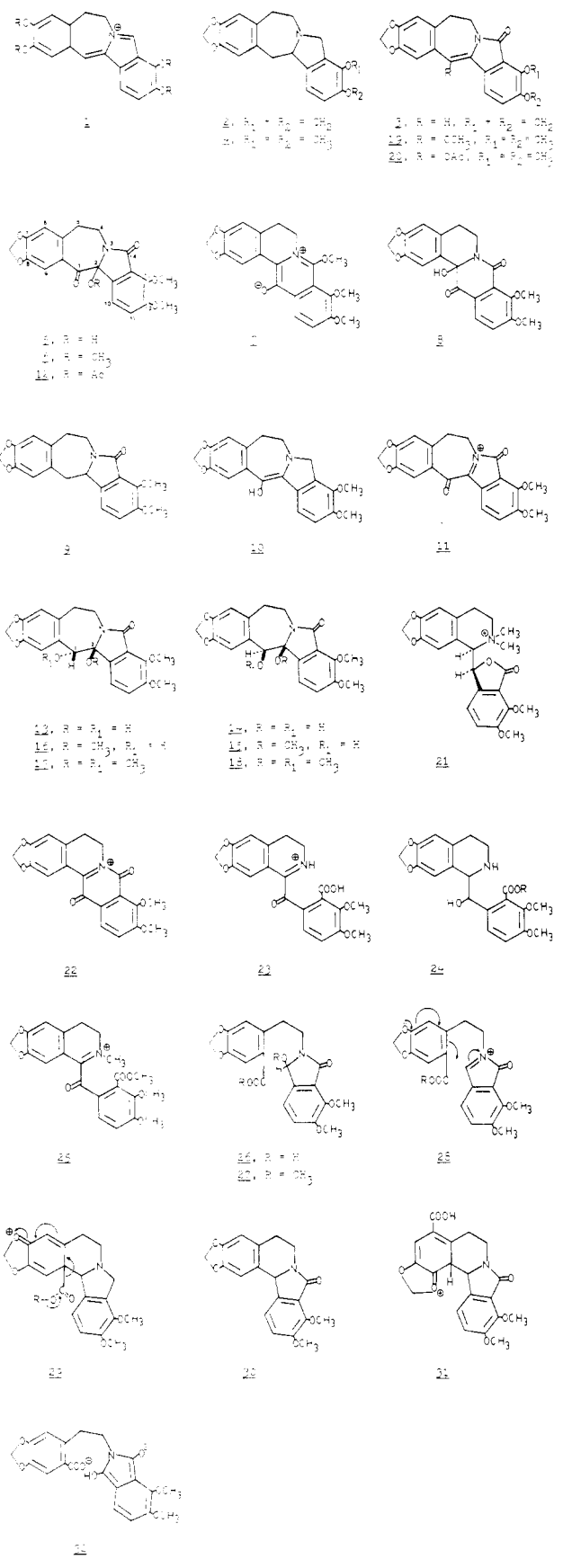
(8) S. Teitel, J. Borgese, and A. Brossi, *Helv. Chim. Acta*, **56**, 553 (1973).

(9) (a) J. L. Moniot and M. Shamma, *J. Am. Chem. Soc.*, **98**, 6714 (1976); (b) *J. Org. Chem.*, companion paper in this issue, and references therein.

(10) M. Shamma, J. L. Moniot, and D. M. Hindenlang, *Tetrahedron Lett.*, 4273 (1977); *J. Org. Chem.*, preceding paper in this issue, and references therein; M. Shamma, D. M. Hindenlang, T.-T. Wu, and J. L. Moniot, *Tetrahedron Lett.*, 4285 (1977).

0022-3263/79/1944-4347$01.00/0

Chart I



Additionally, the C-9 aromatic proton in isomer **15** is spatially close to the C-1 hydroxyl group and is present downfield as a singlet at δ 6.91, while the same proton in **16** is located further upfield at δ 6.82. The magnitude and direction of the shifts of the C-1 methoxy resonances in diethers **17** and **18** (upfield and downfield, respectively) are in keeping with the above shifts for C-1 protons when out of and in the plane of the aromatic ring A. A very similar set of ^{1}H NMR shift correlations is known for the cis- and trans-fused natural rhoeadine bases.[11]

As a further indication of the stereochemistry, it was established that when the cis tetramethoxy ether **18** was briefly warmed to 50 °C in glacial acetic acid, trans elimination of methanol readily occurred to give rise to the yellow enol ether **19**. No such facile elimination of methanol occurred from the trans compound **17** under these mild conditions. In line with these findings, the trans glycol **13** required heating at 60 °C for 18 h in acetic anhydride and pyridine before the yellow-green enol acetate **20** was formed, while no heating of the cis glycol **14** was required to obtain the identical enol acetate, since the required trans relationship between the C-1 hydrogen and the C-2 hydroxyl obtains.

While acidic treatment of the above glycols and ethers simply effects eliminations to enolamide systems, it was recognized that the blue-black iminium salt **11**, generated from aporhoeadanes **5** or **6** on strong-acid treatment, contains an *N*-acyliminium function and should therefore undergo solvolysis. When **5** was refluxed in 35% sulfuric acid, a red solution developed which was not decolorized by the addition of water or methanol. The reaction mixture was neutralized, and the crude product was immediately reduced with sodium borohydride and then treated with excess methyl iodide. The product isolated proved to be crystalline (±)-β-hydrastine methiodide (**21**), which must have formed in stages through the intermediacy of the homoannular α-keto carbinolamide **8**, the iminium salts **22** and **23**, and after borohydride reduction, the amino alcohol **24**. It can, therefore, be concluded that whereas ammonium hydroxide causes the rearrangement of the homoannular α-keto carbinolamide **8** to its hetero analogue **5**, concentrated sulfuric acid induces the reverse rearrangement with subsequent formation of iminium salts **22** and **23**. The borohydride reductive step bears in fact a distinct similarity to the previously encountered reduction of the iminium salt **25** which led to (±)-β-hydrastine.[10]

An additional aspect of the study of the chemistry of the oxidized aporhoeadanes concerns their behavior in warm aqueous methanolic potassium hydroxide. The product of alkaline treatment of **5** following acidification proved to be the colorless imidol **26**, ν_{max}^{KBr} 1705, 3300, and 3400 cm^{-1}, the result of a Haller–Bauer-type cleavage of the nonenolizable ketone function.

Methyl iodide–sodium hydride treatment of **26** afforded the dimethyl derivative **27**, $\nu_{max}^{CHCl_3}$ 1617 (w) and 1695–1725 cm^{-1}, in high yield. Significantly, the coupled $CDCl_3$ ^{13}C NMR spectrum of this derivative **27** contained a quartet of doublets centered at 49.5 ppm (J_{CH} = 143 Hz, J_{COCH} = 6.8 Hz) for the carbon of the methoxyl group attached to the five-membered ring, thus providing additional evidence regarding the nature of this ring.

When either **26** or **27** was dissolved in TFA, a deep red coloration initially developed, but effervescence due to evolution of carbon dioxide ensued accompanied by fading of the color to a pale yellow. In each case, the same colorless lactam **30**, $\nu_{max}^{CHCl_3}$ 1690 cm^{-1}, was isolated in near-quantitative yields. Confirmation of this structural assignment was obtained from the ^{1}H NMR spectrum of **30** which contained singlets at δ 7.37 and 6.68 for the C-1 and C-4 aromatic protons, and from the $CDCl_3$ ^{13}C NMR

(11) M. Shamma, J. A. Weiss, S. Pfeifer, and H. Döhnert, *Chem. Commun.*, 212 (1968); see also E. Brochmann-Hanssen and K. Hirai, *J. Pharm. Sci.*, **56**, 1658 (1967).

spectrum which has been summarized.[16]

The formation of **30** from **26** (or **27**) can be understood in terms of the red keto iminium intermediate **28** which undergoes intramolecular Friedel–Crafts alkylation to the cation **29** which then decarboxylates as indicated. Specially noteworthy is that electrophilic attack occurred at the substituted ring A aromatic carbon of **28** rather than at the alternate unsubstituted site. This preference for a substituted site over an unsubstituted one must be due to the fact that para spiroquinone intermediates are intrinsically more stable than their ortho analogues, so that in the conversion of **26** to **30**, intermediate **29** is preferred over **31**.[12]

The extreme facility of this decarboxylative cyclization to a C-noroxyberberine is further shown by the fact that the base peak in the electron impact mass spectra of **26** and **27** is the singly charged ion m/e 339 that also corresponds to the parent peak of **30**.

To summarize, in the strong acid–dissolving-metal reduction of aporhoeadanes **5** or **6**, the species being reduced is iminium **11**, and the isolation of products **9** and **10** indicates that reduction of this highly conjugated electron-deficient system can proceed from either the C-1 or C-14 end of the system. As expected, reduction from the C-1 terminus predominates. Under mild reducing conditions with sodium borohydride, the promotion or preclusion of intramolecular participation in the reduction of the heteroannular α-keto carbinolamides **5** and **6** leads predominantly to the trans- and cis-oxygenated patterns, respectively.

For aporhoeadanes (e.g., **5**, **6**, or **12**), nucleophilic exchange at C-2 is the major reaction under nonforcing acidic treatment. Significantly, the ring contraction of the highly oxygenated aporhoeadane **5** upon heating in strong mineral acid is in line with previous observations for the acidic treatment of C-1-functionalized 3-benzazepine systems.[13-15]

In contrast to the acid solvolysis above, alkaline hydrolysis of the heteroannular α-keto carbinolamide system results in C(1)–C(2) rather than amide-bond scission, reflecting preferential attack of hydroxide ion at the ketonic center in **5** due to the high resonance stability of the resulting anion **32**.

Experimental Section

General Experimental Procedures. See ref 9b. The $CDCl_3$ ^{13}C NMR spectra for **5**, **6**, **26**, **27** and **30** have been summarized in diagrams 399–403 in ref 16.

Preparation of 5. (a) From 13-Hydroxyoxoberberine.[9b,10] A slurry of 13-hydroxyoxoberberine (2.7 g, 7.3 mmol) in chloroform (400 mL) was poured into a separatory funnel containing water (100 mL) and concentrated ammonium hydroxide (100 mL). After 5–10 min of vigorous mixing, the organic layer was removed, dried, filtered, and evaporated. The residue was purified by column chromatography using silica gel and yielded 1 g (35%) of product.[9,10]

(b) 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 chloroform layer was stirred for 20 min with 40 mL of 5% ammonium hydroxide–1% ammonium chloride solution. The organic layer was separated and dried, and the solvent was evaporated. Decolorization with Norit in chloroform, filtration through Celite, and solvent evaporation left a residue which crystallized from methanol: 0.16 g (0.42 mmol, 61%); mp 154–155 °C.[9,10]

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

7,8-(Methylenedioxy)-12,13-dimethoxy-14-oxoaporhoeadane (9). To a stirred slurry of **5** (0.34 g, 0.88 mmol) in 50% aqueous acetic acid containing 2 mL of concentrated hydrochloric acid was added excess zinc metal powder. The mixture was heated to reflux for 4 h, cooled, filtered through Celite, diluted with water, and extracted with chloroform. The organic layer was dried and evaporated to a residue which after purification by preparative TLC yielded as the major product amide **9** (0.11 g, 35%), which crystallized from methanol as fine colorless needles (mp 228–229 °C) identical with the known compound (lit.[4] mp 228 °C).

1-Hydroxy-7,8-(methylenedioxy)-12,13-dimethoxy-Δ^1-aporhoeadene (10). The aqueous layer from the above reaction was adjusted to pH 7 and extracted with chloroform. The organic layer was dried and the solvent evaporated. The residue was purified by preparative TLC to furnish 21 mg (7%) of needles: mp 161–162 °C (ether); ^1H NMR ($CDCl_3$) δ 2.7–3.8 (m, 4 H, CH_2CH_2), 3.05, 4.30 (AB q, 2 H, J = 13 Hz, H-14), 3.79 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 5.82 (s, 2 H, OCH_2O), 6.58 (s, 1 H, H-6), 6.70 (1 H, H-9), 6.76 (s, 2 H, H-10 and H-11).

High-resolution mass spectrum: calcd for $C_{20}H_{19}NO_5$ 353.1258; found, 353.1234.

1,14-Dioxo-2-acetoxy-7,8-(methylenedioxy)-12,13-dimethoxyaporhoeadane (12). A solution of **5** (0.13 g, 0.34 mmol) in pyridine (2 mL) and acetic anhydride (1 mL) was allowed to stand overnight at room temperature, and the solvent was then removed. The residue was extracted with ether and water. The organic layer was dried and the solvent evaporated. The residue crystallized from methanol (0.086 g, 60%) as colorless prisms: mp 139–140 °C; λ_{max}^{MeOH} 263 (sh), 274 (sh), 303, 377 nm (log ϵ 3.84, 3.84, 3.85, 4.31); ^1H NMR ($CDCl_3$) δ 2.42 (s, 3 H, acetate), 3.08 (m, 2 H, benzylic CH_2), 3.90 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.15 (m, 2 H, CH_2N), 5.95 (s, 2 H, OCH_2O), 6.64 (s), 6.87 (s) (2 × 1 H, ring A aromatic H), 7.08, 7.51 (AB q, 2 H, J = 8.5 Hz, ring D aromatic H).

High-resolution mass spectrum: calcd for $C_{22}H_{19}NO_7$, 409.1160; found, 409.1199.

***trans*-1,2-Dihydroxy-7,8-(methylenedioxy)-12,13-dimethoxy-14-oxoaporhoeadane (13).** A slurry of **5** (0.42 g, 1.1 mmol) in methanol (70 mL) was treated portionwise with sodium borohydride (0.8 g) over 3 h, and the solution was allowed to stir overnight. The mixture was diluted with water and extracted with chloroform. Drying and evaporation of the organic solvent left a residue which crystallized from methanol (0.27 g, 64%) as colorless needles: mp 193–194 °C; ν_{max}^{KBr} 1680, 3380 cm^{-1}; ^1H NMR (Me_2SO) δ 2.7–4.5 (br m, 4 H, CH_2CH_2), 3.78 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.81 (s, 1 H, CHOH), 5.92 (s, 2 H, OCH_2O), 6.70 (s), 6.79 (s) (2 × 1 H, ring A aromatic H), 7.17, 7.37 (AB q, 2 H, J = 8.5 Hz, ring D aromatic H).

High-resolution mass spectrum: calcd for $C_{20}H_{19}NO_7$, 385.1160; found, 385.1159.

***cis*-1,2-Dihydroxy-7,8-(methylenedioxy)-12,13-dimethoxy-14-oxoaporhoeadane (14).** From the above reduction, the alkaline aqueous layer was acidified to pH 5 and reextracted with chloroform. After workup the following was obtained: 0.14 g (33%); mp 156–157 °C (MeOH–ether); ν_{max}^{KBr} 1685 cm^{-1}; ^1H NMR

(12) Preferential electrophilic attack at the para position of para-substituted oxyarenes has a venerable history. See: R. T. Dean and H. Rapoport, *J. Org. Chem.*, **43**, 2115, 4183 (1978); S. Natarajam, B. R. Pai, R. Rajaraman, C. S. Swaminathan, K. Nagarajan, V. Sundarsanam, D. Rogers, and A. Quick, *Tetrahedron Lett.*, 3573 (1975); C. Tani, S. Takao, H. Endo, and E. Oda, *Yakugaku Zasshi*, **93**, 268 (1973); D. V. Nightingale, *Chem. Rev.*, **40**, 117 (1947); A. H. Salway, *J. Chem. Soc.*, **95**, 115 (1909); J. Jobst and O. Hesse, *Justus Liebigs Ann. Chem.*, **199**, 17 (1879). We thank Professor H. Rapoport for suggesting some of these references.

(13) S. Kasparek, *Adv. Heterocycl. Chem.*, **17**, 88 (1974). See also ref 2 above, pp 402 and 407.

(14) W. Klötzer, S. Teitel, and A. Brossi, *Helv. Chim. Acta*, **55**, 2228 (1972).

(15) T. Kametani, T. Ohsawa, S. Hirata, M. S. Premila, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.*, **25**, 321 (1977).

(16) M. Shamma and D. M. Hindenlang, "Carbon-13 NMR Shift Assignments of Amines and Alkaloids", Plenum Press, New York, 1979.

(Me_2SO) δ 2.8–4.2 (br m, 4 H, 2 × CH_2), 3.85 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 4.71 (br s, 1 H, H-1), 5.86 (s, 2 H, OCH_2O), 6.60 (s, 1 H, H-6), 6.93 (s, 1 H, H-9), 7.01, 7.34 (AB q, 2 H, J = 8.5 Hz, ring D aromatic H); m/e 385 (M^+, 20), 367 (45), 351 (50), 338 (60), 324 (5), 308 (10), 220 (base), 208 (8), 193 (50), 176 (80), 148 (70).

High-resolution mass spectrum: calcd for $C_{20}H_{19}NO_7$, 385.1160; found, 385.1149.

***cis*-1-Hydroxy-2-methoxy-7,8-(methylenedioxy)-12,13-dimethoxy-14-oxoaporhoeadane (15).** A slurry of **6** (0.11 g, 0.27 mmol) was reduced with sodium borohydride as above to afford after preparative TLC as the major product **15**: 0.08 g (74%); mp 204–205 °C (MeOH); $\nu_{max}^{CHCl_3}$ 1695, 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.8–4.2 (br m, 4 H, CH_2CH_2), 2.75 (s, 3 H, C-2, OCH_3), 3.85 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 4.75 (s, 1 H, H-1), 5.84 (s, 2 H, OCH_2O), 6.54 (s, 1 H, H-6), 6.91 (s, 1 H, H-9), 6.98, 7.32 (AB q, 2 H, J = 8.5 Hz, H-10 and H-11).

High-resolution mass spectrum: calcd for $C_{21}H_{21}NO_7$, 399.1312; found, 399.1294.

***trans*-1-Hydroxy-2-methoxy-7,8-(methylenedioxy)-12,13-dimethoxy-14-oxoaporhoeadane (16).** The minor product from the above reduction, which was also purified by TLC, crystallized from methanol–ether: 0.019 g (17%); mp 168–169 °C; $\nu_{max}^{CHCl_3}$ 1700, 3580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.8–4.2 (br m, 4 H, CH_2CH_2), 2.83 (s, 3 H, C-2 OCH_3), 3.92 (s, 3 H, OCH_3), 4.07 (s, 3 H, OCH_3), 5.00 (s, 1 H, H-1), 5.95 (s, 2 H, OCH_2O), 6.70 (s, 1 H, H-6), 6.82 (s, 1 H, H-9), 7.12, 7.28 (AB q, 2 H, J = 8.5 Hz, H-10 and H-11).

High-resolution mass spectrum: calcd for $C_{21}H_{21}NO_7$, 399.1312; found, 399,1309.

***trans*-1,2-Dimethoxy-7,8-(methylenedioxy)-12,13-dimethoxy-14-oxoaporhoeadane (17).** Solutions of either the trans glycol 13 or the trans hydroxy ether **16** (0.2 g) in THF–DMF (10:4) (20 mL) were treated as above to afford white needles (~80%): mp 186–187 °C (ether); ν_{max}^{KBr} 1695 cm^{-1}; λ_{max}^{EtOH} 293, 314 (sh) nm (log ε 3.72, 3.20); ^1H NMR ($CDCl_3$) δ 2.8–4.4 (br m, 4 H, CH_2CH_2), 2.76 (s, 3 H, C-2 OCH_3), 2.99 (s, 3 H, C-1 OCH_3), 3.89 (s, 3 H, OCH_3), 4.08 (3 H, OCH_3), 4.36 (s, 1 H, H-1), 5.90 (s, 2 H, OCH_2O), 6.64 (s, 1 H, H-6), 6.70 (s, 1 H, H-9), 7.05, 7.24 (AB q, 2 H, J = 8.5 Hz, H-10 and H-11)

High-resolution mass spectrum: calcd for $C_{22}H_{23}NO_7$, 413.1468; found, 413.1457.

***cis*-1,2-Dimethoxy-7,8-(methylenedioxy)-12,13-dimethoxy-14-oxoaporhoeadane (18).** A solution of the cis hydroxy ether **15** (0.21 g, 0.53 mmol) in THF–DMF (10:2) (20 mL) was treated with sodium hydride (0.2 g) and after 5 min, methyl iodide (1 mL) was added. The cloudy mixture was stirred for 5 h. A little methanol was added, and then water and chloroform were added. The organic layer on workup supplied 0.17 g (78%) of fine white needles: mp 228–229 °C (ether); $\nu_{max}^{CHCl_3}$ 1690 cm^{-1}; λ_{max}^{EtOH} 292, 312 (sh) nm (log ε 3.66, 3.19); ^1H NMR ($CDCl_3$) δ 2.8–4.4 (br m, 4 H, CH_2CH_2), 2.70 (s, 3 H, C-2 OCH_3), 3.25 (s, 3 H, C-1 OCH_3), 3.91 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.16 (s, 1 H, H-1), 5.86 (s, 2 H, OCH_2O), 6.60 (s, 1 H, H-6), 7.06 (s, 1 H, H-9), 7.08, 7.45 (AB q, 2 H, J = 8.5 Hz, H-11 and H-12).

High-resolution mass spectrum: calcd for $C_{22}H_{23}NO_7$, 413.1468; found, 413.1445.

1-Methoxy-7,8-(methylenedioxy)-12,13-dimethoxy-14-oxo-Δ^1-aporhoeadene (19). A solution of **18** (0.23 g, 0.55 mmol) in glacial acetic acid (30 mL) was warmed to 50 °C for 0.5 h. The resulting yellow-green solution was diluted with water and evaporated to dryness. The residue crystallized from methanol as yellow crystals (0.20 g, 93%); mp 231–232 °C (MeOH); λ_{max}^{EtOH} 275, 308, 328 (sh), 380, 393 (sh) nm (log ε 3.91, 4.00, 3.90, 4.44, 4.37); ^1H NMR ($CDCl_3$) δ 2.95 (t, 2 H, J = 5.5 Hz, H-5), 3.63 (s, 3 H, enolic OCH_3), 3.86 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 4.15 (t, 2 H, J = 5.5 Hz, H-4), 5.92 (s, 2 H, OCH_2O), 6.59 (s, 1 H, H-6), 7.05 (s, 1 H, H-9), 7.05, 7.84 (AB q, 2 H, J = 8.5 Hz, H-11 and H-12).

High-resolution mass spectrum: calcd for $C_{21}H_{19}NO_6$, 381.1207; found, 381.1194.

Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.14; H, 5.00. Found: C, 66.18; H, 4.74.

1-Acetoxy-7,8-(methylenedioxy)-12,13-dimethoxy-14-oxo-Δ^1-aporhoeadene (20). To a stirred solution of **13** (0.2 g, 0.52 mmol) in pyridine (4 mL) was added acetic anhydride (2 mL), and the mixture was heated to 60 °C for 18 h. Water (15 mL) was then added, and the solvent was evaporated. The residue crystallized from methanol (0.15 g, 71%) as yellow green needles: mp 214 °C (MeOH); ν_{max}^{MeOH} 263 (sh), 274 (sh), 303, 377 nm (log ε 3.84, 3.85, and 4.31); ^1H NMR ($CDCl_3$) δ 2.42 (s, 3 H, acetate CH_3), 3.08 (m, 2 H, H-5), 3.90 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.15 (m, 2 H, H-4), 5.95 (s, 2 H, OCH_2O), 6.64 (s), 6.87 (s) (2 × 1 H, H-6 and H-9), 7.08, 7.51 (AB q, 2 H, J = 8.5 Hz, H-10 and H-11).

High-resolution mass spectrum: calcd for $C_{22}H_{19}NO_7$, 409.1160; found, 409.1199.

Imidol 26. To a solution of **5** (0.3 g, 0.78 mmol) in methanol (200 mL) was added 20 mL of 40% aqueous sodium hydroxide, whereupon a yellow color rapidly developed. The solution was stirred at 50 °C for 3 h, diluted with water (400 mL) and extracted with chloroform. The aqueous layer was adjusted to pH 5 and reextracted with chloroform. The organic layer was dried and evaporated. The residual gum crystallized from methanol (0.21 g, 67%) as white needles: mp 171–172 °C; m/e 401 (M^+, 0.5), 399 (2), 383 (10), 339 (base), 338 (35), 324 (30), 308 (25), 206 (20), 193 (10), 192 (15), 165 (10); ^1H NMR (pyridine-d_5) δ 3.80 (t, 2 H, J = 7 Hz, benzylic CH_2), 3.73 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.25 (t, 2 H, J = 7 Hz, CH_2N), 5.91 (s, 2 H, OCH_2O), 6.41 (s, 1 H, NCHOH), 7.01 (s, 1 H, aromatic H), 7.83 (s, 1 H, aromatic H ortho to COOH), 7.00, 7.63 (AB q, 2 H, J = 8.5 Hz, aromatic H), 9.41 (br s, 2 H, OH and COOH).

High-resolution mass spectrum: calcd for $C_{20}H_{19}NO_8$, 401.1105; found, 401.1088.

Conversion of 5 to β-Hydrastine Methiodide (21). To 30 mL of aqueous sulfuric acid (35%) was added 0.2 g (0.52 mmol) of finely powdered **5** with stirring to afford a blue-black solution of salt **11**. The mixture was slowly heated to reflux (over 3 h). The color gradually changed to a persistant dark red which was not discharged upon addition of water, and heating was stopped at this point. The solution was chilled in an ice–salt bath, diluted with 200 mL of water and saturated ammonium chloride solution (20 mL), and adjusted to pH 7 with powdered potassium hydroxide. The cloudy aqueous layer was extracted with chloroform, the organic layer was dried and filtered, and the solvent was evaporated to leave a reddish gum. This residue was immediately taken up in methanol (20 mL), and the solution was treated with sodium borohydride (0.3 g). The mixture was stirred for 5 h, diluted with water, and acidified with concentrated hydrochloric acid, and the pH was adjusted to 7. Extraction with chloroform was followed by drying and solvent evaporation to provide a light yellow oil which was dissolved in acetonitrile and treated with methyl iodide (1 mL) at room temperature overnight. After removal of the solvent, the residue crystallized from methanol–ether to yield 0.09 g (33%) of fine white needles (mp 205–206 °C) identical in terms of melting point, mixture melting point, IR, ^1H NMR, and mass spectra with an authentic sample of (±)-β-hydrastine methiodide.

Imidol Ether 27. A solution of **26** (0.3 g, 0.74 mmol) in acetonitrile (50 mL) was treated with 1 mL of methanol, solid potassium carbonate (0.2 g), and methyl iodide (1 mL), and the mixture was refluxed overnight. The residue after removal of the solvent was partitioned between chloroform and water. The organic layer was dried and the solvent evaporated. TLC on silica gel gave as the major product 0.19 g of fine white needles: mp 117–118 °C (effervescence) (MeOH); $\nu_{max}^{CHCl_3}$ 1220, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) 2.7–4.2 (m, 4 H, 2 × CH_2), 2.97 (s, 3 H, aliphatic OCH_3), 3.95 (s, 3 H, $COOCH_3$), 3.86 (s), 4.00 (s) (2 × 3 H, 2 × OCH_3), 6.00 (s, 2 H, OCH_2O), 6.80 (s, 1 H, ring A aromatic H), 7.43 (s, 1 H, ring A aromatic H), 7.05, 7.55 (AB q, 2 H, J = 8.5 Hz, ring D aromatic H); m/e 429 (M^+ 20), 413 (5), 397 (10), 382 (20), 339 (base), 226 (40), 206 (90), 193 (10), 175 (10), 162 (5).

High-resolution mass spectrum: calcd for $C_{22}H_{23}NO_8$, 429.1421; found, 429.1402.

Lactam 30. Trifluoroacetic acid (1 mL) was added to 0.1 g of **26** or **27** to provide an initially red solution which effervesced with fading of the color to pale yellow. Following evaporation of the TFA, the residue crystallized from methanol to afford 0.08 g (91%) of fine white needles: mp 210–211 °C; $\nu_{max}^{CHCl_3}$ 1690 cm^{-1}; λ_{max}^{EtOH} 260, 280 (sh) nm (log ε 3.92, 3.22); ^1H NMR ($CDCl_3$) 2.85 (t, 2 H, J = 7 Hz, $ArCH_2$), 3.95 (t, 2 H, J = 7 Hz, $ArCH_2N$), 3.96 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 5.62 (s, 1 H, $NCH(Ar)_2$), 5.86, 5.94 (AB q, 2 H, J = 1.5 Hz, OCH_2O), 6.68 (s, 1 H, ring A aromatic

H), 7.37 (s, 1 H, ring A aromatic H), 7.12, 7.68 (AB q, 2 H, J = 8.5 Hz, ring D aromatic H); m/e 339 (M^+, base), 324 (60), 308 (40).

High-resolution mass spectrum: Calcd for $C_{19}H_{17}NO_5$, 339.1102; found 339.1101.

Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.26; H, 5.01. Found: C, 67.26; H, 5.04.

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Registry No. (±)-**5**, 71700-15-7; (±)-**6**, 71700-16-8; (±)-**9**, 38542-77-7; **10**, 71700-17-9; **11**, 66408-32-0; (±)-**12**, 71733-83-0; (±)-**13**, 71700-18-0; (±)-**14**, 71700-19-1; (±)-**15**, 71700-20-4; (±)-**16**, 71700-21-5; (±)-**17**, 71700-22-6; (±)-**18**, 71700-23-7; (±)-**19**, 38542-77-7; **20**, 66408-31-9; (±)-**21**, 71748-78-2; (±)-**26**, 71700-24-8; (±)-**27**, 71700-25-9; (±)-**30**, 71700-26-0; 13-hydroxyberberine, 66408-27-3; berberine chloride, 633-65-8; oxybis(berberine), 66419-60-1.

Synthesis of Certain β-D-Ribofuranosylthiazole *C*-Nucleosides from a Versatile Precursor[1]

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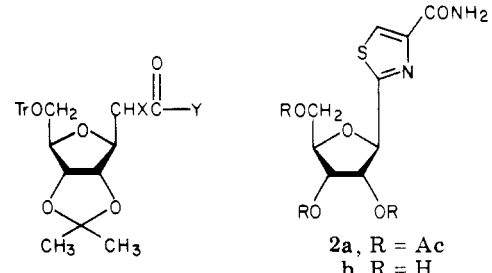
A synthesis of the versatile *C*-nucleoside precursor 3,6-anhydro-2-bromo-2-deoxy-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptose (**1c**) is described. Treatment of **1c** with various thiocarbamoyl-containing compounds (**6**) in hexamethylphosphoramide results in the formation of protected 2-substituted-5-*C*-ribosylthiazoles **7–9**. Liberation of the nucleosides **10–12** is accomplished with either methanolic hydrogen chloride or aqueous formic acid. Complete ^{13}C and ^1H NMR data are presented for all compounds.

Since the discoveries that several of the naturally occurring *C*-nucleosides have interesting biological properties,[2,3] considerable effort has been directed toward the synthesis of many structural analogues.[4] One of the principal synthetic methods employed in the *C*-nucleoside area has been the formation of "ribose"-derived intermediates in which a side chain of from one to three carbon atoms, variously functionalized, is attached through a β linkage to the original anomeric carbon. This side chain has then formed the basis for the construction of a multitude of heterocyclic rings.[4]

During the course of our research, we have developed a convenient preparation of the versatile *C*-nucleoside precursor 3,6-anhydro-2-bromo-2-deoxy-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptose (**1c**). We present herein the details of the synthesis of **1c** and demonstrate the utility of **1c** through the construction of certain 2-substituted-5-*C*-ribosylthiazoles.

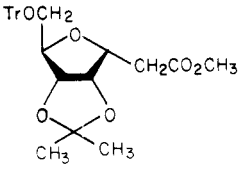
Recently, syntheses of several 2-*C*-ribosylthiazoles have been developed via a thiocarboxamide-substituted carbohydrate.[5-7] Two of these compounds (**2a,b**) have shown useful antiviral activity, a clue to their activity perhaps being that both compounds are active inhibitors of guanine nucleotide biosynthesis.[7] Other thiazole *C*-nucleosides have also been reported, such as those where the thiazole is attached to an acyclic carbohydrate moiety or is attached to the carbohydrate at a site other than the anomeric carbon.[8-12]

The starting point for the preparation of **1c** was the crystalline ester **1a**, readily available from D-ribose in three steps.[13,14] It has been determined that **1a** undergoes a facile base-catalyzed epimerization via an open-chain intermediate to the α anomer **3**, with the equilibrium lying well on the side of **3**.[13] Thus, a synthetic procedure was



1a, X = H; Y = OCH_3
b, X = Y = H
c, X = Br; Y = H

2a, R = Ac
b, R = H



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sought which would avoid this isomerization, since the majority of naturally occurring *C*-nucleosides possess the β configuration.

Treatment of **1a** with 1.1 equiv of diisobutylaluminum hydride in toluene at −78 °C afforded solely the β aldehyde

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