Hammett equation plot between log k_{obsd} and the σ^- values[26] for the reaction in cyclohexane. The insert in Figure 2 shows the corresponding correlation between log k_{obsd} and the σ values.[26] It is clear that the latter scale is not appropriate since the points for X = CN and NO_2 deviate considerably from the straight line. On the other hand, an excellent correlation with σ^- was obtained, as shown in Figure 2 and from the statistical data in Table I.

The correlation with σ^- rather than σ implies that XC_6H_4–O^- is the leaving group and that the collapse of the intermediate is rate limiting. This is similar to the conclusions drawn concerning the mechanism of ester aminolysis in chlorobenzene and in acetonitrile.[21] That is, it appears that the micellar reaction is similar, both in the mechanism and in the rate-limiting step to its counterpart in aprotic solvents.[27]

Of the two possibilities proposed to explain the role of the carboxylate ion as a general-base catalyst (eq 4 and 7), we think that the former is more plausible for the following reasons. First, eq 4 is similar to eq 2. The latter is probably the most reasonable way to explain the reaction with DAP since the carboxylate group is the strongest base available to accept a proton from the ammonium ion.[28] Note that ^1H NMR studies demonstrated that there exists a strong hydrogen bonding between the ammonium and the carboxylate ions of DAP.[10] Thus the mode of action of the general base is the same in both cases.[29] Ester aminolysis by DA in benzene, as well as in other aprotic solvents, is second order in the amine.[6,21] The DAP-catalyzed reaction is, however, first order in both DA and DAP, showing that the latter probably substitutes the second amine molecule as a general base.[6] On the other hand, eq 6 rests on the assumption that the attacking amine is not hydrogen bonded to the surfactant head ions which form the micellar core. In view of the demonstrated association of hydrogen bond donors with alkylammonium carboxylates,[30] the above-mentioned assumption seems unlikely. Finally, eq 4, which pictures the attacking species as $(RCO_2$–$H_2NR)^-$ and not as RNH_2, is in agreement with the mechanism given to explain the catalytic role of the carboxylate group in the esterolysis reaction in benzene[18] and is similar to the charge-relay mechanism for enzymatic catalysis.[31]

Acknowledgment. We thank the CNPq, FAPESP, and FINEP research foundations for financial support, Marcia Dimov and Anicleide A. de Oliveira for their excellent technical assistance, and Hoechst do Brasil for help.

Registry No. $CH_3CO_2C_6H_4$-*p*-OCH_3, 1200-06-2; $CH_3CO_2C_6H_4$-*p*-CH_3, 140-39-6; $CH_3CO_2C_6H_5$, 122-79-2; $CH_3CO_2C_6H_4$-*p*-Br, 1927-95-3; $CH_3CO_2C_6H_4$-*p*-CN, 13031-41-9; $CH_3CO_2C_6H_4$-*p*-NO_2, 830-03-5; $CH_3(CH_2)_{10}CH_2NHOCH_3$, 3886-80-4; $CH_3(CH_2)_{10}CH_2NHOCCH_2CH_3$, 62855-82-7; CH_3-$(CH_2)_{10}CH_2NHOCC_6H_4$-*p*-$OCH_3$, 1854-15-5; $CH_3COOCOCH_2CH_3$, 13080-96-1; $CH_3COOCOC_6H_4$-*p*-OCH_3, 83511-12-0; DAPA, 83511-11-9; DAP, 17448-65-6; dodecylamine, 124-22-1.

(24) Our (k_{obsd}) values in cyclohexane are higher than those reported before.[25] It is possible that the lower rates were obtained because of the presence of residual moisture in the surfactant solution. It was reported that the solubility limit of DAP in cyclohexane at 25 °C is <0.10 M.[25] We were able, however, to prepare a 0.25 M DAP solution at the same temperature. On drying, DAP looses between 1.3% and 1.5% of its weight. In one experiment we tried to prepare a 0.25 M DAP solution using a partially dried surfactant (weight loss 0.6%); a turbid solution was obtained.

(25) O'Connor, C. J.; Ramage, R. E. *Aust. J. Chem.* **1980**, *33*, 771.

(26) Exner, O. "Correlation Analysis in Chemistry"; Chapman, N. B.; Shorter, J., Eds.; Plenum Press: New York, 1978.

(27) The micellar ρ values are smaller than those observed for ester aminolysis by pyrrolidine in aprotic solvents.[21] The fact that the reaction is carried out in a medium with very different properties (the micellar microenvironment) probably plays a role in determining the value of ρ. It is relevant, however, that Menger's rate data[21] correlate with σ^- much better than with σ. The use of the former scale results in a substantial decrease in the value of ρ.

(28) This is in contrast to another mechanism in which the ester CO group, acting as a base, accepts this proton.[7]

(29) The intermediate shown in eq 4 must revert back to reactants faster than it goes to products; i.e., eq 5 is rate limiting. According to the principle of microscopic reversibility this can be established by protonating the nitrogen atom of the intermediate by the formed propionic acid.

(30) El Seoud, O. A.; Fendler, E. J.; Fendler, J. H. *J. Chem. Soc., Faraday Trans. 1* **1974**, *70*, 450, 459. El Seoud, O. A.; Ribeiro, F. P. *J. Org. Chem.* **1976**, *41*, 1365.

(31) Blow, D. M. *Acc. Chem. Res.* **1976**, *9*, 145 and references therein.

Hofmann Degradation of β-Hydroxy Ammonium Salts. α- and β-Hydroxylaudanosine, 7-Hydroxyglaucine, and 13-Hydroxyxylopinine

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Received June 21, 1982

The four related β-hydroxy ammonium methiodide salts of α-hydroxylaudanosine (**2a**), β-hydroxylaudanosine (**2b**), 7-hydroxyglaucine (**5a**), and 13-hydroxyxylopinine (**8a**) have been subjected to Hofmann degradation. Although precedent dictates that such materials should form either epoxides or ketones, these are not found. Only products of (a) fragmentation and elimination (from **2a** and **2b**), (b) dehydration and elimination (from **5a**), and (c) elimination and oxidation (from **8a**) are obtained. The results are accounted for by consideration of the molecular geometries of the β-hydroxy ammonium salts as experimentally determined from single-crystal X-ray studies and the geometric requirements for epoxide and ketone formation.

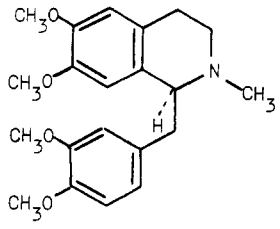
Late-stage oxidation (often with introduction of oxygen) of alkaloids has been proposed to account for, in part, structural modifications in the elaborated bases.[1,2] In some cases, biosynthetic work has supported such speculation by delineating the relationship between coisolated or biogenetically "related" but separately found materi-

(1) Robinson, R. "The Structural Relations of Natural Products"; Clarendon Press: Oxford, 1955.

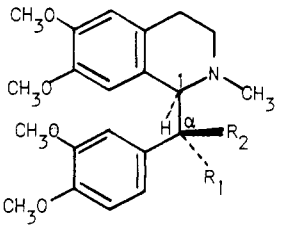
(2) Dalton, D. R. "The Alkaloids: The Fundamental Chemistry, A Biogenetic Approach"; Marcel Dekker: New York, 1979.

0022-3263/82/1947-5141$01.25/0

als.[3,4] Typical of these proposed relationships are those between the following: (i) laudanosine (1) and *N*-

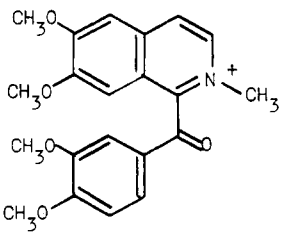


1



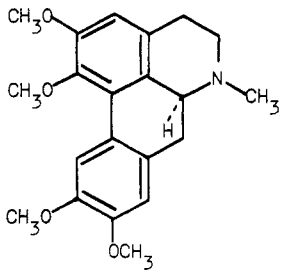
2a R_2 = H; R_1 = OH (1R,αR)

2b R_1 = H; R_2 = OH (1R,αS)



3

methylxanthaline (3) which might be presumed to involve the α- and β-hydroxylaudanosines (**2a** and **2b**, respectively); (ii) glaucine (4) and the unnamed 1,2,9,10-tetra-



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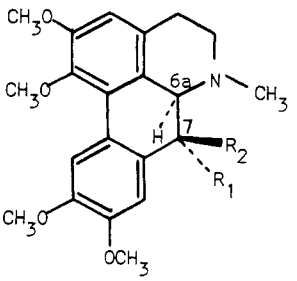
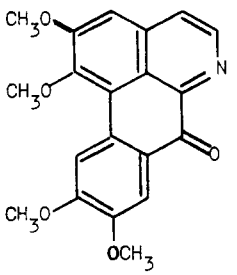


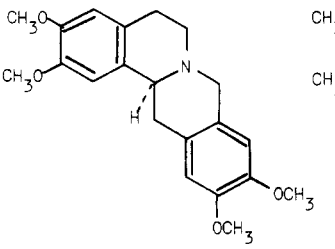
5a R_1 = H; R_2 = OH (6aR,7S)

5b R_2 = H; R_1 = OH (6aR,7R)



6

methoxyoxoaporphine (6) from *Liriodendron tulipfera*[5] which might be related through a 7-hydroxyglaucine (**5a** or **5b**); neither of the enantiomeric 7-hydroxyglaucines (**5a,b**) has yet been reported as naturally occurring, but more than 15 aporphines bearing oxygen at C7 (OH or OCH_3) are known;[6] (iii) the tetrahydroprotoberberine xylopinine (norcoryaldine, 7) and the phthalidisoquinoline



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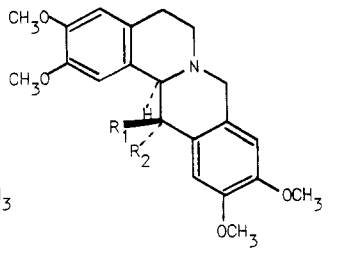
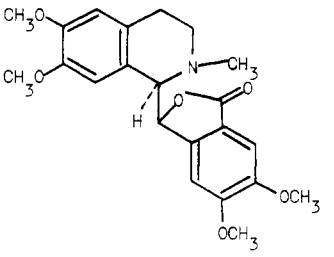


8a R_1 = H; R_2 = OH (13S,14R)

8b R_2 = H; R_1 = OH (13R,14S)



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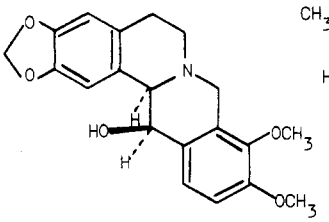
9, which has not been isolated and, indeed, has the "wrong"[2] oxygenation pattern but which, on the basis of the known in vivo conversion of scoulerine (10) to ophiocarpine (11)[3] and of scoulerine (10) to narcotine (12),[4] could be related to 7 through **8a,b**.[7]



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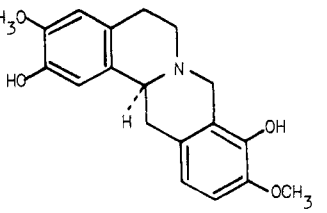

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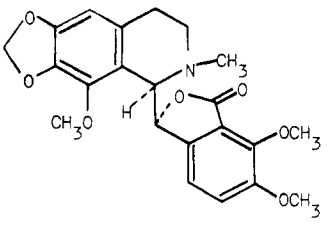


12

The value of the Hofmann degradation to structure elucidation has been demonstrated and catalogued.[8a] In the normal course of events, nitrogenous bases such as the alkaloids listed above are exhaustively methylated and, as

(3) Jeffs, P. W.; Scharver, J. D. *J. Am. Chem. Soc.* **1976**, *98*, 4301–4310.
(4) Battersby, A. R.; Hirst, M.; McCaldin, D. J.; Southgate, R.; Staunton, J. *J. Chem. Soc. C* **1968**, 2163–2172.
(5) (a) Buchanan, M. A.; Dickey, E. E. *J. Org. Chem.* **1960**, *25*, 1388–1391. (b) Taylor, W. I. *Tetrahedron* **1961**, *14*, 42–45.
(6) Shamma, M. "The Isoquinoline Alkaloids"; Academic Press: New York, 1972.
(7) Although the epimer at C9 of (−)-α-narcotine (12; i.e., (−)-β-narcotine) has not been isolated from natural sources, many variously substituted phthalide isoquinolines have been isolated as racemates, and diastereoisomeric pairs also are known. While this might imply various nondiscriminatory oxidative pathways, our present knowledge is equally compatible with late-state epimerization processes as well as different specific processes giving rise to each specific isomer. See, also: Battersby, A. R.; Staunton, J.; Wiltshire, H. R.; Bircher, B. J.; Fuganti, C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1162–1171.

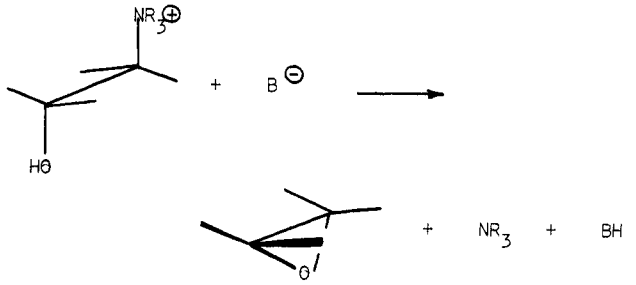


Figure 1. Epoxide formation from a β-hydroxy ammonium salt during Hofmann elimination. The hydroxyl and ammonium groups are anticoplanar, and it is presumed that the leaving of the latter occurs with participation of the former.

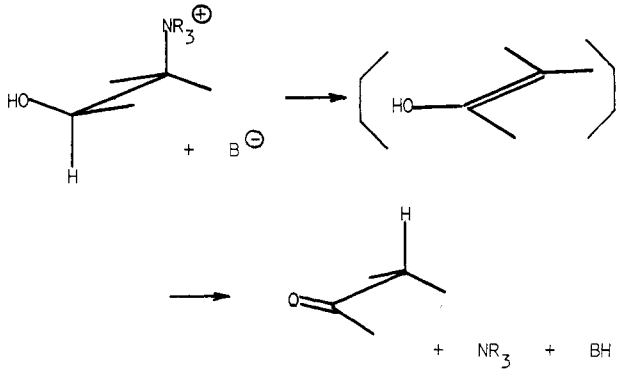


Figure 2. Ketone formation from a β-hydroxy ammonium salt during Hofmann elimination. The proton lost in the elimination is anticoplanar to the ammonium group and on the carbon bearing oxygen. The resulting enol tautomerizes to the ketone.

their hydroxides, induced to undergo decomposition to alkenes and tertiary amines (Hofmann elimination). In this process, a proton on a carbon β to the quaternary nitrogen is abstracted. The proton lost is from the least substituted alkyl group (the Hofmann rule) unless a substituent on the β-carbon enhances the acidity of that particular proton or conformational or steric effects dictate otherwise.[8a] Anticoplanar elimination to form *cis*-alkenes and syncoplanar elimination to form *trans*-alkenes have been found.[8b]

There is some evidence[8c] that the course of the Hofmann elimination is different from that adumbrated above when a hydroxyl group is on the β-carbon. Thus, it has been posited that if the hydroxyl is held, or allowed to rotate, into a conformation where it is anticoplanar to the leaving nitrogen, participation by oxygen should result in epoxide formation (Figure 1). Alternatively, if a proton occupies the position anticoplanar to the quaternary leaving group, enol formation followed by rapid tautomerization to the corresponding ketone is expected (Figure 2).[8c] If neither of these conformations obtains, the situation is less clear.

The six possible intermediate alcohols indicate above, **2a,b**, **5a,b**, and **8a,b**, possess a hydroxyl function β to nitrogen and might be expected to undergo base-catalyzed elimination with participation of oxygen. This report deals with the examination of four (viz., **2a,b**, **5a**, and **8a**) of the compounds in this set under the conditions of the Hofmann elimination.

Methods

(A) Preparation of the Amines 2a,b, 5a, and 8a. (i) α- and β-Hydroxylaudanosines (Racemic 2a and 2b).

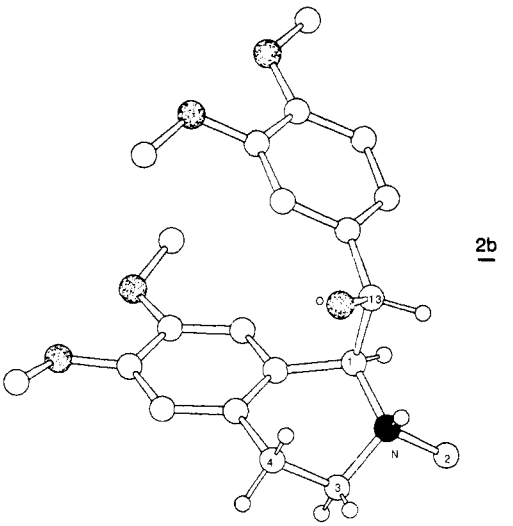
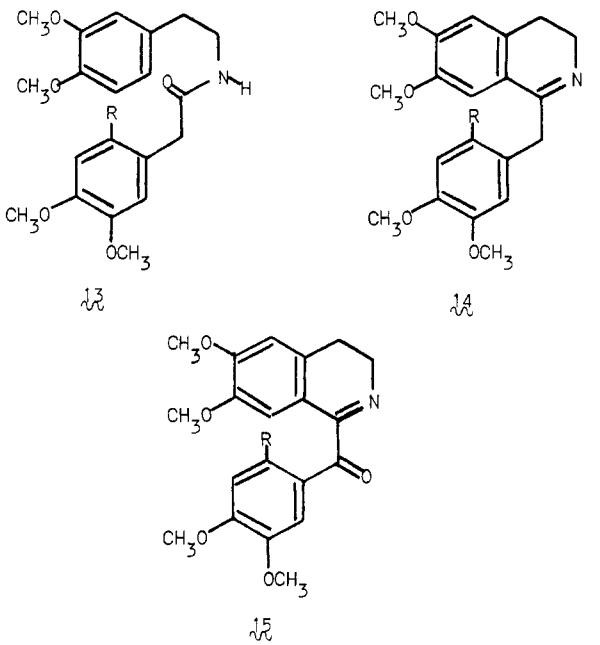


Figure 3. β-Hydroxylaudanosine (**2b**) cation. The torsion angle N–C1–C13–O is –64° and is related, in part, to the N–H···Br and O–H···Br hydrogen bonds which form in the crystalline state. In solution, free rotation about the C1–C13 bond should be possible, but since no epoxide or ketone is isolated from the Hofmann elimination, apparently the anticoplanar conformation is not realized for either O or H13. The observed products result from N–C3 and C1–C13 bond cleavage.

The hydroxylaudanosines were prepared by modification of previous procedures.[9,10] The amide **13** (R = H) was



formed in a typical Schotten–Baumann reaction between (3,4-dimethoxyphenyl)ethanoyl chloride and (3,4-dimethoxyphenyl)ethylamine in 68% yield. Condensation to the imine **14** (R = H) by using phosphorus pentachloride in a modified Bischler–Napieralski reaction was followed by rose bengal catalyzed photooxidation to provide (78%) 3,4-dihydropapaveraldine (**15**, R = H).[11] Methylation with

(8) (a) Cope, A. C.; Trumbull, E. R. *Org. React.* **1960**, *11*, 317 ff. (b) Sicher, J. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 200–214. (c) See, specifically, pp 352–355 and 388–390 of ref 8a.

(9) King, F. E.; L'Ecuyer, P. *J. Chem. Soc.* **1937**, 427–432.
(10) Bentley, K. W.; Murray, A. W. *J. Chem. Soc.* **1963**, 2491–2497.
(11) We thank Dr. J. R. Williams for suggesting this method of oxidation on which two of us (K.L.W. and D.R.D.) reported at the 174th National Meeting of the American Chemical Society, Chicago, IL, 1977 (Abstract ORGN 200). We have been informed by private communication that Professor N. H. Martin had first carried out this reaction in 1970 under different conditions (O_2–methylene blue–2-propanol) and had reported on similar systems in 1976 and 1978 at the Southeastern Regional ACS meetings.

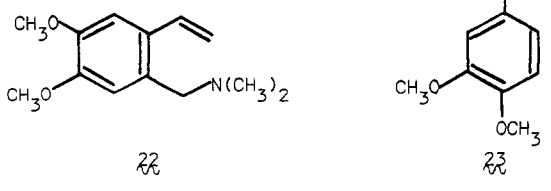
methyl iodide provided the corresponding methiodide (96%), and reduction with sodium borohydride yielded a 1:1 mixture of the racemic diastereomers α- and β-hydroxylaudanosine, readily separable by fractional crystallization or preparative thin-layer chromatography (TLC). For racemic α-hydroxylaudanosine (**2a** and its mirror image) the melting point was 138 °C (lit.[9] mp 138 °C), and $J_{1,\alpha}$ = 8.0 Hz, while for racemic β-hydroxylaudanosine (**2b** and its mirror image) the melting point was 108–109 °C (lit.[9] mp 108–109 °C), and $J_{1,\alpha}$ = 3.0 Hz. In concert with these coupling constants, X-ray analysis[12] of the crystalline hydrobromide of racemic β-hydroxylaudanosine (mp 209–211 °C) defines this isomer as erythro (1*R*,α*S* and 1*S*,α*R*; Figure 3). Presumably, α-hydroxylaudanosine is thus the threo (1*R*,α*R* and 1*S*,α*S*) isomer.

(ii) 7-Hydroxyglaucine (Racemic 5a). The preparation of racemic 7-hydroxyglaucine (**5a** and its mirror image) has been reported elsewhere.[13] The details of the conversion of the amide **13** (R = NO_2) [formed by condensation of (4,5-dimethoxy-2-nitrophenyl)ethanoic acid with 3,4-dimethoxyphenethylamine using *N*,*N*′-carbonyldiimidazole in 80% yield] to the imine **14** (R = NO_2) with the Langheld ester (PPE; 80%), photooxidation to the ketone **15** (R = NO_2) as indicated above (82%), methylation to the corresponding methiodide (100%), and reduction to the diamine **16** (80%; see Chart I) followed by Pschorr cyclization to the oxoaporphine **17** (22%),[14] corunnine (**18**, 8%),[15] *N*-methylcoryaldine (**19**, 8%), papaveraldine (**20**, 5%), and the ketone **21** (5%), and the final conversion of the oxoaporphine **17** by methylation with methyl iodide (100%) and reduction with potassium borohydride to the desired racemic 7-hydroxyglaucine (**5a** and its mirror image, 60%) are provided in the Experimental Section. The supposition (based on the observed $J_{6a,7}$ = 3.0 Hz coupling constant) that racemic **5a** was erythro (6a*R*,7*S* and 6a*S*,7*R*) was confirmed by X-ray analysis of the corresponding methiodide (Figure 4).[12]

(iii) 13-Hydroxyxylopinine (Racemic 8a). The preparation of racemic (13*S*,14*R* and 13*R*,14*S*)-*threo*-13-hydroxyxylopinine (**8a** and its mirror image) has been reported from **15** (R = H).[16] The stereochemistry earlier deduced from the large coupling constant was confirmed by X-ray analysis of the corresponding methiodide (Figure 5).[12]

(B) Hofmann Degradation. (i) Hydroxylaudanosines. The racemic hydroxylaudanosines (**2a,b** and their respective mirror images) were individually converted to their respective methiodides.[9]

Decomposition of both methiodides in refluxing 10% aqueous sodium hydroxide yielded the styrene **22**, veratraldehyde (**23**), 3,4-dimethoxybenzyl alcohol (veratryl alcohol), and 3,4-dimethoxybenzoic acid (veratric acid). Both veratryl alcohol and veratric acid are produced from veratraldehyde (**23**) under the conditions of the reaction. When the decomposition was carried out with sodium deuteroxide in ^2H_2O, incorporation of deuterium into the amine **22** occurred. Mass spectrometric examination of the deuterated amine indicated that the material contained, on the average, between two and three deuterium atoms/molecule. ^1H noise-decoupled ^{13}C NMR spectra define the deuterium as residing exclusively on the two benzylic positions of the styrene **22** and, in conjunction with ^1H NMR spectra, indicate that the styrene α-carbon is completely deuterated while the benzylic carbon bearing the nitrogen has, on the average, more than one, but less



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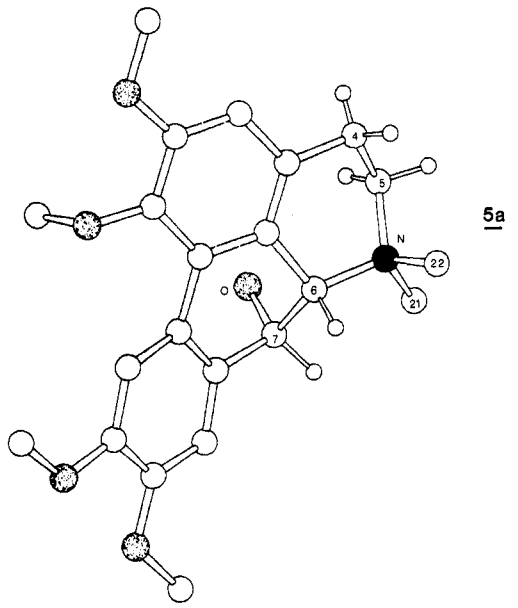
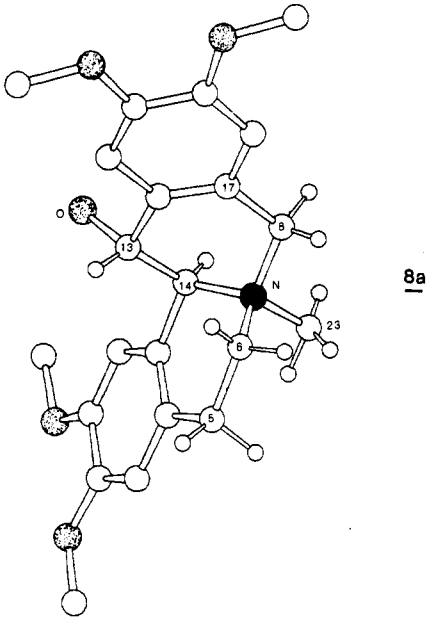


5a

Figure 4. *N*-Methyl-7-hydroxyglaucine (**5a**) cation. The N–C6–C7–O and N–C6–C7–H7 torsion angles are sterically fixed at the nonanticoplanar values 73° and −47°, respectively. The H6–C6–C7–O torsion angle is −167°, approaching anticoplanarity, and promotes dehydration to form the C6–C7 double bond.

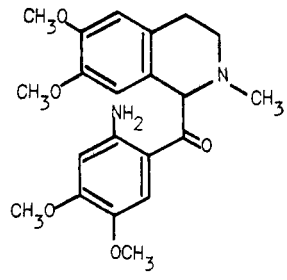


8a

Figure 5. *N*-Methyl-13-hydroxyxylopinine (**8**) cation. The N–C14–C13–O torsion angle is sterically fixed at 155°, 25° away from anticoplanarity and unfavorable for Hofmann elimination with participation of oxygen or hydrogen to give either epoxide or ketone product.

(12) The details of the X-ray crystallographic determination are given in part B of the Experimental Section.
(13) Chackalamannil, S.; Dalton, D. R. *Tetrahedron Lett.* **1980**, 2029–2032.
(14) Buchanan, M. W.; Dickey, E. E. *J. Org. Chem.* **1960**, *25*, 1389–1391.
(15) Ribas, I.; Sâa, J.; Castedo, L. *Tetrahedron Lett.* **1973**, 3617–3618.
(16) Kametani, T.; Matsumoto, H.; Sato, Y.; Nemoto, H.; Fukumoro, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 376–382.

Chart I



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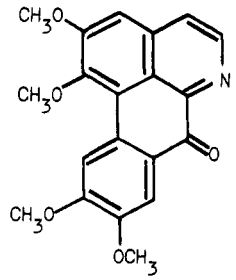

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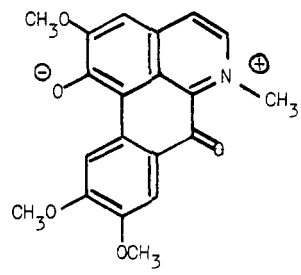

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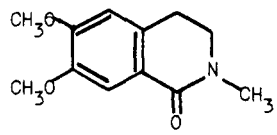

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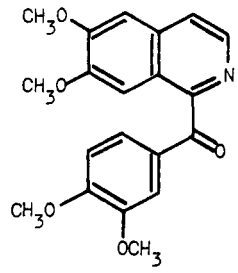

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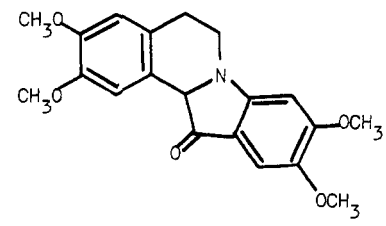
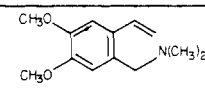
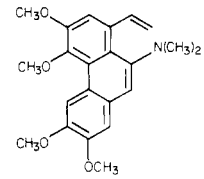
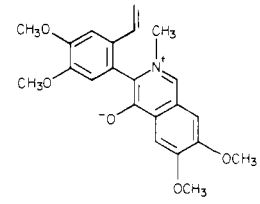
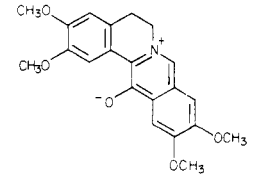


21

Table I. Torsion Angles[a]

figure	bond cleaved: C-C↓N-C	H-C↓N-C	C-C-N↓C	C↓N-C-H	major products (% yield)
3	C4-C3-N-C2 (173)	H1-C3-N-C1 (−75) H2-C3-N-C1 (151)	C13-C1-N-C3 (123)	C3-N-C1-H (129)	
4[a]	C4-C5-N-C22 (a, 58; b, 178) C4-C5-N-C21 (a, 177; b, 60)	H-C5-N-C6 (a, 173; b, 172)	C7-C6-N-C5 (a, −98; b, 173)	C5-N-C6-H (a, 156; b, −80)	 24 (95)
5[b]	C5-C6-N-C8 (a, −177; b, 179)	H-C6-N-C14 (a, 169; b, 167) H2-C23-N-C8 (a, −174; b, 87)	C13-C14-N-C6 (a, 60; b, −60) C17-C8-N-C23 (a, 172; b, −173)	C6-N-C14-H (a, −173; b, 167) C6-N-C8-H2 (a, −177; b, 53)	 25 (84)
		H3-C23-N-C8 (a, 65; b, −176) H3-C23-N-C14 (a, −178; b, −58) H2-C23-N-C14 (a, −56; b, −155)	C13-C14-N-C23 (a, −176; b, −177) C17-C8-N-C6 (a, −68; b, 68)	C6-N-C8-H1 (a, −39; b, 161) C23-N-C8-H1 (a, 82; b, 43) C23-N-C8-H2 (a, −57; b, −66)	 26 (12)

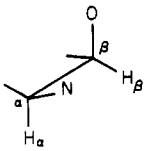
[a] The atoms involved are given followed by the angle in degrees in parentheses. [b] Molecule a shown. [c] Molecule b shown.

than two, deuterium atoms per molecule.

Additionally, (a) both α- and β-hydroxylaudanosine methiodides gave, within experimental error, the same results, (b) in both cases, methiodides recovered from reactions halted before degradation was complete have not, within experimental error, incorporated deuterium, and (c) the product styrene (**22**) does not incorporate deuterium under the conditions of the reaction.

(ii) 7-Hydroxyglaucine. The methiodide of 7-hydroxyglaucine (racemic **5a**) was heated in 10% aqueous

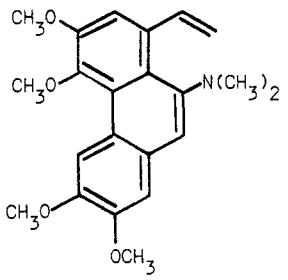
Table II. Torsion Angles[a]



torsion angle	β-hydroxylaudanosine hydrobromide	7-hydroxyglaucine methiodide[b]	13-hydroxyxylopinine methiodide[b]
H_β-C_β-C_α-N	47	47 (47)	91 (69)
O-C_β-C_α-N	64	71 (73)	155 (160)
O-C_β-C_α-H_α	171	174 (167)	36 (31)
	177 [HC4-C4-C3-N][c]	171 (167) [HC4-C4-C5-N][c]	154 (167) [HC5-C5-C6-N][c]

[a] Given in degrees. [b] The angles given in parentheses are for the isomer *not* shown in Figures 4 and 5, respectively. [c] Angles for elimination to form styrene. The atoms involved are given in brackets.

sodium hydroxide under the same conditions used for decomposition of the hydroxylaudanosine (racemic **2a** and **2b**) methiodides. Crystalline **24** (95%) was isolated on extraction of the reaction mixture.



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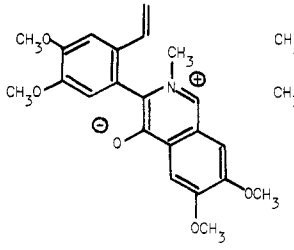
(iii) 13-Hydroxyxylopinine. The methiodide of 13-hydroxyxylopinine (racemic **8a**) was heated in 10% aqueous sodium hydroxide under the same conditions used for the decomposition of the hydroxylaudanosine (racemic **2a** and **2b**) methiodides. The products were separated by extraction and purified by preparative TLC (silica gel, 1:1 v/v chloroform/ethyl acetate). The major product (84%) was identified as the zwitterionic alkene **25**. A small



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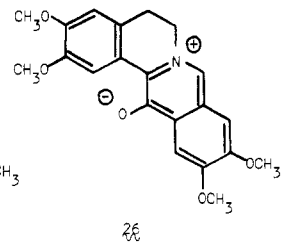

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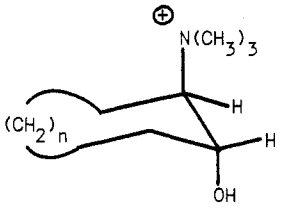
amount (ca. 12%) of material identical with independently prepared 13-hydroxydehydroxylopinine (**26**), the product of demethylation and oxidation of the methiodide of racemic **8a**, also was found.

It is clear, however, that neither of these materials is a primary product of the reaction. Thus, the degradation products soluble in chloroform and chromatographed as indicated above gave rise to four bands: the origin and three mobile materials (R_f 0.93, 0.59, and 0.39). The material corresponding to R_f 0.39 (12%) on removal from silica gel was shown to be **26**. However, **26**, with the same eluant, does not move on silica gel. The second band (R_f 0.59) yielded the zwitterionic alkene **25** (72%), which also does not move on TLC under the conditions of its isolation. The last band (R_f 0.93) also yields only **25** (12%) on removal from silica gel.

Discussion

The formation of epoxides from β-hydroxy ammonium salts under the conditions of the Hofmann elimination reaction has been known for somewhat more than a century.[17] The observation that ketones also can be formed in this reaction is more recent,[18] and the beginnings of a systematic investigation[8] show that at least one such β-hydroxy ammonium salt is reported to be recovered unchanged on attempted degradation. Thus, to pick typical examples, *trans*-2-aminocyclohexanol (**27**, $n = 2$) yields the



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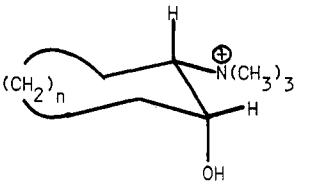

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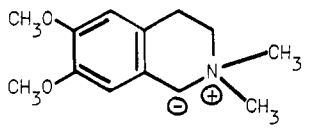
expected oxide[19] (74%), and the corresponding cis analogue (**28**, $n = 2$) is recovered unchanged,[20] while for *trans*-2-aminocyclodecanol (**27**, $n = 6$) the corresponding oxide (85%) is formed, and the cis analogue (**28**, $n = 6$) yields ketone (80%) and some unidentified alkene.[21]

However, the isolation of products resulting from fragmentation of the carbon–carbon bond between the carbon bearing the hydroxyl and that bearing the quaternary nitrogen appears unique to the particular cases of the hydroxylaudanosines and closely related compounds.[9,10] While this may reflect somewhat on isolation techniques,[22] it also may be a function of the population of rotational isomers available to the quaternary ammonium starting materials. Thus, to the extent that the ground-state conformations reflect the transition-state conformations for epoxide formation or elimination to the enol, both may be unfavorable and thus allow the intrusion of the fragmentation pathway.

(17) Claus, A. *Ber.* 1878, *11*, 1820–1827.
(18) Turner, R. B.; Woodward, R. B. "The Alkaloids"; Manske, R. H. F., Holmes, H. L., Eds.; Academic Press: New York, 1953; Vol. 3, pp 1–63.
(19) Wilson, N. A. B.; Read, J. *J. Chem. Soc.* **1935**, 1269–1273.
(20) See ref 8a, p 352, footnote 105.
(21) Svoboda, M.; Sicher, J. *Collect. Czech. Chem. Commun.* **1958**, *23*, 1540–1550.
(22) The decomposition of the quaternary salts of ephedrine (erythro) and pseudoephedrine (threo) leads to, respectively, 30% and 25% epoxide products which were isolated by steam distillation. The report does not allude to the composition of the remaining (major) product(s) although it is clear that some carbonyl-containing material(s) also forms.[23]
(23) Witkop, B.; Foltz, C. M. *J. Am. Chem. Soc.* **1957**, *79*, 197–205.

Tables I and II present selected torsional angles for racemic β-hydroxylaudanosine (**2b** and its mirror image) hydrobromide (Figure 3), racemic 7-hydroxygalucine (**5a** and its mirror image) methiodide (Figure 4), and racemic 13-hydroxyxylopinine (**8a** and its mirror image) methiodide (Figure 5). The racemic methiodides of both **5a** and **8a** have two isomers present in the crystal. For the former, this is doubtlessly due to the lack of planarity of the aporphine system[6] while for the latter it is either a similar twisting of the framework or methylation of the nitrogen from opposite faces which gives rise to this result. Regardless of this, however, for the most part, the differences in angles are small and, given the rigidity of the framework, solution conformations of these systems probably approximate what is found in the crystalline state. However, for racemic β-hydroxylaudanosine, greater flexibility should be possible in solution. Thus, although we have shown that ground-state conformations availabe to *N*-substituted tetrahydroisoquinolines are limited,[24] the observed $O-C_\beta-C_\alpha-CH_\alpha$ torsional angle (Table II) for racemic β-hydroxylaudanosine hydrobromide of 171° (which might lead to the prediction of facile dehydration) need not obtain in solution for the corresponding methiodide while the similar angle of 174° in racemic 7-hydroxyglaucine (**5a** and its mirror image) methiodide, where flexibility is limited, can be used to justify loss of water. It is also clear that for racemic β-hydroxylaudanosine (**2b** and its mirror image) hydrobromide (and thus also presumably for the methiodide) neither the conformation required for epoxide formation nor that required for elimination to the enol can be attained, and, as a consequence, carbon–carbon bond cleavage to yield the ylide **29**, as originally proposed,[10] is



29

energetically the lowest pathway available. Unfortunately, mechanistic confirmation for the intermediacy of ylide **29** cannot be adduced from the limited data available. However, if **29** is assumed to be an intermediate, incorporation of a single deuterium atom on the benzylic carbon α to nitrogen in the product **22** would be expected from the reaction in $NaO^2H/^2H_2O$. Additionally, depending upon the details of the elimination process,[32] exchange of protons β to nitrogen for deuterium in the solvent might also occur. That such exchange does occur and that deuterium is found on the benzylic carbon α to nitrogen (more than one deuterium but less than two) militates against rapid exchange of the α-protons which are both benzylic and α to nitrogen (relative to the elimination process) and argues in favor of the intermediacy of the zwitterion **29**. According to this scheme of things, protonation (or deuteriation) of **29** yields the corresponding tetrahydroisoquinolinium ion which then undergoes exchange of protons β to nitrogen prior to Hofmann elimination to **22**.

In the case of racemic 7-hydroxyglaucine (**5a** and its mirror image) methiodide (Figure 4) the pinning together of the rings does result in a situation where, as with β-hydroxylaudanosine (**2b** and its mirror image), neither the hydroxyl nor the hydrogen at C7 is anticoplanar to the quaternary nitrogen, and thus both epoxide and enol formation are precluded. However, the rigidly fixed anticoplanarity of the hydroxyl at C7 and the hydrogen at C6 (174°) leads to dehydration. Subsequently, the normally expected Hofmann elimination in the B ring generates **24**.

For 13-hydroxyxylopinine (**8a** and its mirror image) methiodide (Figure 5), it appears that although angles different from those above obtain and the hydroxyl at C13 approaches anticoplanarity (155°) to the quaternary nitrogen, neither formation of the enol nor formation of the epoxide is energentically favorable, and, additionally, dehydration should not occur. However, the known[6] proclivity of these systems to aromatize via oxidation frustrates the expected cleavage reaction, and it is probable that the Hofmann elimination in the B ring and partial oxidation proceed apace to yield only the fully oxidized materials on isolation.

Thus we conclude that carbon–carbon bond fragmentation in the particular case of the hydroxylaudanosines (**2a,b** and their mirror images) results from (a) failure to achieve the appropriate conformations for epoxide formation or elimination to the enol, (b) the stability of the proposed[10] zwitterionic intermediate, and (c) the absence of any other energetically lower lying pathway, such as elimination of water or oxidation, for the reaction.

Experimental Section

(A) Chemicals.[25] ***N*-(3,4-Dimethoxyphenethyl)(3,4-dimethoxyphenyl)acetamide (13, R = H).** In a 2-L three-necked flask equipped with a mechanical stirrer and dropping funnel were placed 3,4-dimethoxyphenethylamine (2.3 g, 1.3 mmol), sodium hydroxide (420 cm^3 of a 10% aqueous solution), water (670 cm^3), and chloroform (120 cm^3). (3,4-Dimethoxyphenyl)ethanoyl chloride (25.0 g, 116 mmol) was slowly added through the addition funnel while the two-phase mixture in the flask was vigorously stirred. Stirring was continued for an additional 0.5 h after the addition was complete, the phases were separated, and the chloroform layer was washed with dilute (5%) aqueous HCl and with water. After drying, the chloroform was removed under reduced pressure. The tan crystalline residue was recrystallized from absolute methanol to yield 28.2 g (67.8% of theory) of white crystals, mp 124 °C (lit.[33] mp 124 °C).

3,4-Dihydropapaverine (14, R = H). With stirring, in a flask equipped with a drying tube, *N*-(3,4-dimethoxyphenyl)(3,4-dimethoxyphenyl)acetamide (**31**, R = H; (20.6 g, 5.6 mmol) was dissolved in chloroform (200 cm^3) and the solution cooled in a dry-ice acetone bath to −78 °C. Phosphorus pentachloride (25.0 g, 12 mmol) was added cautiously. The mixture was allowed to reach room temperature and was stirred for an additional 24 h. Absolute ethanol (30 cm^3) was added, dropwise, with stirring to decompose the phosphorus oxychloride and any remaining phosphorus pentachloride, and the clear yellow solution was poured into ether (500 cm^3) An amorphous precipitate formed at once, and this was dissolved by adding water. The aqueous layer was separated, made basic with 10% aqueous sodium hydroxide, and extracted with chloroform. The chloroform extract was filtered and evaporated at reduced pressure to a thick dark oil. Addition of methanol induced crystallization. Recrystallization from methanol (anhydrous) yielded 8.31 g (43%; mp 187 °C) of material which formed a picrate, mp 168 °C (lit.[33] mp 168 °C).

3,4-Dihydropapaveraldine (15, R = H). 3,4-Dihydropapaverine (**14**, R = H; 4.39 g, 12.9 mmol) was dissolved in methanol with heating. Rose bengal (0.36 g) was added, and the solution was saturated with oxygen. The solution was irradiated for 7 h with a tungsten halide lamp (Sylvania, Type DWY) under

(24) Dalton, D. R.; Ramey, K. C.; Gisler, H. J., Jr.; Lendvay, L. J.; Abraham, A. *J. Am. Chem. Soc.* **1969**, *91*, 6367–6371.

(25) Infrared spectra were recorded on a Beckman IR 5A spectrophotometer, NMR spectra on a Varian XL-100-15 spectrometer equipped with a Nicolet pulse unit and data system, and mass spectra on a Hitachi RMU-6 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, or Schwarzkopf Microanalytical Laboratory, Woodside, NY.

an atmosphere of oxygen. The methanol was evaporated under reduced pressure and the residue dissolved in chloroform. The chloroform solution was passed through a column of neutral alumina (Woelm activity grade I) to remove the rose bengal. After removal of the chloroform by evaporation at reduced pressure, the residue was recrystallized from absolute methanol: 3.6 g (78.5%); mp 190–192 °C (lit.[33] mp 190–191 °C).

α- and β-Hydroxylaudanosine (2a,b and Their Mirror Images). 3,4-Dihydropapaveraldine (15, R = H) was converted to the corresponding methiodide by heating a solution of the imine in methanol with an excess of methyl iodide for 5 h. Evaporation of the solvent and excess methyl iodide left a glassy residue which crystallized on addition of ether: mp 178 °C; 2.37 g (96.7%). The methiodide (6.1 g, 12.5 mmol) was dissolved in methanol (600 cm^3) to which a few drops of water were added. Sodium borohydride (13 g, 343 mmol) was added slowly while the solution's color changed from yellow to white. When the addition was complete, the reaction mixture was heated on a steam bath for 0.5 h at reflux, and the methanol was then removed at reduced pressure. The residue was dissolved in water and extracted with benzene. The benzene extract was washed with potassium carbonate (10% aqueous solution) and dried over calcium carbonate, and the solvent was removed at reduced pressure. The oily residue readily crystallized from ethanol, but only small crops (mp 104–134 °C) could be collected. Separation by repeated crystallizations and combination of high- and low-melting crops or by preparative TLC (silica gel, 7% ammonium hydroxide in 1:1 (v/v) benzene/ethyl acetate) yielded the α isomer **2a** [mp 138 °C (lit.[9] mp 138 °C); 1.01 g] and the β isomer **2b** [mp 108–109 °C (lit.[9] mp 108–109 °C)]; 1.06 g (total 2.07 g, 44.4%).

The hydrobromide of β-hydroxylaudanosine (mp 209–211 °C) was prepared by addition of aqueous (48%) HBr to a methanol solution of the amine and evaporation of the solvent at reduced pressure. Recrystallization for X-ray analysis was effected from absolute methanol (Figure 3).

***N*-(3,4-Dimethoxyphenethyl)(4,5-dimethoxy-2-nitrophenyl)acetamide (13, R = NO_2).** To a suspension of (4,5-dimethoxy-2-nitrophenyl)ethanoic acid (29.8 g, 123.4 mmol)[26] in dichloromethane cooled to 5 °C with an ice–water bath was added *N,N'*-carbonyldiimidazole (20.0 g, 123 mmol) with stirring in one portion. Complete dissolution of the solids occurred with evolution of carbon dioxide, and, after the mixture was stirred for 10 min at 5 °C, 3,4-dimethoxyphenethylamine (23.3 g, 129 mmol) dissolved in dichloromethane (25 mL) was added dropwise. After 2 h, the solution was evaporated to dryness at reduced pressure and the residue recrystallized from chloroform–methanol to give the amide: mp 170–171 °C; 42.4 g (85%); IR (KBr) λ_{max} 1670 cm^{-1} (C=O) Anal. Calcd for $C_{20}H_{24}N_2O_7$: C, 58.46; H, 5.64; N, 7.18. Found: C, 58.59; H, 5.83; N, 6.44.

1-(4',5'-Dimethoxy-2'-nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (14, R = NO_2). (a) Preparation of the Langheld Ester (pPE). Fresh phosphorus pentoxide (200 g) was suspended in a mixture of anhydrous ether (200 cm^3) and chloroform (200 cm^3) in a 1-L round-bottomed flask fitted with an efficient condenser and drying tube. The contents were refluxed gently on a steam bath for 24 hrs. The clear solution so obtained was concentrated under vacuum to remove the solvents, and the light brown viscous oil which remained was used directly in the condensation reactions.

(b) Cyclization to 14 (R = NO_2). The amide **13** (R = NO_2; 10 g, 24.75 mmol) was dissolved in boiling chloroform (50 mL) under moisture-free conditions. Freshly prepared PPE (50.0 g) was added to this in one portion, and the refluxing was continued for 24 h. The reaction mixture was cooled in an ice bath, and aqueous potassium hydroxide (30%) was added dropwise, with stirring, until the exothermic reaction ceased and the aqueous layer was strongly basic. The layers were separated, the aqueous phase was washed with chloroform, and the combined chloroform extracts were dried over magnesium sulfate and concentrated at reduced pressure. The green residue so obtained was dissolved in methylene chloride and filtered through a column of alumina (Woelm, activity grade II). The red solution which resulted was concentrated, and the residue was crystallized from methanol to give light yellow crystals: mp 126–126 °C; 7.74g (81%). The ready oxidation of this material precluded accurate elemental analyses: IR λ_{max} 1640 (C=N), 1493 and 1316 cm^{-1} (Ar NO_2); ^1H NMR ($CDCl_3$, Me_4Si) 3.42 (CH_2, 2 H, s), 4.87 (OCH_3, 3 H, s), 4.92 (OCH_3, 9 H, s), 7.68, 7.10, 6.86, and 6.71 ppm (H_5, H_8, $H_{2'}$, $H_{5'}$, 4 H, 4 s).

1-(4',5'-Dimethoxy-2'-nitro-α-oxobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (15, R = NO_2). The oxidation was carried out as indicated above for 3,4-dihydropapaveraldine (15, R = H). From 8.0 g (20.7 mmol) of **14** (R = NO_2) there was obtained 7.13 g (17.4 mmol, 86%) of **15** (R = NO_2): IR λ_{max} 1692 cm^{-1} (C=O); ^1H NMR 7.68, 7.60, 7.10, and 6.70 (H_5, H_8, $H_{2'}$, $H_{5'}$, 4 H, 4 s), 3.95–4.05 ppm (4 OCH_3, 12 H, m).

1-(2'-Amino-4',5'-dimethoxy-α-oxobenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (16). The keto imine (15, R = NO_2) was dissolved in acetone (20 cm^3), and iodomethane (15 cm^3) was added. The mixture was refluxed gently on a steam bath for 24 h, the solvent and excess iodomethane were evaporated at reduced pressure, and the residue was crystallized from methanol to give bright, orange-red crystals: mp 169–171 °C; 3.74 g (6.90 mmol). Anal. Calcd for $C_{21}H_{23}IN_2O_7$: C, 46.49; H, 4.20; I, 23.43. Found: C, 46.59; H, 4.43; I, 23.59. The imine methiodide (2.0 g, 3.7 mmol) was dissolved in absolute methanol (350 cm^3) and the solution placed in a Parr bottle. Hydrogenation was effected with 5% Pt/C catalyst at about 2 atm of hydrogen to yield **16** (1.11 g, 2.95 mmol, 78%) which was purified by TLC (silica gel, 4:4 benzene/THF v/v); IR (KBr) λ_{max} 1695 cm^{-1} (C=O). For the corresponding acetate from acetic anhydride, M^+ was at *m/e* 428 (calcd *m/e* 428).

1,2,9,10-Tetramethoxy-4-oxoaporphine (17). The Pschorr Cyclization. The amine **16** (4.00 g, 7.38 mmol) was dissolved in glacial acetic acid (30 cm^3), and concentrated sulfuric acid (7 cm^3) was added, dropwise, to the stirred solution. After about 0.5 h at room temperature, sodium nitrite (1.20 g, 17.39 mmol) in water (3 cm^3) was added dropwise. This solution was allowed to stir at room temperature for 45 min and sulfamic acid (0.60 g) was added to destroy the excess sodium nitrite. After an additional 10 min, the reaction mixture was diluted with acetone (100 cm^3), and freshly prepared, EDTA-activated, Gatterman copper was added with vigorous stirring. Foaming and evolution of gas was observed and, 10 min later, the reaction mixture was heated to reflux for 0.5 h on a steam bath. The cooled reaction mixture was filtered through Celite, the residue was washed with fresh acetone until the washings were colorless, the acetone was removed at reduced pressure, and the remaining aqueous solution was cooled and made basic with aqueous ammonia. The basic reaction mixture was continuously extracted with ether for 24 h, the ether was removed at reduced pressure, and the residue was chromatographed on neutral alumina (200 g, Woelm, activity grade II; column dimensions 3 × 48 cm). Elution with benzene–ether yielded papaveraldine [**20**: 50 mg; mp 208 °C (lit.[34] mp 208–209 °C)], identical with an authentic sample (IR, UV, TLC) obtained from the Aldrich Chemical Co., Milwaukee, WI, and elution with chloroform–ether yielded *N*-methylcorydaldine [**19**: 80 mg; mp 125–126 °C (lit.[35] mp 125–126 °C)], identical with an authentic sample (IR, TLC) independently prepared. Further elution with chloroform–ether yielded the presumed ketone **21** [50 mg; mp 191–192 °C (ethanol); mass spectrum, *m/e* 354 M^+ calcd 354); IR λ_{max} 1663 cm^{-1} (C=O); ^1H NMR (Me_4Si) 3.79 (OCH_3, 3 H, s), 3.92–3.94 ppm (3 OCH_3, 9 H); Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.79; H, 5.65. Found: C, 67.84; H, 5.78.], an unidentified ketone

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[13 mg; mp 212 °C dec; IR (KBr) λ_{max} 1650 cm^{-1} (C=O); ^1H NMR (Me_4Si) 7.56 (s, 1 H), 7.27 (s, 1 H), 7.16 (s, 2 H), 3.90 (s, 6 H), 3.80 ppm (s, 6 H); mass spectrum, *m/e* 198 (M^+)], and the oxoaporphine **17**: 420 mg; mp 225–228 °C (lit.[36] mp 235–236 °C) UV (ethanol) λ_{max} 244 nm (log ε 4.46), 273 (4.43), 365 (4.04); identical with an independently prepared sample.[37] With chloroform–methanol, corunnine [**18**: 95 mg; mp 254–256 °C (lit.[38] mp 255–257 °C)] was obtained. This material was identical (IR, TLC) with a sample independently prepared.[15]

7-Hydroxyglaucine. The finely powdered oxoaporphine **17** (400 mg, 1.14 mmol) was suspended in iodomethane (15 cm^3) under argon. The suspension was heated to 40–45 °C for 12 h, and the solvent was evaporated under reduced pressure to give violet crystals of the iodide (545 mg, 1.11 mmol, 97%). The methiodide could not be prepared by using methyl iodide in acetone; only corunnine (**18**) resulted from such reactions. The oxoaporphine methiodide (580 mg, 0.92 mmol) was suspended in absolute methanol (15 cm^3), and potassium borohydride (270 mg, 5.0 mmol) was added in one portion. As the vigorous reaction occurred, the suspended methiodide gradually dissolved. Four subsequent additions of potassium borohydride (270 mg each) were made at 10-min intervals, and, when the last addition had been made, the reaction mixture was allowed to stir for an additional 15 min. The reaction mixture was concentrated at reduced pressure to about half its original volume, the residue was suspended in chloroform and washed several times with water to remove inorganic impurities, and the chloroform layer was dried and evaporated to dryness at reduced pressure. Preparative TLC on silica gel (cyclohexane/THF/Et_2NH, 5:5:1) yielded (R_f 0.4) the desired racemic 7-hydroxyglaucine (**5a** and its mirror image; 205 mg, 0.55 mmol, 60%). A second, slow-moving band (R_f 0.3) consisted of what is presumed to be the product of demethylation, 1,7-dihydroxy-2,9,10-trimethoxyaporphine: ^1H NMR (Me_4Si) 8.20 (s, 1 H), 7.30 (s, 1 H), 6.95 (s, 1 H), 6.52 (s, 1 H), 4.76 (d, 1 H, *J* = 2.5 Hz), 3.80–4.0 (s, 9 H), 2.60 (s, 3 H).

Hofmann Degradation of α- and β-Hydroxylaudanosine (2a,b and Their Mirror Images) Methiodides. Each methiodide was prepared by allowing excess methyl iodide to react at reflux with the corresponding base. Excess methyl iodide was then removed at reduced pressure. The iodides were crystallized from benzene–ethanol. α-Hydroxylaudanosine methiodide [**2a** and its mirror image; mp 170–171 °C (lit.[9] mp 168 °C)] and β-hydroxylaudanosine methiodide [**2b** and its mirror image; mp 226–227 °C (lit.[9] mp 223–225 °C)] were obtained. Each methiodide was allowed to decompose under the same conditions: 1.12 g (2.99 mmol) of the methiodide was suspended in aqueous 10% sodium hydroxide (40 cm^3), and the solution was brought to reflux and held there for about 12 h. On cooling, the two-phase reaction mixture was extracted with chloroform, the chloroform extract dried, and the solvent removed at reduced pressure. A small amount of polymeric material (320 mg) was present at the water/chloroform interface. The oily residue obtained on removal of the chloroform slowly deposited white powdery crystals (162 mg; mp 240 °C) identified as *N,N*-dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydroxide by comparison with a sample prepared independently by methylation of the known tetrahydroisoquinoline and exchange of iodide for hydroxide by treatment with silver oxide. Infrared, mass, and nuclear magnetic resonance spectra were superimposable. The remaining oil was separated by preparative TLC (silica gel, 10% methanol in chloroform) to yield veratraldehyde (**23**, 38 mg), veratryl alcohol (230 mg), and *N,N*-dimethyl 6-vinylveratrylamine (**22**, 166 mg). The remaining aqueous solution was made slightly acidic with dilute (6 N) hydrochloric acid and continuously extracted with chloroform. Removal of the chloroform at reduced pressure left white crystals (188 mg) of veratric acid.

Hofmann Degradation of 7-Hydroxyglaucine (5a) Methiodide. The amino alcohol **5a** (200 mg, 0.54 mmol) was dissolved in acetone (4 cm^3), and iodomethane (3 cm^3) was added. The mixture was brought to reflux, and the progress of the reaction was followed by TLC until all of the starting material was consumed (2 h). The solvent and excess methyl iodide were removed at reduced pressure, and the residue was crystallized from methanol to yield the corresponding methiodide, mp 207–208 °C dec. Anal. Calcd for $C_{22}H_{28}INO_5$: C, 51.47; H, 5.50; N, 2.73. Found: C, 51.28; H, 5.58; N, 2.75. This methiodide (198 mg, 0.39 mmol) was suspended in aqueous sodium hydroxide (10%) and the suspension brought to reflux. Dissolution of the methiodide slowly took place, and an oily layer appeared on the surface of the aqueous phase. After 12 h, the reaction mixture was cooled, diluted with water (10 cm^3), and extracted several times with an equal volume of chloroform. The combined chloroform extracts were dried and concentrated at reduced pressure, and the trace of water remaining was removed by azeotropic distillation with absolute ethanol. The residue was crystallized form methanol (137 mg, 0.37 mmol, 95%) and was identified as the styrene **24**: UV (ethanol) λ_{max} 335 nm (10000), 300 (16660), 265 (58880); mass spectrum, *m/e* 367 (M^+), 352 ($M^+ - CH_3$), 336 ($M - OCH_3$).

Hofmann Degradation of 13-Hydroxyxylopinine (8a) Methiodide. 13-Hydroxyxylopinine[16] (Figure 5; 500 mg, 1.35 mmol) was dissolved in methyl iodide (15 cm^3) and acetone (15 cm^3) and the solution brought to reflux. After 4 h, the white crystalline mass was allowed to cool, and the crystals were removed by suction filtration: mp 226–227 °C; 592 mg (1.15 mmol, 85%). The methiodide (592 mg, 1.15 mmol) was suspended in 10% aqueous sodium hydroxide (25 cm^3) and the suspension heated to reflux for 10 h, at which time all of the solid had disappeared, and an oil was observed on the surface of the aqueous solution. After cooling to room temperature, the oil was dissolved in chloroform and the remaining aqueous solution extracted twice with an equal volume of chloroform. The combined chloroform extracts were dried and the solvent removed at reduced pressure. The residue was chromatographed by preparative TLC (silica gel, 1:1 chloroform/ethyl acetate) to yield three mobile materials (R_f 0.93, 0.59, 0.39). The first two bands (368 mg, 84%) proved identical and were demonstrated to be the zwitterionic alkene **25**: mass spectrum, *m/e* 381 (M^+); mp 206–207 °C (recrystallized from ethanol). Anal. Calcd for $C_{22}H_{23}NO_5 \cdot CH_3CH_2OH$: C, 67.45; H, 6.80; N, 3.28. Found: C, 67.83; H, 6.82; N, 3.40. 13-Hydroxydehydroxylopinine (**26**) was prepared by oxidative dehydration of 13-hydroxyxylopinine (**8a**) to dehydroxylopinine chloride followed by reduction of the immonium double bond to 13,14-dehydroxylopinine and oxidation with *m*-chloroperbenzoic acid to **26**.[27]

Oxalyl chloride (0.77 cm^3, 8.8 mmol) was dissolved in dichloromethane (10 cm^3). Dimethyl sulfoxide (1.3 cm^3, 16.8 mmol), dried by distillation over calcium hydride, in dichloromethane (2 cm^3) was added, dropwise, to the stirred solution. After 5 min, 13-hydroxyxylopinine (**8a**; 925 mg, 2.5 mmol) in dichloromethane (25 cm^3) was added over 15 min, and, after a further 15 min, triethylamine (5.4 cm^3, 38.6 mmol) was added. The solution was allowed to warm to room temperature overnight. Water (20 cm^3) was added, and the solution was filtered. The filtrate was extracted with dichloromethane, the dichloromethane extract was combined with the original organic extract and dried with calcium chloride, and the solvent was removed at reduced pressure. The residue crystallized from methanol to yield dehydroxylopinine chloride: 820 mg (2.1 mmol, 84%); mp 206 °C. Anal. Calcd for $C_{21}H_{22}NO_4Cl$: C, 65.12; H, 5.68. Found: C, 65.15; H, 5.55.

The chloride (895 mg, 2.54 mmol) was suspended in pyridine (25 cm^3) and, with stirring, sodium borohydride (90 mg) was added. After the mixture was stirred for an additional 20 min, a second 90-mg portion of sodium borohydride was added and the solution stirred for an additional 20 min. The entire reaction mixture was poured into ice and the aqueous mixture allowed to come to room temperature. Filtration of the aqueous solution yielded a solid which was recrystallized from 95% ethanol and identified as 13,14-didehydroxylopinine: 570 mg (1.61 mmol, 63%); mp 179–181 °C. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.39; H, 6.52. Found: C, 71.30; H, 6.50. Addition of *m*-chloroperbenzoic acid (1.2 mmol) dissolved in dichloromethane (25 cm^3) to a dichloromethane (25 cm^3) solution of 13,14-dehydroxylopinine (353 mg, 1.0 mmol) under an atmosphere of nitrogen at −78 °C followed by gradual warming of the solution to room temperature over a period of 12 h, extraction of the reaction mixture with water

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saturated with sodium chloride, drying by filtration, and removal of the solvent at reduced pressure yielded an orange residue. Recrystallization from 95% ethanol containing a trace of hydrogen chloride yielded 13-hydroxy-14-dehydroxylopinine (**26**): 253 mg (0.63 mmol, 63%); mp 262–263 °C; MS, *m/e* 367 (M^+). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.64; H, 5.72; N, 3.81. Found: C, 68.58; H, 5.70; N, 3.84.

(B) X-ray Structure Determinations. Certain experimental procedures and manipulations of data are common to the structure determinations and are as follows.

Three-dimensional X-ray diffraction data were collected from single crystals with a computer-controlled four-circle diffractometer by using the variable θ–2θ scan technique and monochromatized X radiation. The raw data were corrected for geometric factors and placed on an absolute scale prior to use in structure solution. The structures were solved by Patterson and Fourier methods. The positional and thermal parameters of nonhydrogen atoms were refined by a full-matrix least-squares procedure using isotropic and then anisotropic temperature factors. Hydrogen atoms which could be located from difference Fourier maps were refined isotropically, as were solvent molecules of crystallization. Idealized positions for hydrogen atoms not so located were included in structure factor calculations with isotropic temperature factors equivalent to those of the atoms of attachment, but their parameters were not refined. The quantity minimized in the refinements was $\sum w(||F_o| - |F_c||)^2$, with the weight $w = 1/\sigma^2(F)$. Values for $\sigma(F)$ were obtained from the relation $\sigma(F) = (F/2)[(\sigma^2(I)/I^2) + \delta^2]^{1/2}$, where I is the integrated intensity observed, $\sigma(I)$ is derived from counting statistics, and δ is the instrumental uncertainty determined from the variation in intensities of standard reflections periodically measured during the data collections. Computer programs used were written in the Molecular Structure Laboratory of the Institute for Cancer Research,[28-30] and the atomic scattering factors are from a collection of published values.[31]

β-Hydroxylaudanosine. The hydrobromide of β-hydroxylaudanosine ($C_{21}H_{28}BrNO_7$, fw 454.37) is monoclinic: space group *Cc*, $a = 10.727$ (2) Å, $b = 27.901$ (7) Å, $c = 7.152$ (2) Å, $\beta = 97.52$ (2)°, $V = 2121.8$ (9) Å^3, $Z = 4$, $\lambda_{CuK} = 1.5418$ Å, $d_{calcd} = 1.42$ g cm^{-3}, $\mu_{CuK} = 31.06$ cm^{-1}, $\delta = 0.025$.

Data were collected for 1990 unique reflections in the θ range 0–69° with a minimum scan rate of 2° min^{-1} on a crystal 0.20 × 0.15 × 0.30 mm in dimensions. The data were corrected for X-ray absorption by using the ellipsoid of revolution approximation, giving 1964 data above the observation threshold of $I \geq 3.0\sigma(I)$. The final residuals are $R = 0.039$ and $R_w = 0.055$.

7-Hydroxyglaucine. The methanol solvate of 7-hydroxyglaucine methiodide ($C_{22}H_{28}INO_5 \cdot CH_4O$, fw 545.42) is triclinic: space group $P\bar{1}$, $a = 11.085$ (2) Å, $b = 19.835$ (3) Å, $c = 10.795$ (2) Å, $\alpha = 94.49$ (1)°, $\beta = 96.52$ (1)°, $\gamma = 83.66$ (1)°, $V = 2338.5$ (6) Å^3, $Z = 4$, $d_{calcd} = 1.55$ g cm^{-3}, $\lambda_{CuK} = 1.5418$ Å, $\mu_{CuK} = 107.72$ cm^{-1}, $\delta = 0.029$.

Data were collected for 8712 unique reflections in the θ range 0–69° on an irregularly shaped crystal having maximum dimensions of 0.45 × 0.40 × 0.20 mm. Half of the data were collected with a minimum scan rate of 2° min^{-1}. This was increased to 6° min^{-1} for the rest when it was noted that the crystal, which was transparent at the beginning of the data collection, gradually became opaque, presumably the result of loss of methanol. This was reflected in a gradual falling off in the intensities of the standard reflections. Accordingly, the data were corrected for this decay as a function of time. An empirical X-ray absorption correction as a function of ρ also was applied as part of the data-reduction process which gave 7541 reflections above the observation threshold of I $3.0\sigma(I)$. The final residues are $R = 0.087$ and $R_w = 0.113$.

13-Hydroxyxylopinine. Crystals of 13-hydroxyxylopinine methiodide hemihydrate hemimethanolate [$2(C_{22}H_{28}INO_5) \cdot CH_4O \cdot H_2O$, fw 1076.81] are triclinic: space group $P\bar{1}$, $a = 11.668$ (6) Å, $b = 20.644$ (7) Å, $c = 10.512$ (6) Å, $\alpha = 97.94$ (4)°, $\beta = 109.28$ (4)°, $\gamma = 75.90$ (3)°, $V = 2313$ (2) Å^3, $Z = 2$, $d_{calcd} = 1.55$ g cm^{-3}, $\lambda = 0.7107$ Å, $\mu_{MoK} = 13.04$ cm^{-1}, $\delta = 0.022$. Data were collected for 8652 unique reflections on a crystal 0.28 × 0.26 × 0.08 mm in size in the θ range 0–25.5° with a minimum scan rate of 1° min^{-1}. The final residuals for the 6350 data above the observation threshold $I \geq 1.0\sigma(I)$ are $R = 0.087$ and $R_w = 0.072$.

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Registry No. (±)-**2a**, 83527-59-7; (±)-**2a** methiodide, 83527-62-2; (±)-**2b**, 83527-60-0; (±)-**2b**·HBr, 83527-61-1; (±)-**2b** methiodide, 83527-63-3; (±)-**5a**, 77520-88-8; (±)-**5a** methiodide methanolate, 83511-46-0; (±)-**8a**, 59414-58-3; (±)-**8a** methiodide hemihydrate hemimethanolate, 83527-66-6; **13** (R = H), 139-76-4; **13** (R = NO_2), 2129-52-4; **14** (R = H), 6957-27-3; **14** (R = H) picrate, 72527-23-2; **14** (R = NO_2), 16251-41-5; **15** (R = H), 20345-69-1; **15** (R = H) methiodide, 20345-96-4; **15** (R = NO_2), 77513-48-5; **15** (R = NO_2) methiodide, 77538-74-0; **16**, 83511-44-8; **17**, 5574-24-3; **17** methiodide, 55974-08-8; **18**, 34421-18-6; **19**, 6514-05-2; **20**, 522-57-6; **21**, 83511-49-3; **22**, 52728-08-2; **23**, 120-14-9; **24**, 83511-48-2; **25**, 83511-47-1; **26**, 83511-51-7; *N,N*-dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydroxide, 83527-64-4; dehydroxylopinine chloride, 30045-17-1; 13,14-didehydroxylopinine, 55276-83-0; 3,4-dimethoxyphenethylamine, 120-20-7; (3,4-dimethoxyphenyl)ethanoyl chloride, 10313-60-7; (4,5-dimethoxy-2-nitrophenyl)ethanoic acid, 73357-18-3; 1,7-dihydroxy-2,9,10-trimethoxyaporphine, 83511-50-6; veratryl alcohol, 93-03-8; veratric acid, 93-07-2.

Supplementary Material Available: Tables of atomic parameters for β-hydroxylaudanosine hydrobromide, 7-hydroxyglaucine, and 13-hydroxyxylopinine as well as observed and calculated structure factors (90 pages). Ordering information is given on any current masthead page.

Contribution of Lipophilicity to the Performance of Crown Ethers. Effect of Bulk and Shape of the Lipophilic Substituents

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15-Crown-5 and 18-crown-6 ethers bearing substituents on the ether ring have been studied as catalysts for the Finkelstein reaction and as agents for solubilization of alkali metal picrates in *n*-heptane. All of these substituted crown ethers form stable complexes with Na^+ and K^+. These with highly lipophilic substituents are much more effective than the parent unsubstituted crown ethers as catalysts and as solubilizing agents. Both types of activity are affected by the bulk and the shape of the lipophilic substituent.

Crown ethers have a dual functionality, with lipophilic segments on the outside of the ring and a polar segment on the inside that can form strong complexes with alkali metal cations. Consequently, the crown ethers can solu-

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