stirred twice in 1 mL of methanol (0 °C) for 5 min, filtered, washed with 1 mL of methanol (0 °C), and dried. This third crop contained 281 mg (10%) of **2**, mp 188–190 °C. The residue (951 mg) from the filtrate and washings was purified by chromatography on 65 g of silica gel, using chloroform/methanol (15:1). A solution of the recovered material (688 mg) in 0.7 mL of *n*-butyronitrile and 1 mL of chloroform was stored for 24 h at 5 °C. The precipitate that separated was collected, suspended in 1 mL of methanol (0 °C) and stirred for 5 min, filtered, washed with 1 mL of methanol (0 °C), and dried to yield a fourth crop of **2**:[14] 130 mg (5%), mp 186–189 °C. The total yield of crystalline **2** was 2.048 g (73%). The material of the second crop (1.096 g, mp 189–191 °C) was recrystallized from 6 mL of *n*-butyronitrile. After being stored for 5 h at 0 °C, the precipitate was filtered, washed with 1.5 mL of cold *n*-butyronitrile and 1.5 mL methanol (0 °C), and dried for 12 h in vacuo to give 350 mg of analytically pure *cis*-**1**: mp 190–192 °C; $[\alpha]^{26}_D$ + 87.5° (*c* 0.85, Me_2SO, 4.5 min, after adding the material); $[\alpha]^{26}_D$ +74.9° (*c* 0.85, Me_2SO, after 3 and 20 h); NMR (Me_2SO-d_6) δ 2.2–4.0 (m, 6 H, C_3-H_2, C_4-H_2, C_1-CH_2), 3.73 (s, 6 H, 2 OCH_3), 5.34 (dd, 1 H, *J* = 8, 4 Hz, C_1-H), 6.64 (s, 2 H, Ar H), 6.69 and 7.02 (2 s, 1 H each, ArH), 7.94 (s, NCHO) 8.6–9.2 (m 2 H, OH); IR (KBr) 3440 (m), 3150 (br), 2840 (w), 1638 (s), 1595 (m), 1573 (w), 1500 (s), 1443 (m), 1433 (m), 1402 (m), 1377 (w), 1362 (w), 1344 (w), 1308 (w), 1284 (m), 1266 (m), 1246 (m), 1227 (m), 1206 (m), 1192 (m), 1107 (m), 1043 (w), 1020 (m), 980 (w), 956 (w), 898 (w), 868 (m), 848 (w), 836 (w), 807 (m) cm^{-1}; MS, *m/e* 421, 423 (M^+).

Anal. Calcd for $C_{19}H_{10}BrNO_5$: C, 54.05; H, 4.75; N, 3.32. Found: C, 54.02; H, 4.94; N, 3.24.

NMR (Me_2SO-d_6) data of *trans*-**2** obtained from a sample containing *cis*- and *trans*-**2**: δ 2.2–4.0 (m, 5 H, C_4-H_α, C_3-H_2, C_1-CH_2), 3.73 (s, 6 H, 2 OCH_3), 4.21 (d, 1 H, *J* = 13, C_4-H_β), 4.65 (t, 1 H, *J* = 7.7 Hz), C_1-H), 6.67 (s, 2 H, Ar H), 6.78 and 7.10 (2 s, 1 H each, Ar H), 7.41 (s, 1 H, NCHO), 8.6–9.4 (m, 2 H, OH).

Optical Rotations of the Pure Rotamers of 2. From the data shown in the table, the specific rotations of the pure cis and trans rotamers of **2** were calculated as +93° and +67°, respectively. These are the averages of the values calculated from six different combinations of the four results.

(*S*)-(+)-6′-Bromo-*N*-norreticuline Hydrochloride Hydrate. A. From Pure *cis*-2. A solution of 99 mg (0.23 mmol) of *cis*-**2** in 3 mL of CH_3OH and 1 mL of 37% HCl was refluxed during 20 h. After evaporation of the solvents, the residue was stirred in 1.5 mL of boiling H_2O for 10 min. After being ice-cooled for 45 min, the crystalline material was filtered, washed with H_2O (2 × 0.5 mL), and dried in vacuo overnight to give 72 mg (69%) of **3**·HCl·H_2O, mp 221–223 °C. Recrystallization from 2-propanol/H_2O (4:1) gave analytically pure material: mp 222–224 °C; $[\alpha]^{22}_D$ +49.1° (*c* 0.70, CH_3OH); NMR (Me_2SO-d_6) δ 2.2–4.0 (m, 6H, C_1-CH_2, C_2-H_2), 3.74 and 3.78 (2 s, 3 H each, 2 OCH_3), 4.45 (m, 1 H, C_1-H), 6.51, 6.74, 6.97 and 7.14 (4 s, 1 H each, $C_{2'}$-H, $C_{5'}$-H, C_5-H, C_8-H), 8.6–9.9 (m, 4 H, C_2-$^+NH_2$, 2 OH); MS, *m/e* 393/395 (M^+).

Anal. Calcd for $C_{18}H_{20}BrNO_4$·HCl·H_2O: C, 48.17; H, 5.16; N, 3.25. Found: C, 48.05; H, 5.20; N, 2.94.

B. From a 2:1 Trans–Cis Rotamer Mixture of 2. a solution of 100 mg (0.24 mmol) of a 2:1 trans–cis rotamer mixture of **2** was treated as under method A to yield 75 mg (71%) of **3**·HCl·H_2O, mp 221–223 °C, $[\alpha]^{23}_D$ +49.3° (*c* 0.69, CH_3OH).

Acknowledgment. We thank Dr. V. Toome, Physical Chemistry Department, Hoffman-La Roche, Inc., Nutley, NJ, for the ORD measurements. Appreciation is also expressed to Mr. William Landis for mass spectra and to Ms. Paula Parisius and Alice Wong for combustion analysis.

Registry No. **1**, 72274-69-2; **2** (rotamer 1), 75879-36-6; **2** (rotamer 2), 75879-37-7; **3**·HCl, 19777-93-6.

Supplementary Material Available: Tables of atomic parameters (2 pages). Ordering information is given on any current masthead page.

A Stereochemical Model of the *Veratrum* Alkaloids

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Received March 12, 1982

A stereoselective synthesis beginning from the tetracyclic isoxazolidine **3** gave an inactive model (**2**) of rings D–F of the hypotensive *Veratrum* alkaloids (**1**). Cleaving, N-demethylating, and epimerizing **3** gave the amino alcohol **5a**. Diazotizing **5a** afforded lactamdiol **10**, which retained the configuration of the carbinamine carbon of **5a**. Reduction of the lactam of **10** yielded **2**. Single-crystal X-ray analysis of **2** confirmed the assignment of relative stereochemistry at C_{6a} and C_{11} of **2** and established that the solid-state conformation was all-chair.

Structure **1** (Table I) depicts the common stereochemistry and sites of oxygenation of three *Veratrum* alkaloids of the cevine class. Natural and semisynthetic esters of **1** are potent, orally active hypotensive agents having a central mechanism of action but undissociated side effects of nausea and vomiting. The relations of the structures of the alkaloids to their emetic activities remain unknown, but Kupchan and Flacke summarized the facts associating the structures and hypotensive activities: "the number, nature, and the positions of the esterifying acids are of importance in determining the degree of hypotensive activity".[1] More highly esterified alkamines are more potent, but esterification or oxidation at C_{16} reduces hypotensive activity.[1]

Reduced potency correlated to chemical changes of the C_{16}-hydroxyl group suggests it composes a pharmacophore mediating intrinsic activity. Such a pharmacophore might also comprise the C_{20}-hydroxyl group and the unshared electrons of the atom of nitrogen, which are the only other polar β-substituents of **1**. These axial neighboring groups might effect hypotensive activity exclusively, while other

(1) Kupchan, S. M.; Flacke, W. E. In "Antihypertensive Agents"; Schittler, E., Ed., Academic Press; New York, 1967; pp 429–458.

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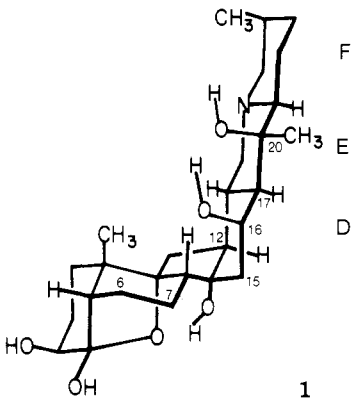
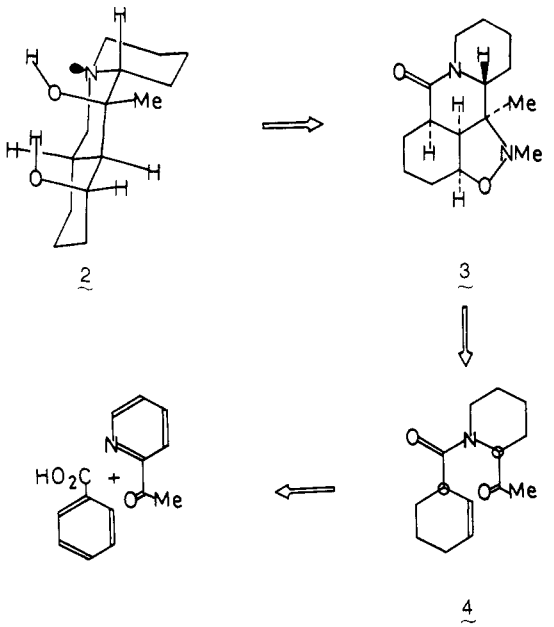
Table I. Common Stereochemistry and Sites of Oxygenation of *Veratrum* Alkamines



1

alkamine	α-positions of extra hydroxyls	
veracevine (1a)		12, 17
germine (1b)	7, 15	
protoverine (1c)	6, 7, 15	

Scheme I



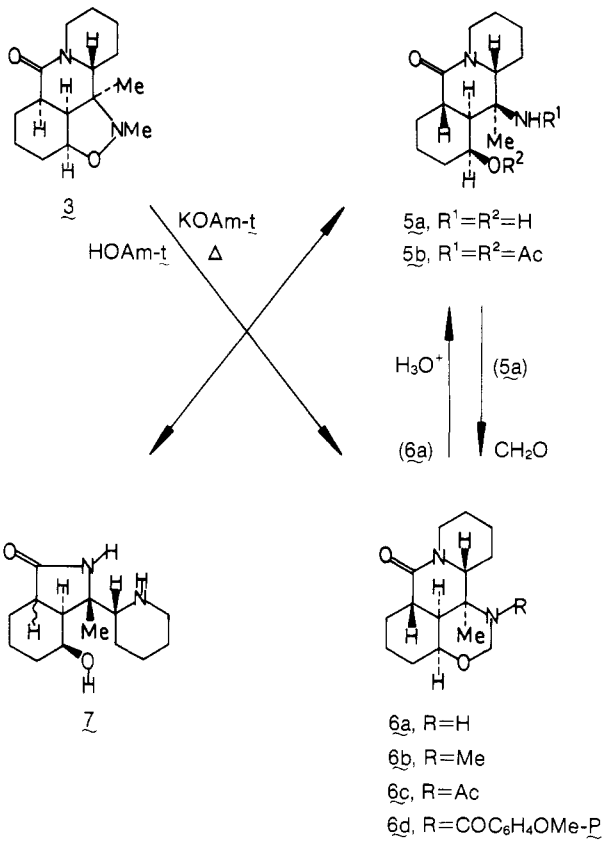
2 3 4

parts of the molecule might cause emesis. To discover hypotension without emesis, we made a stereochemical model (**2**, Scheme I) of rings D, E, and F of the *Veratrum* alkaloids (**1**).[2]

Results and Discussion

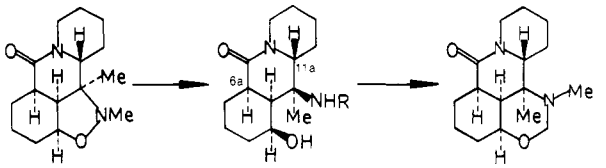
Ketalization and catalytic reduction of 2-acetylpyridine followed by amidation of the product with 2-cyclohexenoyl chloride and hydrolysis formed the diastereomeric pair of ketones **4**.[3] Diastereoselective cycloaddition of one *N*-methylnitrone of ketones **4** then gave the tetracyclic isoxazolidine exclusively.[3] The illustrated absolute stereochemistry (**3**) of the racemic isoxazolidine dictated the synthesis of **2**, since only one epimerization was needed if exchange of oxygen for nitrogen occurred with retention of configuration. Both enantiomers needed reduction, cleavage of the N–O bond, N-demethylation, and epimerization, and modifying LeBel's conditions[5] for cleaving isoxazolidines met the last three needs. Hot KO-*t*-Am in *t*-AmOH changed **3** to a mixture containing **5a** and **6a** predominantly (Scheme II). The mixture also contained the intramolecular transamidation product **7**. Chromatographing the mixture gave **5a**, **6a**, and **7** in a ratio of 3:1:1, while crystallizing separated **5a** and **6a** from **7**. Fractional crystallization also separated the acetic acid salt of **5a** from that of **6a**. Treatment of a mixture of **5a** and **6a** with dimedone in acidic, aqueous ethanol hydrolyzed **6a** to **5a**

Scheme II



3 5a, $R^1=R^2=H$ 5b, $R^1=R^2=Ac$ 7 6a, R=H 6b, R=Me 6c, R=Ac 6d, R=COC_6H_4OMe-*p*

Scheme III



3 8a, R=Me 8b, R=H 9

(2) (a) References 2b–m include all acknowledged models of cevine *Veratrum* alkaloids known to us as well as other compounds having related structures. (b) Tani, C.; Ishibashi, K. *J. Pharm. Soc. Jpn.* **1956**, *76*, 1064–1067. (c) Sam, J.; Plampin, J. N. *J. Am. Chem. Soc.* **1960**, *82*, 5205–5209. (d) Bradsher, C. K.; Yarrington, N. L. *J. Org. Chem.* **1960**, *25*, 294–295. (e) Flouret, J. R. Dissertation, University of Wisconsin, Madison, WI, 1963; *Diss. Abstr.* **1963**, *24*, 1408. (f) Kupchan, S. M.; Flouret, G. R.; Matuszak, C. A. *J. Org. Chem.* **1966**, *31*, 1707–1712. (g) Kupchan, S. M.; Balon, A. D. J.; De Grazia, C. G. *Ibid.* **1966**, *31*, 1713–1716. (h) Kupchan, S. M.; De Grazia C. G. *Ibid.* **1966**, *31*, 1716–1720. (i) Sam, J.; Nobles, D. *J. Pharm Sci.* **1967**, *56*, 729–731. (j) Sam, J. *Ibid.* **1967**, *56*, 1360–1361. (k) Sam, J.; Vacik, D. N.; Aboul-Enein, M. N. *Ibid.* **1971**, *60*, 936–939. (l) Mathison, I. W.; Solomons, W. E.; Jones, R. H. *J. Org. Chem.* **1974**, *39*, 2852–2855. (m) Mathison, I. W.; Solomons, W. E.; Jones, R. H. *J. Heterocycl. Chem.* **1975**, *12*, 165–167.

(3) Brambilla, R.; Friary, R.; Ganguly, A.; McPhail, A. T. Onan, K. D.; Puar, M. S.; Sunday, B. R.; Wright, J. J. *Tetrahedron* **1981**, *37*, 3615–3625.

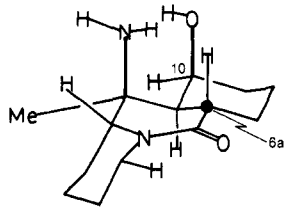
(4) All chiral compounds prepared in this work were racemic, but only one enantiomer is shown.

(5) LeBel, N. A.; Lajiness, T. A.; Ledlie, D. B. *J. Am. Chem. Soc. 1967*, *89*, 3076–3077.

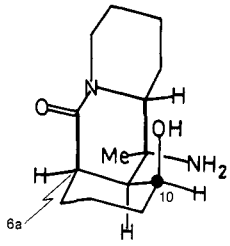
Table II. ^{13}C NMR Chemical Shifts of Chiral Carbons of 5a and 8a[a]

compd	δ value				
	C_{6a}	C_{10}	C_{10a}	C_{11}	C_{11a}
5a (≡**5c**)	43.8	72.7	35.0	52.0	66.2
8b (≡**8c**)[b]	50.6	67.2	35.2	51.7	65.3

[a] $CDCl_3$. [b] δ values from ref 3.



5c (≡**5a**)



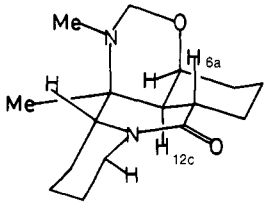
8c (≡**8b**)

(75% from **3**) and precipitated the dimedone–formaldehyde adduct. Potassium *t*-butoxide in hot *t*-BuOH incompletely epimerized **3** without cleaving it.

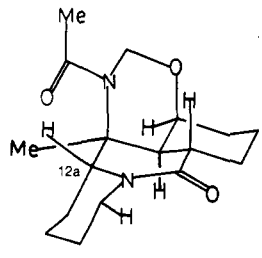
Assignments of the 6- and 5-lactam structures of **5a**, **6a**, and **7** followed from IR and ^{13}C NMR spectroscopy. The 6-lactam carbonyls absorbed at lower frequencies and resonated at higher fields than did the 5-lactam carbonyl group of **7**. Microanalysis and mass and ^1H and ^{13}C NMR spectra distinguished **5a** from **6a**; moreover, **5a** formed a diacetate (**5b**) and a cyclic urethane. Interconverting **5a** and **6a** confirmed the structural assignments and showed that **5a** and **6a** had the same relative stereochemistry. Formaldehyde closed **5a** to **6a** (86%; HOAc, H_2O, MeCN) while dilute HCl opened **6a** to **5a** (75%; 2 days, reflux).

Converting **5a** to **6b**, and converting **3** to **9** via **8a** (Scheme III), showed that epimerization α to the lactam carbonyl had been realized in **5a**. Condensation and reductive methylation (CH_2O, $Na(CN)BH_3$) changed **5a** to **6b**; hydrogenolysis of **3** followed by condensation of the resulting **8a** with formaldehyde gave **9**. Comparison proved that **6b** differed from **9** (mp, IR, ^{13}C and ^1H NMR). Comparing **5a** to **8b**[3] showed that the site of epimerization was C_{6a} of **5a**. The C_{10} resonance of **8b** was 5.5 ppm upfield of that in **5a**, while the C_{6a} resonance of **5a** was 6.8 ppm upfield of that in **8b** (Table II). Stereomodels (**5c** = **5a** vs. **8c** = **8b**) explained that 1,3-synaxial shieldings[6] of C_{6a} in **5a** and of C_{10} in **8b** caused the upfield shifts.

^1H NMR spectroscopy confirmed the assignments of β stereochemistry to the protons α to the lactam carbonyls of **6b**, **6c**, and **11**. The H_{6a} resonance of **6b** was downfield from that of **9** ($\Delta\delta \geq 0.4$ ppm) consistent with van der Waals interactions (cf. **6e** = **6b**).[7] We expected no such

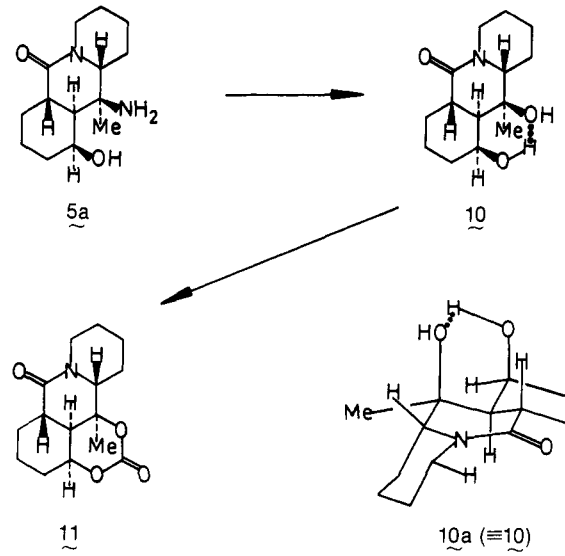


6e (≡**6b**)



6f (≡**6c**)

Scheme IV



5a **10** **11** **10a** (≡**10**)

deshielding in **9**. The H_{6a} resonances of **6b** and **6c** were triplets of doublets with axial–axial couplings ($J_{6a-12c} = J_{6a-6\alpha} = 12$ Hz). Irradiation located the H_{12c} resonance of **11**, which was a doublet of doublets with $J_{6a-12c} = 13$ Hz. Anisotropy of the acetamide carbonyl[8] of **6c** deshielded the resonance of H_{12a} to δ 5.4 from values of δ 3.02 (**6a**) and 3.42 (**6b**). ^{13}C NMR spectroscopy supported the assignment of the 5.4-ppm resonance; irradiation at the H_{12a} frequency collapsed the doublet resonance of C_{12a} to a singlet. Coplanarity of H_{12a} and the acetamide carbonyl group in a stereomodel of **6f** (= **6c**) explained the Δδ values.

Diazotizing **5a** in dilute aqueous acetic acid exchanged nitrogen for oxygen with retention of configuration (Scheme IV). Lactam diol **10** resulted (21%) after a workup including nitrogen ebullition.[9] Material balance did not exceed 57%, but neither crystallization nor chromatography yielded any acetate or any diol save **10**. IR dilution experiments showed that **10** was intramolecularly H bonded, implying that its C_{11}–OH was β. Intramolecular H bonding in the C_{11} epimer of **10** was unlikely since two rings would be boat-shaped, while in **10** these rings may be chair-shaped (cf. **10** = **10a**).

Lactam diol **10** formed the cyclic carbonate **11**, but formation of **11** did not evidence the β stereochemistry of the C_{11}–OH of **10**. Although all rings of **10** and **11** except the lactams were chair-shaped in models, the ^1H NMR spectrum of **11** showed that $H_{9\alpha}$ and the lactam carbonyl were not coplanar as expected.[8] Both the chemical shift and pattern of the $H_{9\alpha}$ resonance of **11** (δ 4.27 (br d of t) were different from those (δ 4.76 (br d) of the corresponding $H_{4\alpha}$ resonance of **10**. Carbonate **11** had suffered an unknown conformational change which might have been consistent with those expected for the C_{11} epimeric carbonate. A stereomodel of the C_{11} epimeric carbonate showed that three of its rings were boat-shaped.

Diazotization of **5a** also gave the isomeric olefins **12** (29%) and **13** (7%). Compound **12**—evidently a product of trans elimination—precipitated from the aqueous reaction mixture while chromatography isolated **13** (Scheme V). Microanalysis and mass spectroscopy distinguished **12**–**13** from **10**, and ^1H NMR spectroscopy distinguished **12** from **13**. The spectrum of **12** showed a vinylmethyl

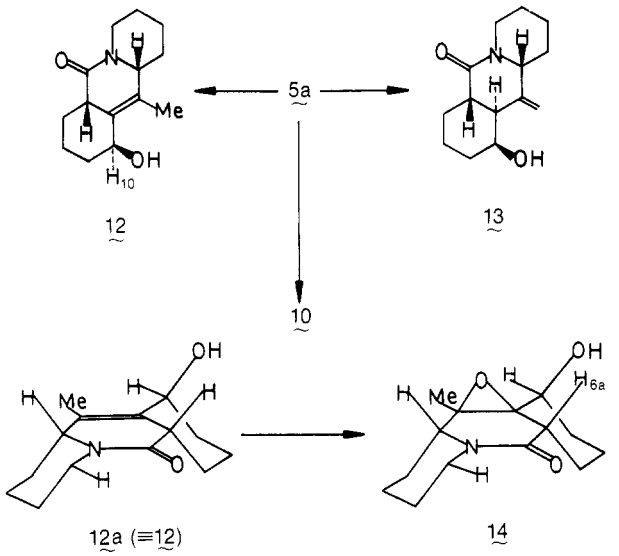
(6) Wehrli, F. W.; Wirtlin, T. "Interpretation of Carbon-13 NMR Spectra"; Heyden and Son; Philadelphia, 1978; p 27.

(7) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: New York, 1969; p 71.

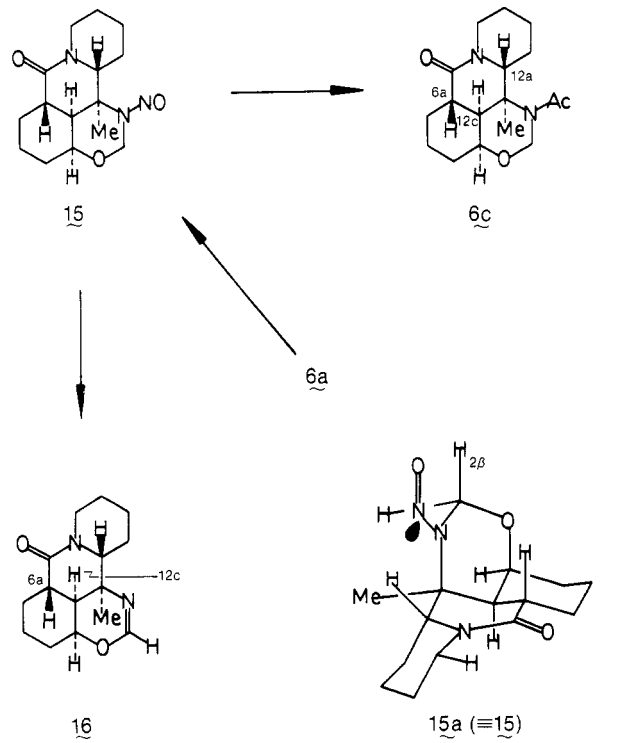
(8) Reference 7, p 240.

(9) Cohen, T.; Botelho, A. D.; Janowski, E. J. *J. Org. Chem.* **1980**, *45*, 2839–2847.

Scheme V



Scheme VI



doublet (δ 1.92 ($J_{CH_3\text{-}12a}$ = 1 Hz) but lacked olefin signals. Anisotropy of the olefin of **12** deshielded H_{10} to $\delta \geq 4.7$ (cf. $\delta_{H_{10}}$ = 4.35 in **10**). The vinylmethylene protons of **13** resonated at δ 5.14, but the spectrum of **13** lacked any methyl resonance. Epoxidizing **12** to **14** (*m*-CPBA, 70%) confirmed the distinction between **12** and **13**. The H_{6a} resonance of **14** was a doublet of doublets (δ 3.16 ($J_{6a\text{-}7\alpha}$ = 13.0, $J_{6a\text{-}7\beta}$ = 4.0 Hz), showing that C_{10a} was quaternary. Crowding on the concave face of **12** and a hydroxyl group on the convex face may have conspired to give the foreseeable β-epoxide **14** exclusively.[10] Excess $LiAlH_4$ in boiling THF (60 h) had no effect on **14** (TLC, IR).

Diazotizing a sample of **5a** contaminated with **6a** yielded compound **15** as well as **10**, **12**, and **13** (Scheme VI). Nitrosating **6a** alone gave 75% of **15**, and two further

(10) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; p 304.

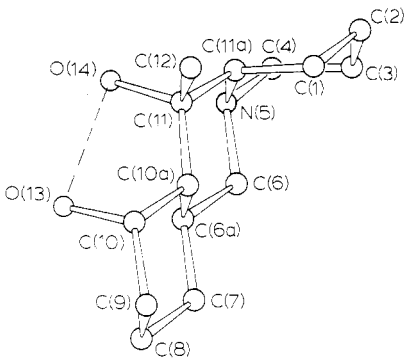
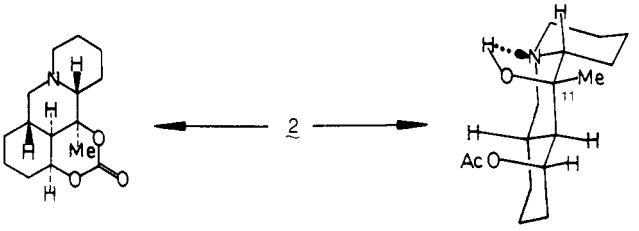


Figure 1. Structure and solid-state conformation of **2**.

experiments confirmed our structural assignment. Acetic anhydride and (dimethylamino)pyridine (140 °C, 69 h) transacylated **15** to **6c** (71%),[11] while pyrolysis of **15** (Al_2O_3, 235 °C (0.1 mmHg)) afforded **16** (22%).[12] Anisotropy of the *N*-nitroso group of **15** (= **15a**) deshielded the signal of $H_{2\beta}$ (δ 6.17 (d, $J_{2\alpha\text{-}2\beta}$ = 11 Hz) by 1.7 ppm relative to that of $H_{2\alpha}$.[13]

Excess $LiAlH_4$ reduced lactam diol **10** to the crystalline amino diol **2** (70%), which formed a carbonate (**17**) and



a monoacetate (**18**). IR dilution experiments showed that **18** was intramolecularly H bonded, presumably through a six-membered ring including the syn amino and hydroxyl groups.[14] Such H bonding would imply that the C_{11} hydroxyl groups of **2** and **18** were β axial. The C_{11} epimer of **18** would have not shown intramolecular H bonding of its anti amino and hydroxyl groups,[14] yet our dilution experiments did not exclude H bonding of the acetate carbonyl through an eight-membered ring to the α-equatorial hydroxyl group. Crystallography answered the question of the relative stereochemistry of **2** and **18**, however.

Single-Crystal X-ray Analysis of 2

Confirmation of the structure and relative stereochemistry of **2** was obtained by single-crystal X-ray analysis, which also provided details of the solid-state conformation. A structure model, derived by routine application of

(11) Belyaev, E. Yu.; Tovbis, M. S.; Suboch, G. A.; El'tsov, A. V. *Zh. Org. Khim.* **1976**, *12*, 466–467.

(12) Baldwin, J. E; Barton, D. H. R.; Gutteridge, N. J. A.; Hartin, R. J. *J. Chem. Soc. C* **1971**, 2184–2192.

(13) Karabatsos, G. J.; Taller, R. A. *J. Am. Chem. Soc.* **1964**, *86*, 4373–4378.

(14) (a) Crabb, T. A.; Newton, R. F.; Jackson, D. *Chem. Rev.* **1971**, *71*, 109–126. (b) Skvortsov, I. M. *Russ. Chem. Rev.* **1979**, *48*, 262–281.

(15) C_{11a} of **2** was not epimerized. Compounds **2** and **17** were unchanged by 10% Pd on C (H_2 at 60 psi, HOAc, 25 °C; 6 and 28 days);[16] 10% Pt on C (H_2 at 60 psi, HOAc, 25 °C, 5 days) also had no effect on **2**.[17]

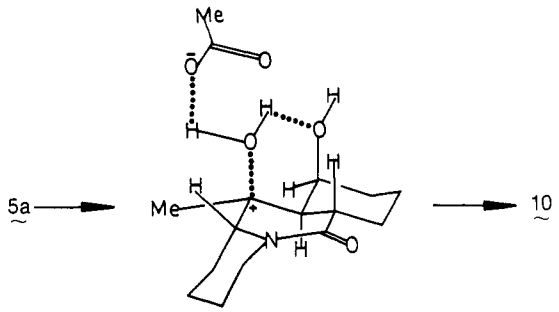
(16) Mandell, L.; Sing, K. P.; Gresham, J. T.; Freeman, W. J. *J. Am. Chem. Soc.* **1965**, *87*, 5234–5236.

(17) Ochial, E.; Okuda, S.; Minato, H. *J. Pharm. Soc. Jpn.* **1952**, *72*, 781–784; *Chem. Abstr.* **1954**, *48*, 2724.

MULTAN76,[18] was refined by least-squares methods to R[19] = 0.060 over 1615 statistically significant reflections. Final atomic positional parameters for the non-hydrogen atoms are in Table III (supplementary material).[20] That all three six-membered rings in **2** have chair conformations[21] in the solid state is evident from the view provided in Figure 1, which also shows the atom numbering scheme. Bond lengths and angles are presented in Figure 2 (supplementary material); a complete list of torsion angles is provided in Table IV (supplementary material).[20] The axially oriented hydroxy substituents are involved in an intramolecular O_{14}–H_{14}···O_{13} hydrogen bond (O_{14}···O_{13} 2.692 Å), and intermolecular O_{13}–H_{13}···N_5 hydrogen bonds (O_{13}···N_5 2.794 Å) between molecules related by crystallographic 2_1 screw axes associate molecules of **2** in the crystal.

Conclusion

Alcohols formed from amines may be nitrosated during diazotization but may be regenerated by passing gaseous nitrogen through the reaction mixtures.[9] Unless the alcohols are regenerated, the ratio of retained to inverted alcohol may be erroneous.[9] Despite nitrogen ebullition, diazotization of **5a** afforded only one C_{11}-oxygenated



[19]

product (**10**). Intramolecular H bonding in the water-separated ion pair[25] (**19**) may account for the retention of configuration realized in **10** and for the absence of stereoisomeric acetates in the mixture of products formed by diazotization of **5a**.

Although the hydroxyls and the nitrogen lone-pair electrons of **2** were cis and β axial as desired, the C_{11a} stereochemistry of **2** was epimeric to that of the corresponding carbon of the *Veratrum* alkaloids, and **2** was not a pharmacological model of these alkaloids. Administered intravenously to conscious, normotensive dogs in doses ranging from 0.0032 to a high of 3.2 mg/kg, racemate **2** had neither hypotensive nor emetic activity. Oral doses of **2** (10 and 75 mg/kg) left the blood pressures and heart rates of spontaneously hypertensive rats unchanged.

Experimental Section

General Methods. Uncorrected melting points were determined on a Kofler block (Thomas Model 40). IR spectra (ν (CH_2Cl_2), cm^{-1}) were recorded on a Perkin-Elmer 727B spectrophotometer, ^1H and proton-decoupled ^{13}C NMR spectra (δ, downfield from Me_4Si, $CDCl_3$ solutions except as noted, coupling constants in Hz) on Varian CFT-20, EM-390, and XL-100 instruments, and medium-resolution mass spectra on a Varian CH5 spectrometer. E. Merck or Analtech supplied silica gel plates for TLC; developed plates were visualized in I_2 vapor (Merck) or (Analtech) by spraying with 5% H_2SO_4–MeOH and charring. For column chromatography, silica gel (0.063–0.200 mm) was purchased from E. Merck and used at the rate of 100 g/g.

1,11bα-Dimethyl-2aα,3,4,5,5aβ,8,9,10,11,11aβ,11b,11cα-dodecahydro-2*H*-isoxazolo[5,4,3-*kl*]benzo[*b*]quinolizin-6-one. A solution of **3** (1.50 g), KO-*t*-Bu (0.355 g), and *t*-BuOH (15 mL) was boiled for 42 h at reflux under N_2, cooled, poured into H_2O (100 mL), and extracted with $CHCl_3$ (10 × 20 mL). The combined extracts were washed with H_2O and brine, dried (Na_2SO_4), and filtered; the solvent was evaporated to give a mixture of **3** and the product (TLC). Chromatography on silica gel and elution with 2% MeOH–$CHCl_3$ gave the product, mp 105.5–106.5 °C after crystallization (Et_2O); two similar experiments beginning with a total of 1.80 g of **3** yielded a total of 0.315 g (17%) of product: IR 1660; ^1H NMR 4.41 (br q, 12, 4, H_{2a}), 4.02 (d of t, 13, 5, 5, $H_{8\alpha}$), 3.67–3.33 (br m, 1 H), 3.23–2.79 (br m, 1 H), 2.74–2.26 (envelope) including 2.71 (s, NCH_3) (total of 5 H), 2.21–1.22 (envelope) including 1.16 (s, CCH_3) (total of 16 H); ^{13}C NMR 175.0 (s, C_6), 72.0 (d, C_{2a}), 70.1 (s, C_{11b}), 61.5 (d, C_{11a}), 56.8 (d, C_{11b}), 40.4 (q, NCH_3), 37.6 (d, C_{5a}), 37.0 (dd, C_8), 24.7 (t), 23.0, 22.4, 22.0, 19.7, 19.0, 17.9 (C_{3-5}, C_{9-11}, CCH_3); MS, m/e 264 (M^+, 1.7), 152 (100).

Anal. Calcd for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 68.42; H, 9.47; N, 10.78.

The relative stereochemistry of the product of mp 105.5–106.5 °C was not determined, so the assignment of 5aβ stereochemistry was tentative. Comparing the chemical shifts of the chiral carbons of **3** to those of the product suggested that only epimerization had occurred and C_{5a} of **3** was the most likely site of base-catalyzed epimerization.[3]

11β-Amino-10β-hydroxy-11α-methyl-1,3,4,6,6aβ,7,8,9,10,-10aα,11,11aβ-dodecahydro-2*H*-benzo[*b*]quinolizin-6-one (5a). (A) From Isoxazolidine 3. Isoxazolidine **3** (55.1 g, 0.208 mol) was added to a solution of KO-*t*-Am in HO-*t*-Am (prepared by heating potassium (10.1 g, 0.258 mol) in dry HO-*t*-Am (500 mL)), and the resulting solution was heated for 6 h under reflux in N_2. Isoxazolidine **3** had been consumed after 5 h (TLC). The cooled, dark red solution was poured into H_2O (1.4 L), and the layers were separated; the larger, lower layer (A) was reserved. The smaller, upper layer (B) was extracted with $CHCl_3$ (300 mL), the $CHCl_3$ extract was reserved, and the aqueous layer was combined with layer A. The resulting solution was extracted with $CHCl_3$ (250 mL, 5 × 150 mL), and *all* $CHCl_3$ extracts were combined. The $CHCl_3$ solution was washed with brine (2 × 150 mL), dried (Na_2SO_4), and filtered. Evaporation of solvent gave a solid mixture of **5a**, **6a**, and **7** (TLC). Crystallization (500 mL of EtOAc; charcoal) gave a mixture of **5a** and **6a** (44.57 g) free from **7** (TLC) in the first and third crops. The second crop (4.30 g) contained compound **7** predominantly, and the contaminants were **5a** and **6a** (TLC).

A sample (0.500 g) of the foregoing mixture of **5a** and **6a** in EtOH (2.5 mL), H_2O (2.5 mL), and HOAc (0.35 mL) was treated with dimedone (0.264 g) at 25 °C, and an exothermic reaction occurred, precipitating the dimedone–formaldehyde adduct (0.249 g) identified by comparison with an authentic sample by TLC. The acidified filtrate (pH 2) was extracted with $CHCl_3$ (2 × 10 mL), basified (pH 10), and extracted with $CHCl_3$ (5 × 10 mL). The 50-mL extract was washed (H_2O), dried (Na_2SO_4), and filtered. Removal of solvent gave a solid crystallizing (EtOAc) to give pure **5a** (0.360 g), which was identified by TLC, IR, and ^1H NMR comparison with an authentic sample. The remaining mixture (44.07 g) of **5a** and **6a** was treated with dimedone for 12 h at 5 °C and otherwise as above, and gave another 39.09 g of **5a**;

(18) Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declerq, J.-P. "MULTAN76, A System of Computer Programmes for the Automatic Solution of Crystal Structures"; Universities of York and Louvain, 1976.

(19) $R = \sum||F_o| - |F_c||/\sum|F_o|$.

(20) Supplementary material; see paragraph at end of paper.

(21) Endocyclic torsion angles, ω_{ij} (°), about the bonds between atoms C_i and C_j in the enantiomer shown in Figure 2 are as follows: $\omega_{1,2}$ −54.6, $\omega_{2,3}$ 54.0, $\omega_{3,4}$ −55.4, $\omega_{4,5}$ 55.7, $\omega_{5,11a}$ −55.8, $\omega_{1,11a}$ 56.1 in piperidine ring A; $\omega_{5,6}$ 60.6, $\omega_{6,6a}$ −56.6, $\omega_{6a,10a}$ 53.5, $\omega_{10a,11}$ −52.9, $\omega_{11,11a}$ 54.4, $\omega_{5,11a}$ −59.1 in piperidine ring B; $\omega_{6a,7}$ 55.1, $\omega_{7,8}$ −54.4, $\omega_{8,9}$ 55.0, $\omega_{9,10}$ −56.4, $\omega_{10,10a}$ 56.0, $\omega_{6a,10a}$ −55.3 in cyclohexane ring C.

(22) Miller, R. W.; McPhail, A. T. *J. Chem. Soc., Perkin Trans 2*, **1979**, 1527–1531.

(23) Cromer, D. T.; Waber, J. T. *Acta Crystallogr.* **1965**, *18*, 104–109.

(24) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175–3187.

(25) White, E. H.; Woodcock, D. J. In "The Chemistry of the Amino Group"; Patai, S., Ed.; Interscience: New York, 1968; pp 440 ff.

the total yield of **5a** from **3** was 75%.

Crystallized from $CHCl_3$–Et_2O, **5a** gave the analytical sample: mp 170–171 °C; IR 3375, 3300–3250, 1630; ^1H NMR 4.73 (br d, 13, H_{4eq}),[8] 4.21 (br q, 2, 5, H_{10}), 2.85 (br q, 13, H_{11a}), 3.1–0.8 (envelope) and 1.24 (s, CH_3) (total of 22 H including 2 exchangeable H); ^{13}C NMR: 170.8 (s, C_6), 72.7 (d, C_{10}), 66.2 (d, C_{11a}), 52.0 (s, C_{11}), 45.4 (dd, C_4), 43.8 (d, C_{6a}), 35.0 (d, C_{10a}), 32.4 (t), 29.9 (t), 28.0 (t), 25.5, 25.4, 20.0 (C_{1-3} and C_{7-9}), 23.1 (q, CH_3); MS, *m/e* 252 (M^+, 11.8), 235 (4.3), 234 (4.6), 140 (100).

Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.29; H, 9.69; N, 11.40.

Compound **5a** was also characterized as the diacetate **5b** (excess Ac_2O, Py, $CHCl_3$, reflux, 3 days): mp 227.0–229.5 °C (EtOAc); IR 3450, 1740, 1680, 1620; ^1H NMR: 6.15 (br s, NH) 5.43 (br m, $W_{h/2}$ = 7 Hz, H_{10}), 4.74 (d of t, 13, 2, 2, H_4e_q), 4.52 (dd, 12.5, 1.5, H_{11a}), 2.85–2.31 (envelope, 3 H including H_{4ax} and H_{6a}), 2.3–1.0 (envelope, 21 H) including 2.13 (s, $NCOCH_3$), 1.91 (s, $OCOCH_3$), 1.47 (s, CCH_3). Incremental treatment of **5b** with Eu^{3+} deshielded the signal of H_{4eq} more than any other, and double resonance experiments with **5b** in Me_2CO-d_6 confirmed the assignments of the H_{10} and H_{4eq} resonances. ^{13}C NMR 169.8 (s), 168.9 (s), 168.4 (s), (C_6, $NHCOCH_3$, $OCOCH_3$), 69.8 (d, C_{10}), 61.8 (d, C_{11a}), 55.7 (s, C_{11}), 45.0 (dd, C_4), 44.1 (d, C_{6a}), 36.0 (d, C_{10a}), 30.4, 29.2, 28.6, 25.6, 25.3, 24.9, 21.3, 20.4 (C_{1-3}, C_{7-9}, CCH_3, $OCOCH_3$, $NHCOCH_3$); MS, *m/e* 278 (29), 277 (M – OAc, 100).

Anal. Calcd for $C_{18}H_{28}N_2O_4$: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.00; H, 8.56; N, 8.27.

Compound **5a** was also characterized as the cyclic urethane, mp 315.5–316.5 °C (EtOAc), prepared with Im_2CO (THF, reflux, 1 h); IR 3420, 3340, 2950, 1700, 1660; ^1H NMR 7.14 (s, NH), 4.70 (br m, $W_{h/2}$ = 5 Hz, H_{3a}), 3.98 (d of t, 13, 4, 4, $H_{9\alpha}$), 3.4–3.0 (envelope, 2 H), 2.6–2.2 (envelope, 2 H), 2.2–1.6 (envelope), and 1.29 (s, CCH_3) (total of 15 H) (addition of Eu^{3+} shifted the spectrum of $H_{9\alpha}$ farther downfield than that of any other proton; ^{13}C NMR 171.0 (s, C_7), 155.7 (s, C_2), 72.8 (d, C_{3a}), 64.0 (d, C_{12a}), 54.4 (s, C_{12b}), 41.9 (d, C_{6a}), 41.3 (t, C_9), 35.8 (d, C_{12c}), 29.6 (t), 26.0, 25.6, 25.2, 23.5, 22.6, 19.8 (t) (C_{4-6}, C_{10-12}, CCH_3); MS, *m/e* 278 (M^+, 13.4), 84 (100).

Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.72; H, 7.97; N, 10.06. Found: C, 64.68; H, 7.98; N, 9.83.

The mixture of **5a**, **6a**, and **7** could also be resolved by chromatography over silica gel. Elution with $CHCl_3$–MeOH–NH_4OH (95:4.5:0.5) gave the most mobile component **6a**, mp 171.0–173.0 °C, after crystallization (Et_2O–CH_2Cl_2), followed by **5a**, mp 170–171 °C (Et_2O–CH_2Cl_2), and then **7**, mp 194–196 °C (Et_2O–CH_2Cl_2). The isolated ratio of **5a** to **6a** to **7** was 3:1:1 and was determined by combining and weighing fractions judged pure by TLC.

Fractional crystallization of acetic acid salts also resolved the mixture of **5a**, **6a**, and **7**. A sample (48.45 g) of the mixture suspended in MeCN (240 mL) containing HOAc (11.5 g) was crystallized to give white crystals (27.48 g) which formed **5a** exclusively on TLC (silica gel, $CHCl_3$–MeOH–NH_4OH, 95:4.5:0.5). Evaporation of MeCN from the filtrate followed by crystallization from EtOAc (50 mL) gave colorless crystals (18.39 g) which formed **6a** on TLC in the same solvent system with silica gel; the filtrate residue contained **7** (TLC), which was not isolated. The reason for the different ratio (1.5:1) of **5a** to **6a** was not determined.

(B) From Hydrolysis of 6a. A solution of **6a** (95 mg, 0.359 mmol) in 1 N HCl (25 mL) was boiled for 2 days under reflux, cooled, basified (pH 9), and extracted with $CHCl_3$ (5 × 10 mL). The combined extracts were washed with H_2O (10 mL), dried, and filtered; evaporation of solvent gave **5a** (71 mg, 75%), identified by IR. Crystallized from EtOAc, **5a** had mp 169.5–171.0 °C, mixed mp 169.0–171.0 °C with an authentic sample; the identity of **5a** from this experiment was also checked by 2-D thin-layer cochromatography with an authentic sample.

Compound **6a** was unaffected by 0.6 N HCl at 25 °C for 4 days and by 6 N HCl at 25 °C for 8 days; **6a** was recovered and identified by IR comparison.

12b-Methyl-1,2,3aα,4,5,6,6aβ,9,10,11,12,12aβ,12b,12cα-tetradecahydrooxazino[6,5,4-*kl*]be zo[*b*]quinolizin-7-one (6a). (A) From Isoxazolidine 3. Treatment of **3** with KO-*t*-Am as described above gave a mixture of **5a**, **6a**, and **7** from which chromatography isolated a pure sample of **6a**, mp 170–171 °C, after crystallization (Et_2O–CH_2Cl_2); IR 1630; ^1H NMR 4.86–4.38 (envelope, H_{9eq}, 2 H_2), 3.98 (br m, $W_{h/2}$ = 5 Hz, H_{3a}), 3.02 (dd, 12, 2, H_{12a}), 2.92 (t of d, 12, 12, 2, H_{6a}), 2.73–2.18 (envelope, 3 H), 2.19–1.00 (envelope) including 1.22 (s, CCH_3) (total of 15 H); ^{13}C NMR 171.7 (s, C_7), 74.3 (t, C_2), 69.3 (d, $C_{3a \text{ or } 12a}$), 68.8 (d, $C_{12a \text{ or } 3a}$), 51.4 (s, C_{12b}), 45.8 (dd, C_9), 42.9 (d, C_{6a}), 35.6 (d, C_{12a}), 31.3 (t), 29.0 (t), 26.2 (t), 25.6 (t), 24.6 (t), 21.3 (t) (C_{4-6}, C_{10-12}), 19.1 q, CCH_3); MS, *m/e* 264 (M^+, 3.8), 152 (100).

Anal. Found for $C_{15}H_{24}N_2O_2$: C, 67.94; H, 8.98; N, 10.92.

Compound **6a** was also characterized as the *p*-methoxybenzamide **6d**, mp 208.0–210.5 °C (EtOAc), prepared with *p*-$MeOC_6H_4COCl$ and $EtN(i\text{-}Pr)_2$ in CH_2Cl_2; IR 2940, 1640, 1600, 1510; ^1H NMR 7.61 (d, 9) and 6.92 (d, 9) (total of 4 H), 5.29 (d, 10.5, $H_{2\beta}$), 5.21 (br d, 11.4, H_{12a}), 4.83 (d, 10.5, $H_{2\alpha}$), 4.44 (br d of t, 13.5, H_{9eq}), 4.13 (br m, $W_{h/2}$ = 7.5 Hz, H_{3a}), 3.86 (s, OCH_3), 3.24 (t of d, 12, 12, 3, H_{6a}), 2.87–2.22 (envelope, 2 H), 2.22–1.00 (envelope) including 1.59 (s, CCH_3); MS, *m/e* 398 (M^+, 8.4), 235 ($M-C_9H_9NO_2$, 37.2), 234(66), 135 (100).

Anal. Calcd for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.15; H, 7.54; N, 7.00.

(B) From 5a. The amino alcohol **5a** (0.500 g, 1.98 mmol) was suspended in MeCN (5 mL), and HOAc (0.11 mL, 1.98 mmol) was added; the prisms of **5a** dissolved and were replaced in 5 min with a fine white precipitate. Formalin (0.156 mL, 2.08 mmol) was added, and the mixture was stirred 3 h at 25 °C; the precipitate dissolved, and the solution gave another precipitate in 1 min. The mixture was diluted with $CHCl_3$ (50 mL) and was washed with 1 N $NaHCO_3$ solution (10 mL) and with H_2O; the $CHCl_3$ solution was dried (Na_2SO_4) and filtered, and the solvent was evaporated. The crystalline residue was identified as **6a** by TLC and IR comparison with an authentic sample; crystallization (EtOAc) gave pure **6a** (0.450 g, 86%) as colorless prisms, mp 174.5–175.5 °C.

3-Methyl-4-hydroxy-3-(2′-piperidyl)-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindol-1-one (7). Treatment of **3** with KO-*t*-Am in HO-*t*-Am as described above gave a mixture of **5a**, **6a**, and **7** from which a pure sample of **7** was isolated by chromatography on silica gel. The analytical sample of **7** had mp 194–196 °C (Et_2O–CH_2Cl_2); IR 3410, 3300–3040, 1690, 1490–1450; ^1H NMR 6.83 (br s, OH, ex), 4.08–3.60 (br m, CHOH), 3.32–2.94 (br m, 2 H), 2.87–3.40 (envelope) including 1.37 (s, CCH_3) (total of 20 H); ^{13}C NMR 179.1 (s, C_1), 69.2 (d, C_4), 68.4 (d, C_2), 64.4 (s, C_3), 50.3 (d, C_{7a}), 47.4 (t, $C_{6'}$), 43.6 (t, $C_{3'}$), 31.1 (t), 27.7, 27.5, 26.6, 24.8 (t), 23.3 (t) ($C_{4'-6'}$ and C_{5-7}), 19.5 (q, CCH_3); MS, *m/e* 253 (M – 1, 2.2), 84 (100).

Anal. Found for $C_{14}H_{24}N_2O_2$: C, 66.74; H, 9.72; H, 10.92. The complete relative stereochemistry was not determined.

1,12bα-Dimethyl-1,2,3aα,4,5,6,6aβ,9,10,11,12,12aβ,12b,12cα-tetradecahydrooxazino[6,5,4-*kl*]benzo[*b*]quinolizin-7-one (6b). Formalin (37%, 0.297 mL, 3.96 (mmol) followed by Na(CN)BH_3 (41 mg, 0.66 mmol) was added to a solution of compound **5a** (500 mg, 1.98 mmol) in MeCN (5 mL) and HOAc (0.11 mL, 2 mmol); the reaction mixture was stirred for 18 h at 25 °C. The mixture was diluted with $CHCl_3$ (50 mL) and washed with 1 N $NaHCO_3$ (10 mL) and with H_2O (2 × 15 mL). The $CHCl_3$ solution was dried and filtered, and the solvent was evaporated; crystallization from Et_2O gave **6b** (388 mg, 70%) pure by TLC and ^1H NMR. The analytical sample showed the following: mp 174.0–177.0 °C (EtOAc); IR 1630; ^1H NMR 4.62 (br d, 12, H_{9eq}), 4.25 (s, 2 H_2), 3.94 (br m, $W_{h/2}$ = 6.5 Hz, H_{3a}), 3.42 (dd, 12, 2, H_{12a}), 3.24 (t of d, 12, 12, 2.5, H_{6a}), 2.60–2.20 (envelope, 3 H including H_{9ax}), 2.18–0.80 (envelope) including 2.09 (s, NCH_3) and 1.01 (s, CCH_3) (total of 17 H). Double resonance experiments confirmed the assignments of the H_{6a}, H_{3a}, and H_{9eq} resonances; a spectrum of **6b** in pyridine-*d*, also confirmed the assignments of the H_{6a}, H_{12a}, H_{9eq}, and H_{9ax} resonances. ^{13}C NMR 171.3 (s, C_7), 81.6 (t, C_2), 70.3 (d, C_{3a}), 63.0 (d, C_{12a}), 55.6 (s, C_{12b}), 45.8 (dd, C_9), 43.8 (d, C_{6a}), 36.1 (d, C_{12c}), 31.4, 30.9, 29.4, 26.6, 26.1, 24.8, 21.2 (t) (C_{4-6}, C_{10-12}, NCH_3), 11.6 (q, CCH_3); MS, *m/e* 278 (M^+, 2.0) 263 (M – CH_3, 1.8), 166 (100).

Anal. Calcd for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.06; H, 9.64; N, 10.28.

10β-Hydroxy-11β-(methylamino)-11α-methyl-1,3,4,6,6aα,7,8,9,10,10aα,11,11aβ-dodecahydro-2*H*-benzo[*b*]-quinolizin-6-one (8a). Isoxazolidine **3** (2.00 g, 7.56 mmol), 20% $Pd(OH)_2$ on C (2.00 g), and EtOH (100 mL) were shaken for 3 days at 25 °C under 60 psi of H_2. The catalyst was removed by

filtration, the solvent evaporated, and the residue crystallized (EtOAc) to give **8a** (1.29 g, 64%) pure by TLC. The analytical sample showed the following: mp 183.0–184.0 °C; IR 3500, 3400–3325, 1630; ^{1}H NMR 4.68 (br d, 12, H_{4eq}), 4.15 (br m, H_{10}), 2.89–3.09 (br m, 2 H), 2.72–3.34 (envelope) including 2.31 (s, $NHCH_3$) (total of 6 H), 2.04–1.00 (envelope) including 1.23 (s, CCH_3) (total of 16 H); ^{13}C NMR 172.2 (s, C_6), 66.2 (d, C_{10} or C_{11a}), 65.4 (d, C_{11a} or C_{10}), 54.8 (s, C_{11}), 44.3 (d, C_{6a}), 43.4 (dd, C_4), 34.9 (d, C_{10a}), 34.1 (t), 27.2, 26.4, 25.3, 24.9, 16.4 (t), (C_{1-3}, C_{7-9}), 28.1 (q, NCH_3), 22.1 (q, CCH_3); MS, *m/e* 266 (M^+, 10.2), 84%.

Anal. Calcd for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.52. Found: C, 67.99; H, 10.00; N, 10.73.

1,12bα-Dimethyl-1,2,3aα,4,5,6,6aα,9,10,11,12,12aβ,12b,12cα-tetradecahydrooxazino[6,5,4-*kl*]benzo[*b*]quinolizin-7-one (9). Formalin (37%, 0.1 mL, excess) was added to a suspension of compound **8a** (0.20 g, 0.75 mmol) in MeCN (5 mL) and HOAc (0.07 mL), and the resulting solution was washed with 1 N $NaHCO_3$ (2 × 10 mL) and with H_2O (2 × 10 mL). The solution was dried (Na_2SO_4) and the solvent evaporated; crystallization (EtOAc) gave **9** (122 mg, mp 144.5–148.0 °C, 58%). The analytical sample showed the following: mp 146.5–150.0 °C (EtOAc); IR 1620; ^{1}H NMR 4.70 (br d, 13, H_{9eq}), 4.27 (d, 14, $H_{2\alpha}$ or $H_{2\beta}$), 4.19 (d, 14, $H_{2\beta}$ or $H_{2\alpha}$), 3.96 (br m, $W_{h/2}$ = 10 Hz, H_{3a}), 3.33 (br d, 11, H_{12a}), 2.80–1.02 (envelope) including 2.08 (s, NCH_3) and 1.09 (s, CCH_3) (total of 21 H); ^{13}C NMR 172.4 (s, C_7), 80.3 (t, C_2), 69.8 (d, C_{3a}), 61.6 (d, C_{12a}), 54.8 (s, C_{12b}), 46.5 (dd, C_9), 39.1 and 38.7 (C_{6a} and C_{12c}), 31.6 (t, NCH_3), 27.5, 26.3, 25.8, 25.4, 22.4 (t), 18.1 (t) (C_{4-6} and C_{10-12}), 12.4 (q, CCH_3); MS *m/e* 278 (M^+, 13.1), 167 (31.8), 166 (100).

Anal. Found for $C_{16}H_{26}N_2O_2$: C, 68.88; H, 9.48; N, 10.07.

The melting point and IR, ^{1}H NMR and ^{13}C NMR spectra of **9** were all differ from those of **6b**.

10β,11β-Dihydroxy-11α-methyl-1,3,4,6,6aβ,7,8,9,10α,10aα,-11,11aβ-dodecahydro-2*H*-benzo[*b*]quinolizin-6-one (10). Sodium nitrite (21.6 g, 0.313 mol) was added to a cold (ice bath) solution of amino alcohol **5a** (39.09 g, 0.155 mol) in H_2O (471 mL) and HOAc (18 mL). The reaction mixture was stirred for 5 h in the ice bath; after 2 and 4 h $NaNO_2$ (21.6 g) and HOAc (18 mL) were added, respectively. Nitrogen was passed through the mixture, and the precipitate (21.52 g of impure (TLC) olefin **12**) was collected by filtration. The combined aqueous filtrates were extracted with $CHCl_3$ (10 × 75 mL), and the combined extracts were washed with 1 N $NaHCO_3$ (3 × 50 mL), with H_2O (50 mL), and with brine (50 mL). The $CHCl_3$ solution was dried (Na_2SO_4) and filtered; the solvent was evaporated to give a yellow oil crystallizing from EtOAc to give diol **10** (8.20g, 21%, pure to TLC). The analytical sample showed the following: mp 217.0–218.0 °C (EtOAc); IR 3610 (sharp), 3500 (br), 3350 (br), 1620; ^{1}H NMR 4.76 (br d, 13, H_{4eq}), 4.35 (br m, $W_{h/2}$ = 7 Hz, H_{10}), 3.85 (s, ex, 10 H), 3.09 (br d, 11, H_{11a}), 2.9–2.2 (envelope, 4 H including H_{6a}), 2.2–0.8 (envelope, 15 H) including 1.32 (s, CCH_3); ^{13}C NMR 170.3 (C_6), 71.4 (C_{11}), 68.4 (C_{10}), 66.5 (C_{11a}), 44.2 and 44.5 (C_{6a} and C_4), 34.9 (C_{10a}), 33.0, 29.6, 27.6, 25.5 (2 coincident signals), 24.1, 19.9 (C_{1-3}, C_{7-9}, CCH_3); MS, *m/e* 253 (M^+, 7.7), 235 (M – H_2O, 3.7), 84 (100).

Anal. Calcd for $C_{14}H_{23}N_1O_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.13; H, 9.14; N, 5.51.

12bα-Methyl-3aα,4,5,6,6aβ,9,10,11,12,12aβ,12b,12cα-dodecahydrodioxa[6,5,4-*kl*]benzo[*b*]quinolizin-2,7-dione (11). Diol **10** was also characterized as the cyclic carbonate **11**, mp 182–184 °C, prepared from **10** with Im_2CO and NaOMe in THF; IR 1750, 1640; ^{1}H NMR 4.84 (br m, $W_{h/2}$ = 6.5 Hz, H_{3a}), 4.27 (br d of t (collapsed to a br d on irradiation at δ 2.4), 12.5, 12.5, 3, $H_{9\alpha}$), 3.48 (dd (collapsed to a d on irradiation at δ 2.4), 11, 3, H_{12a}), 2.93 (t of d (collapsed to a q on irradiation at δ 4.3), 12.5, 12.5, 4, $H_{9\beta}$), 2.5–2.0 (envelope, 4 H including $H_{10\alpha}$ and $H_{12\beta}$), 2.0–1.0 (envelope, 17 H) including 1.92 (dd (collapsed to a d on irradiation at δ 4.8), 13, 2.5, H_{12c}) and 1.46 (s, CCH_3); ^{13}C NMR 168.8 (s, C_7), 149.1 (s, C_2), 81.5 (s, C_{12b}), 74.4 (d, C_{3a}), 63.8 (d, C_{12a}), 42.7 (dd, C_9), 39.2 (d, C_{6a}), 35.3 (d, C_{12c}), 29.2 (t), 27.3 (t), 24.7, 24.0, 23.6, 19.9 (t) (C_{4-6} and C_{10-12}), 22.9 (q, CCH_3); MS; *m/e* 279 (M^+, 21), 192 (12), 84 (100).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.42; H, 7.42; N, 4.95.

10β-Hydroxy-11-methyl-1,3,4,6,6aβ,7,8,9,10α,11aβ-decahydro-2*H*-benzo[*b*]quinolizin-6-one (12). Another diazotization of amino alcohol **5a** (9.86 g) similar to that above, then extraction of the reaction mixture (without filtration) with $CHCl_3$, and aqueous workup gave a mixture which was chromatographed on silica gel. $CHCl_3$–MeOH–concentrated aqueous NH_3 (95:4.5:5) eluted pure **12** (TLC) (1.63 g after crystallization from EtOAc) third and then a mixture of diol **10** and **12** from which another 0.77 g of **12** could be obtained by fractional crystallization from EtOAc. The yield of olefin **12** was 29% (corrected for the amount of **6a** that contaminated the starting amino alcohol **5a**; the amount of the contaminant was determined from the amount of nitrosooxazine **15**, which was eluted first). The analytical sample of **12** showed the following: mp 171–173 °C (EtOAc); IR 3620, 3540–3240, 1630; ^{1}H NMR 4.9–4.6 (envelope, H_{4eq} and H_{10}), 3.50 (br d, 11, H_{11a}), 3.07 (br d, $J_{6a-7\alpha}$ = 12 Hz, H_{6a}), 2.7–0.8 (envelope, 17 H) including 1.68 (d, 1.5, $CHCH_3$); ^{13}C NMR (169.2 (C_6), 131.7 and 123.0 (C_{10a} and C_{11}), 65.4 (C_{10}), 63.0 (C_{11a}), 42.8 (C_4), 38.2 (C_{6a}), 33.8, 33.5, 33.2, 25.5, 25.2, 20.4, 14.5 (C_{1-3}, C_{7-9}, CCH_3); MS, *m/e* 235 (M^+, 73), 220 (M – CH_3, 35), 218 (M – OH, 18), 217 (M – H_2O, 36), 176 (100).

Anal. Calcd for $C_{14}H_{21}N_1O_2$: C, 71.45; H, 8.99; N, 5.95. Found: C, 71.52; H, 8.82; N, 5.80.

10β-Hydroxy-11-methylene-1,2,3,4,6aβ,7,8,9,10α,10aα,11aβ-undecahydro-2*H*-benzo[*b*]quinolizin-6-one (13). Compound **13** (0.81 g (after crystallization), 7% from 48.0 mmol of **5a**) was eluted fourth from silica gel by 95:4.5:0.5 $CHCl_3$–MeOH–concentrated aqueous NH_3; the complete order of elution was **15**, **13**, **12**, and **10**. The analytical sample of **13** showed the following: mp 172.5–173.0 °C (EtOAc); IR 3600, 3510–3325, 1630; ^{1}H NMR 5.14 (br d, CCH_2, 2 H), 4.76 (br d, 13, H_{4eq}), 4.40 (br s, $W_{h/2}$ = 10 Hz, H_{10}), 3.95–3.70 (br m, 1 H), 2.7–2.1 (envelope, 4 H), 2.1–1.0 (envelope, 12 H) including 1.80 (d, ex, OH); ^{13}C NMR 170.7 (C_{6a}), 145.2 (C_{11}), 108.9 (CH_2C_{11}), 65.6 (C_{10}), 63.2 (C_{11a}), 43.3 and 43.1 (C_4 and C_{6a}), 38.5 (C_{10a}), 36.4, 32.9, 28.6, 25.2, 25.1, 19.4 (C_{1-3}, C_{7-9}), MS; *m/e* 235 (M^+, 96), 220 (56), 206 (57), 164 (100).

Anal. Found for $C_{14}H_{21}NO_2$: C, 71.55; H, 9.06; N, 5.79.

10aβ,11β-Epoxy-10β-hydroxy-11aα-methyl-1,3,4,6,6aβ,7,-8,9,10,10aα,11,11aβ-dodecahydro-2*H*-benzo[*b*]quinolizin-6-one (14). *m*-Chloroperbenzoic acid (1.58 g, 85% purity) was added to a cold (ice bath) suspension of the olefin **12** (1.75 g, 0.744 mmol) and CH_2Cl_2 (17.5 mL); the resulting mixture was allowed to stir and to warm to 25 °C overnight. After 1 day, the reaction mixture was diluted with CH_2Cl_2 (50 mL), and the CH_2Cl_2 solution was washed with 1 N $NaHSO_3$, with 1 N $NaHCO_3$, and with brine. The solution was dried (Na_2SO_4) and filtered, and the solvent was evaporated. (In another experiment identical except for scale, a ^{1}H NMR spectrum of the residue at this stage was identical with that of a pure, crystalline sample of **14**). Crystallization from EtOAc gave colorless prisms of **14** (1.314g, 70%, pure by TLC). The analytical sample showed the following: mp 186.5–189.5 °C (EtOAc); IR 3600, 3500–3350, 1640; ^{1}H NMR 4.68 (br d, 13, H_{4eq}), 3.80 (br m, $W_{h/2}$ = 9 Hz, H_{10}), 3.47 (br d, 12, H_{11a}), 3.12 (dd, 13, 4, H_{6a}), 2.6–1.0 (envelope, 17 H) including 2.0 (s, ex, OH) and 1.42 (s, CCH_3); ^{13}C NMR 168.2 (s, C_6), 67.8 (s, C_{10a}), 67.6 (d, C_{10}), 62.8 (s, C_{11}), 61.5 (d, C_{11a}), 44.0 (dd, C_4), 40.0 (d, C_{6a}), 32.1 (t), 31.3 (t), 30.3 (t), 25.4 (2t), 18.7 (t) (C_{1-3}, C_{7-9}), 16.3 (q, CCH_3); MS, *m/e* 251 (M^+, 24), 84 (100).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.84; H, 8.24; N, 5.49.

Attempted Reduction of 14. Epoxide **14** (251 mg, 0.999 mmol) and $LiAlH_4$ (37 mg, excess) in THF (5 mL; dried by passage through Woelm Superbasic Al_2O_3) were boiled for 61 h under reflux under a $CaCl_2$ drying tube. TLC monitoring showed only **14**. The cooled mixture was worked up with H_2O (0.04 mL), 15% aqueous NaOH solution (0.04 mL), and H_2O (0.04 mL), diluted with Et_2O and EtOAc, and filtered through diatomaceous earth. The filtrate was washed with brine and dried (Na_2SO_4). Evaporation of solvents gave yellow crystals of **14** (203 mg), identified by IR.

12bα-Methyl-1-nitroso-1,2,3aα,4,5,6,6aβ,9,10,11,12,12aβ,-12b,12cα-tetradecahydrooxazino[6,5,4-*kl*]benzo[*b*]-quinolizin-7-one (15). Oxazine **6a** (500 mg, 1.89 mmol) was suspended in THF (3 mL) and H_2O (6 mL) and was cooled (ice bath); HOAc (0.44 mL) followed by NaNO2 (260 mg) was added. The resulting solution was allowed to stir and to warm to 25 °C overnight. The precipitate was collected, washed with H_2O, and dried to give **15** (414 mg, 75%, mp 211.5–213.5 °C). The analytical

sampled had mp 210.5–212.0 °C (EtOAc); IR 1640, 1080; ^{1}H NMR 6.17 (d, 11, $H_{2\beta}$), 4.7–4.3 (overlapping signals of $H_{9\alpha}$ and $H_{2\alpha}$) including 4.45 (d, 11, $H_{2\alpha}$) and 4.22 (br m, $W_{h/2}$ = 6 Hz, H_{3a}) (total of 3 H), 2.8–2.3 (envelope), 2.3–1.0 (envelope) including 1.87 (dd, 11.5, 1.5) and 1.55 (s, CCH_3) (total of 19 H); MS; *m/e* 293 (M^+, 9.4), 263 (M – NO, 13.2), 84 (100).

Anal. Calcd for $C_{15}H_{23}N_3O_3$: C, 61.41; H, 7.90; N, 14.32. Found: C, 61.47; H, 7.75; N, 14.13.

1-Acetyl-12bα-methyl-1,2,3aα,4,5,6,6aβ,9,10,11,12,12aβ,-12b,12cα-tetradecahydrooxazino[6,5,4-*kl*]benzo[*b*]-quinolizin-7-one (6c). *N*-Nitrosooxazine **15** (700 mg, 2.39 mmol) dissolved in Ac_2O (3.5 mL) containing 4-(dimethylamino)pyridine (30 mg, 2.39 mmol) was heated for 3 days under reflux, cooled, diluted with toluene, and filtered. The filtrate was combined with that from a similar experiment beginning with 100 mg of **15**, and the solvents were evaporated. The residue was chromatographed over silica gel, and 99:1 $CHCl_3$–MeOH eluted compound **6c** (591 mg, 71%, pure by TLC and ^{1}H NMR). The analytical sample showed the following: mp 154–157 °C (Et_2O); IR 1660, 1630; ^{1}H NMR: 5.5–5.2 (overlapping resonances of H_{12a} and $H_{2\alpha}$ or $H_{2\beta}$ 2 H) including 5.43 (br d, 2, $^1/_2$ of the dd of H_{12a}) and 5.25 (d, 9, $H_{2\beta}$ or $H_{2\alpha}$), 4.26 (br d of t, 13, $H_{9\alpha}$), 4.06 (br m, $W_{h/2}$ = 6 Hz, H_{3a}), 2.89 (t of d, 12, 12, 3, H_{6a}), 2.7–2.4 (envelope, $H_{9\beta}$ and H_{12c}), 2.10 (s, $COCH_3$) and 2.0–1.1 (envelope) including 1.44 (s, CCH_3). The resonance of H_{12a} of **6c** appeared at δ 5.37 (dd, 12, 2) in CD_3CN. ^{13}C NMR 171.2 (s), 170.8 (s) (C_7 and $COCH_3$), 74.9 (t (s on irradiation at δ 5.3), C_2), 70.7 (d, C_{3a}), 62.0 (d (s on irradiation at δ 5.3), 59.5 (s, C_{12b}), 45.2 (dd (d on irradiation at δ 2.9), C_9), 43.5 (d (s on irradiation at δ 2.9), C_{6a}), 36.1 (d (s on irradiation at δ 2.9), C_{12c}), 30.5, 29.8, 26.6, 25.9, 25.3, 24.7, 21.0 (t) ($COCH_3$, C_{4-6}, C_{10-12}), 17.9 (q, CCH_3); MS, *m/e* 306 (M^+, 18), 235 (35), 234 (86), 151 (100).

Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.67; H, 8.92; N, 9.03.

When a solution of nitrosooxazine **15** (300 mg) and NaOAc (250 mg) in Ac_2O (1.5 mL) was heated for 138 h at reflux, no reaction could be detected by TLC.

12bα-Methyl-3aα,4,5,6,6aβ,9,10,11,12,12aβ,12b,12cα-dodecahydrooxazino[6,5,4-*kl*]benzo[*b*]quinolizin-7-one (16). *N*-Nitrosooxazine **15** (750 mg, 2.56 mmol) in CH_2Cl_2 was mixed with Al_2O_3 (activity I, basic; 7.5 g) and the solvent evaporated. The residue was heated for 16 h at 235 °C (0.1 mmHg) (Kügelrohroffen temperature); the volatile product was washed from the air condenser with CH_2Cl_2, the solvent evaporated, and the residue crystallized to give **16** (146 mg, 22%), mp 154–158 °C (Et_2O). Recrystallization gave the analytical sample: mp 161.0–163.5 °C; IR 1630; ^{1}H NMR 7.07 (s, H_2), 4.65–4.30 (overlapping signals of H_{3a} and $H_{9\alpha}$), 3.39 (dd, 12, 2, H_{12a}), 2.8–2.2 (envelope, 2 H), 2.2–1.0 (envelope, 16 H) including 1.21 (s, CCH_3); ^{13}C NMR 170 (C_7), 149.7 (C_2), 69.9 (C_{3a}), 67.8 (C_{12a}), 53.0 (C_{12b}), 44.5 (C_9), 39.5 (C_{6a}), 36.2 (C_{12c}), 29.8, 28.7, 26.1, 25.0, 24.7, 20.5 (C_{4-6}, C_{10-12}, CCH_3); MS, *m/e* 262 (M^+, 23), 217 (45), 149 (59), 84 (100).

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.79; H, 8.56; N, 10.96.

10β,11β-Dihydroxy-11α-methyl-1,3,4,6,6aβ,7,8,9,10α,-10aα,11,11aβ-dodecahydro-2*H*-benzo[*b*]quinolizine (2). $LiAlH_4$ (2.45 g, excess) was added to a cold (ice bath) solution of lactam diol **10** (8.20 g, 27.8 mmol) and THF (80 mL; dried by passage through Woelm Superbasic Al_2O_3, activity I), and when evolution of gas had ceased the mixture was heated for 18 h under reflux under a $CaCl_2$ tube. The cooled mixture was treated with H_2O (2.45 mL), 15% aqueous NaOH (2.5 mL) and H_2O (2.5 mL). The resulting mixture was diluted with $CHCl_3$ and filtered through diatomaceous earth. The filtrate was washed with brine, and the brine was extracted with $CHCl_3$; the combined $CHCl_3$ extracts were dried (Na_2SO_4) and filtered. Evaporation of solvent gave a yellow oil (8.7 g) which was chromatographed on silica gel; $CHCl_3$–MeOH–concentrated aqueous NH_3 (90:9:1) eluted compound **2** (5.48 g, 70%, pure by TLC and ^{1}H NMR). A sample crystallized from EtOAc had mp 89.0–91.0 °C; IR 3440; ^{1}H NMR 4.42 (d, 2, ex, $C_{10}OH$), 3.1–2.1 (complex envelope, 2 H_4, 2 H_6, and H_{11a}), 2.1–0.9 (envelope, 17 H) including 1.22 (s, CCH_3); ^{13}C NMR: 73.6 (C_{11}), 68.8 (C_{10}), 65.9 (C_{11a}), 54.6 (C_4 or C_6), 50.8 (C_6 or C_4), 46.0, 33.2, 30.7, 30.4, 25.5, 22.3, 19.5, 18.3, 17.5; MS, *m/e* 239 (M^+, 9.9), 222 (M – OH, 3.4), 98 (100).

Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85%. Found: C, 70.52 and 70.41; H, 11.01 and 11.11; N, 5.83 and 5.83. An acceptable value for hydrogen was not obtained.

12bα-Methyl-3aα,5,6,6aβ,7,9,10,11,12,12aβ,12b,12cα-dodecahydro-2*H*,4*H*-[1,3]benzodioxino[4,4a,5-*ab*]-quinolizin-2-one (17). Compound **2** was characterized as the carbonate **17**, mp 173.0–174.5 °C (EtOAc), which **2** and Im_2CO in THF at 25 °C formed; IR 1730; ^{1}H NMR 4.80 (br m, $W_{h/2}$ = 6 Hz, H_{3a}), 3.1–2.3 (envelope, 6 H including 2 H_7, 2 H_9, and H_{12a}), 2.3–1.0 (envelope, 16 H) including 1.36 (s, CCH_3); MS, *m/e* 265 (M^+, 42), 237 (M – CO, 16%), 220 (237 – OH, 17), 83 (100).

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 68.02; H, 8.64; N, 5.25.

10β-Acetoxy-11β-hydroxy-11α-methyl-1,3,4,6,6aβ,7,8,9,-10α,10aα,11,11aβ-dodecahydro-2*H*-benzo[*b*]quinolizine (18). Compound **2** gave the acetate **18**, mp 138 °C (EtOAc), with Ac_2O and Py; IR 3480, 1720; ^{1}H NMR: 5.40 (br m, $W_{h/2}$ = 6 Hz, H_{10}), 3.27 (s, $C_{11}OH$), 2.4–1.8 (envelope, 6 H including 2 H_4, 2 H_6, and H_{11a}), 1.8–0.9 (envelope, 19 H) including 2.01 (s, $OCOCH_3$) and 1.11 (s, CCH_3); MS, *m/e* 281 (M^+, 11), 238 (M – C_2H_3O, 25), 222 (31), 98 (100).

Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.41; H, 9.15; N, 5.10. An acceptable value for hydrogen was not obtained.

Attempted Epimerization of 2. (A) With 10% Pd on C.[16] The amino diol **2** (200 mg) in HOAc (10 mL) containing 10% Pd on C (200 mg) was shaken for 160 h at 25 °C in a Parr apparatus under 60 psi of H_2; the mixture was filtered and the solvent evaporated from the filtrate. The residue in H_2O was basified (pH 9) and extracted (CH_2Cl_2). The combined extracts were washed (H_2O), dried (Na_2SO_4), and filtered; evaporation of solvent and drying in vacuo gave **2** (139 mg), identified by TLC, IR, and ^{1}H NMR.

(B) With 10% Pt on C.[17] Compound **2** (200 mg) in HOAc (4 mL) containing 10% Pt on C (200 mg) was shaken in a Parr apparatus for 120 h at 25 °C. After a workup like that in part A above, compound **2** (196 mg) was recovered and identified by TLC, IR, and ^{1}H NMR.

Attempted Epimerization of 17. Carbonate **17** (200 mg) in HOAc (11 mL) containing 10% Pd on C (210 mg) was shaken for 28 days at 25 °C under 60 psi of H_2 in a Parr apparatus. The mixture was filtered, the solvent was evaporated, and the residue in $CHCl_3$ was basified with 1 N $NaHCO_3$. The $CHCl_3$ solution was washed with H_2O and brine, dried (Na_2SO_4), and filtered. Evaporation of solvent gave a yellow oil (330 mg, overweight) identified as **17** by TLC and IR.

IR Dilution Experiments. A solution of compound **10** showing $\nu(CH_2Cl_2)$ 3500 cm^{-1} was qualitatively diluted over an 8-fold concentration range, and the intensity of the 3500-cm^{-1} band was compared with those of bands at 2950 and 1640 cm^{-1}; both sets of ratios were constant. When a solution of **18** ($\nu(CH_2Cl_2)$ 3480 cm^{-1}) was qualitatively diluted over a 16-fold concentration range, the ratios of the intensities of the 3480 and 920-cm^{-1} bands were constant.

Biological Evaluation. (A) Conscious, Normotensive Dogs. Blood pressure and heart rate were measured in two conscious, normotensive dogs that were free to move about within their cages. Indwelling arterial and venous catheters were implanted with sterile technique at least 48 h prior to experimental studies. Dogs were fasted overnight before testing. The drug was given by intravenous infusion over 5 min at doses of 3.2, 10, 32, 100, 320, 1000, and 3200 μg/kg separated by 30-min intervals. In no instance was a reduction in blood pressure or heart rate observed; no untoward behavioral effects were noted.

B. Conscious, Spontaneously Hypertensive (SH) Rats. Blood pressure and heart rate were measured directly in two SH rats dosed orally with 10 mg/kg and in another two SH rats challenged with 75 mg/kg. Drugs were suspended in 0.4% methylcellulose and were administered by oral gavage. There was no effect in behavior, blood pressure, or heart rate at these doses.

X-ray Analysis of Compound 2

Crystal data are as follows for $C_{14}H_{25}NO_2$ (**2**): mol wt 239.4; monoclinic, a = 10.437 (5) Å, b = 8.663 (4) Å, c = 16.720 (8) Å, β = 114.31 (2)°, U = 1378 Å^3, Z = 4, d_{calcd} = 1.154 g cm^{-3}; Cu Kα radiation, λ = 1.5418 Å; absorption coefficient for Cu Kα radiation,

$\mu = 6.1$ cm^{-1}. Space group $P2_1/c(C_{2h}^5)$ was uniquely established from the systematic absences: $0k0$ when $k \neq 2n$, $h0l$ when $l \neq 2n$.

Crystallographic Measurements. Preliminary unit cell parameters and space group information were obtained from oscillation and Weissenberg photographs taken with Cu Kα radiation. For intensity measurements, a crystal of dimensions ca. 0.16 × 0.26 × 0.50 mm was oriented on an Enraf-Nonius CAD-3 automated diffractometer (Ni-filtered Cu Kα radiation), where values for all unique reflections with $\theta < 67°$ were recorded by means of the θ–2θ scanning procedure as described previously.[22] A total of 1615 observed [$I > 2.0\sigma(I)$] intensities were corrected for the usual Lorentz and polarization effects and used in the structure analysis. Refined unit cell parameters were derived by least-squares treatment of the diffractometer setting angles for 40 reflections widely separated in reciprocal space.

Structure Analysis. The structure was solved routinely by direct methods using the MULTAN76[18] suite of programs. Approximate positions for all non-hydrogen atoms were obtained from an E map based on the largest 250 $|E|$ values and phases that yielded the highest combined figure of merit. Three cycles of full-matrix least-squares adjustment of atomic positional and isotropic thermal parameters reduced R[19] to 0.15 from a value of 0.26 for the initial model. Variation of hydrogen atom positional and isotropic thermal parameters in addition to non-hydrogen atom positional and anisotropic thermal parameters in the subsequent least-squares iterations converged to $R = 0.060$. Final non-hydrogen atom positional parameters are in Table III.[20] Anisotropic thermal parameters (Table V), hydrogen atom positional and thermal parameters (Table VI), and a list of observed and calculated structure amplitudes (Table VII) are available as supplementary material.[21]

Atomic scattering factors used in all structure factor calculations were those for carbon, nitrogen, and oxygen from ref 23 and for hydrogen from ref 24. In the least-squares iterations, $\sum w\Delta^2$ ($\Delta = ||F_o| - |F_c||$) was minimized, with weights, w, assigned according to the scheme: $w^{1/2} = 1$ when $|F_o| < 12.0$, and $w^{1/2} = 12.0/|F_o|$ when $|F_o| > 12.0$.

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Registry No. (±)-**2**, 82741-75-1; (±)-**3**, 82795-66-2; (±)-**3** (C_{52} epimer), 82795-67-3; (±)-**5a**, 82795-68-4; (±)-**5a** cyclic urethane, 82741-77-3; (±)-**5b**, 82741-76-2; (±)-**6a**, 82752-57-6; (±)-**6b**, 82796-02-9; (±)-**6c**, 82741-78-4; (±)-**6d**, 82741-79-5; **7**, 82741-80-8; (±)-**8a**, 82741-81-9; (±)-**8b**, 82795-69-5; (±)-**9**, 82741-82-0; (±)-**10**, 82741-83-1; (±)-**11**, 82741-84-2; (±)-**12**, 82741-85-3; (±)-**13**, 82741-86-4; (±)-**14**, 82741-87-5; (±)-**15**, 82741-88-6; (±)-**16**, 82741-89-7; (±)-**17**, 82741-90-0; (±)-**18**, 82741-91-1; 4-methoxybenzoyl chloride, 100-07-2.

Supplementary Material Available: Bond lengths and angles (Figure 2), tables of non-hydrogen atom fractional coordinates (Table III), torsion angles (Table IV), anisotropic thermal parameters (Table V) and hydrogen atom parameters (Table VI) (6 pages). Ordering information is given on any current masthead page.

Photochemical Three-Membered-Ring Cleavage of α-Cyclopropyl Ketones: A Theoretical Study

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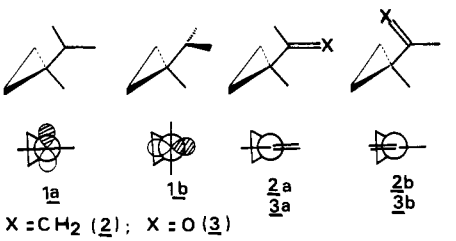
Ab initio SCF–CI calculations on cyclopropyl carboxaldehyde **3** have been carried out in order to simulate the various possibilities of ring cleavage induced by excitation of the CO chromophore. The preferential cleavage of the adjacent CC bond is interpreted in terms of the efficiency of the avoided crossing found along the potential energy surface of the lowest excited state. Selectivity as a function of conformation can be discussed by using simple perturbational arguments.

Owing to the pseudo π character of its Walsh MO's,[1] the cyclopropane ring interacts with an adjacent center bearing a p-type orbital. It has been shown, both experimentally[2] and theoretically,[3] that the strong conformational preference (about 18 kcal mol^{-1}) for a bisected conformation, **1a**, found in the cationic species results from a stabilizing two-electron two-orbital interaction. The stability difference between **1a** and **1b** is much less in the related cyclopropylcarbinyl radical,[4] but conformation **1a** is still prefered: three electrons are now involved in the dominant HOMO–LUMO interaction. On the same grounds, the related anion (four-electron interaction) is predicted to



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