evaporated to give 14 as an oil in quantitative yield. Compound 14 was purified by HPLC (μ-Porasil, 25% EtOAc in isooctane). The ^{19}F NMR chemical shift for the CF_3 group in ester 14, measured in $CDCl_3$ solution at 188 MHz, was determined to be 5.89 ppm (downfield from external trifluoroacetic acid in $CDCl_3$). Ester 15 was synthesized by reaction of 7 (10 mg) with (-)-MTPA-Cl and purified as described above. The CF_3 group for ester 15 gave a ^{19}F NMR chemical shift of 6.21 ppm.

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Registry No. 1, 82798-97-8; 2, 82798-98-9; 5, 82798-99-0; 6, 82838-28-6; 7, 82799-00-6; 8, 82799-01-7; 9, 82799-02-8; 10, 82799-03-9; 11, 82799-04-0; 12, 82799-05-1; 13, 82799-06-2; 14, 82799-07-3; 15, 82838-29-7; (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, 20445-31-2; (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 20445-33-4; (-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, 17257-71-5; (-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 39637-99-5.

Spectroscopic, Optical, and Crystallographic Properties of (*S*)-(+)-*cis*-6′-Bromo-*N*-formylnorreticuline

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A rotamer mixture of (*S*)-*N*-formyl-*N*-norreticuline (1) was brominated regioselectively in the 6′-position to afford the corresponding mixture of 6′-bromo rotamers (2) from which the thermodynamically less stable cis rotamer could easily be isolated by direct crystallization. This rotamer was stable in crystalline condition but equilibrated to a 1:2 cis–trans mixture on standing in solution. This equilibration was easily followed by observation of changes in optical rotation and the ratio of *N*-formyl protons in the NMR spectrum. Assignment of the cis structure to the rotamer isolated by crystallization was confirmed by a single-crystal X-ray analysis, which also confirmed the absolute configuration of this rotamer made independently from established stereochemical relationships. The crystals of 2 have space group $P2_1$ and cell dimensions a = 6.616 (1) Å, b = 10.985 (1) Å, c = 13.084 (2) Å and β = 95.61 (1)°. The structure was refined to an R factor of 4.3%.

The presence of rotamer pairs was repeatedly observed in the series of 1-benzyl-substituted *N*-formyl-1,2,3,4-tetrahydroisoquinolines (TIQ) by routine TLC and ^1H NMR analysis.[2-5] The latter method can be used to quantitate the individual amounts of cis and trans rotamers (cis = C_1–N bond cis to C=O of NCHO)[5] by the different chemical shifts of the *N*-formyl proton. Recently Olieman and van Koningsfeld[6] presented the first X-ray crystallographic study of the structure of an *N*-formyl-1-benzyl-1,2,3,4,5,8-hexahydroisoquinoline, a close relative of this class of compounds. We now supplement this information by describing the physical and crystallographic properties and particularly the optical behavior of another member of the class of TIQ.[4]

Table I

expt	time, min	cis–trans ratio[a]	α_{obsd}[b]	$[\alpha]^{26}D$, deg
1	5	83:17	0.742	87.5
2	30	54:46	0.686	80.9
3	60	41:59	0.657	77.5
4	180	33:67	0.636	74.9

[a] Determined by integration of the formyl proton NMR resonance in 0.85% solution in Me_2SO. [b] In 0.85% solution in Me_2SO.

Bromination of (*S*)-(+)-*N*-formyl-*N*-norreticuline (1), consisting of a rotamer mixture,[2] afforded a cis–trans rotamer mixture of the corresponding (*S*)-(+)-6′-bromo-*N*-

(1) Visiting fellow from Swiss Federal School of Technology, Zurich, Switzerland.
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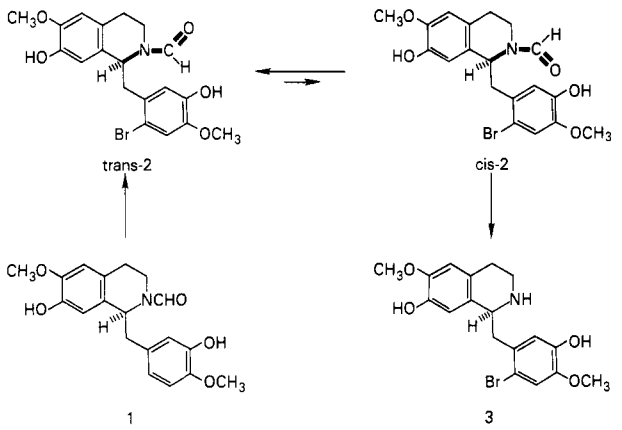
Scheme I



formyl-N-norreticuline (2), which was easier and better separable on TLC than the rotamers of 1. The absolute configuration of 2 follows from the absolute stereochemistry previously established for 1. Interestingly, a number of solvents[7] could be used for crystallization of 2 and in each case, crystalline material containing one of the rotamers in practically pure form was obtained. The cis structure of the crystalline rotamer[2] was suggested by the presence of the N-formyl proton at δ 7.94 (Me_2SO-d_6), in good agreement with Szántay's findings.[5] This was confirmed by the crystal structure analysis discussed in detail below.

The specific optical rotation of the chemically and optically[2] pure cis-rotamer 2 in a 0.85% Me_2SO solution showed a value of $[\alpha]^{26}_D$ +87.5°, which decreased after standing for 3 h at room temperature to $[\alpha]^{26}_D$ +74.9°. The rotamer ratio in this solution did not change after prolonged standing, suggesting that an equilibrium had been reached. The composition measured by ^1H NMR [δ(cis-NCHO) 7.94, δ(trans-NCHO) 7.41] indicated the presence of a 2:1 trans–cis rotamer mixture.

According to this observation it follows that the crystallizable cis isomer must be the thermodynamically less stable isomer. Realizing that equilibration had begun during dissolution of the cis rotamer, the specific rotation of the hypothetically pure trans isomer (which has not yet been obtained in crystalline condition) and of the pure cis isomer were calculated from the data in Table I as +67° and +93°, respectively. The observed changes in the specific optical rotation by going from pure cis rotamer to a trans-cis mixture of rotamers was also observed with ORD measurements and does not arise from epimerization of the adjacent benzylic hydrogen atom. This also followed from the results of the hydrolysis of pure (S)-(+)-cis-2 and its equilibrium mixture with 10% HCl, affording the same optically active (S)-(+)-6'-bromo-N-norreticuline hydrochloride monohydrate (3·HCl·H_2O) in 70% yield (Scheme I).

The considerable difference in the specific optical rotation of individual rotamers in the N-formyl TIQ series is noteworthy and suggests that measurements of optical purity should be carried out after complete equilibration or after elimination of the N-formyl function.

Crystal Data and X-ray Experimental Data. Slow crystallization from butyronitrile under reduced pressure gave crystals suitable for X-ray analysis. Molecular formula, $C_{19}H_{20}NO_5Br$; molecular weight, 422.27 daltons; habit, flat colorless plates; radiation, Cu Kα (graphite monochromator); wavelength, 1.5418 Å; space group, $P2_1$ (no. 4); cell dimensions (from least-squares refinement of $\pm\theta$ data), a = 6.616 (1) Å, b = 10.985 (1) Å, c = 13.084 (2) Å, β = 95.61 (1)°, V = 946.35 Å^3, Z = 2, D_m = 1.47 (1) g cm^{-3}, D_x = 1.482 g cm^{-3}; crystal size, 0.15 × 0.14 × 0.07 mm^3; reflections (hemisphere), 3825 (676 < 1σ):); maximum sin θ/λ, 0.6231 Å^{-1}, diffractometer, Nonius CAD-4. The phase problem was solved by a combination of Patterson and direct methods (using MULTAN 78).[8] All H atoms were found and successfully refined (positional parameters only). A full hemisphere of X-ray data was collected and used in the refinement. The expected S enantiomer, shown in Figure 1, was confirmed since the R factor was 5.4% for the R enantiomer in contrast to 4.3% for the S enantiomer. Scattering factors and anomalous dispersion connections were taken from ref[9]. Least-squares weighting was from Peterson and Levy;[10] function minimized was $\sum w\Delta^2$; anisotropic temperature factor was $\exp(-2\pi^2(\sum_i\sum_j U_{ij}a^*a_i^*h_ih_j)$; the bond angles are given in Table II. Tables of atomic parameters were submitted to the reviewers and are available as supplemental material. Structure factor tables can be obtained from J.V.S.

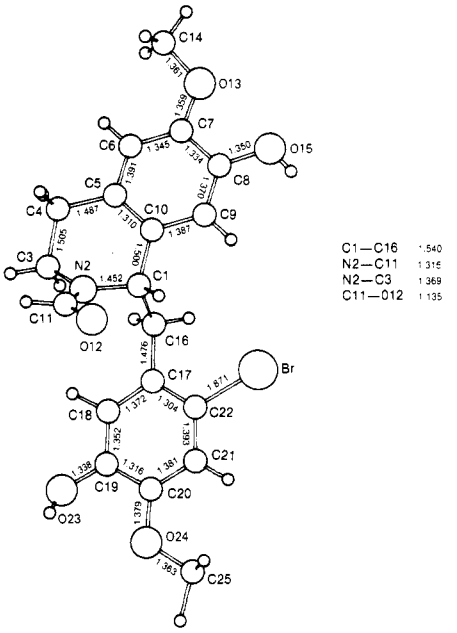


Figure 1. PLUTO[10] drawing showing crystal conformation and bond lengths. O(24)–C(25) has an esd of 0.01 Å, and all other bonds have esd's ≤ 0.007 Å.

Discussion of the X-ray Results. Bond lengths and angles do not present any surprising values. The amide group C(11), O(12), and H(11) is essentially coplanar with the C(1), N(2), C(3) triangle. Coplanarity was also observed in racemic N-formyl-1,2,3,4,5,8-hexahydro-1-(4-methoxybenzyl)-6-methoxyisoquinoline,[6] but in this case the rotamer was trans. Intermolecular packing appears to be controlled by hydrogen bonding. The bond O(15)–H(15)···O(12) in the direction of the screw axis has a length of 2.726 Å (H···O, 1.940 Å). O(23) appears involved in a bifurcated bond to O(13 and O(15) along the c axis. The C···O distances are 2.778 and 2.895 Å and the H···O

(7) For example: ethyl acetate, methanol, 1-butanol, acetonitrile, tetrahydrofuran, cyclohexanone, N-methylmorpholine, chloroform.

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Table II. Bond Angles (deg) for the Heavier Atoms (Estimated Standard Deviations Are Given in Parentheses)

N(2)-C(1)-C(10)	111.8 (3)	N(2)-C(1)-C(16)	110.8 (3)
C(10)-C(1)-C(16)	110.6 (4)	C(1)-N(2)-C(3)	114.7 (4)
C(1)-N(2)-C(11)	125.4 (3)	C(3)-N(2)-C(11)	119.0 (4)
N(2)-C(3)-C(4)	108.2 (3)	C(3)-C(4)-C(5)	115.0 (4)
C(4)-C(5)-C(6)	121.9 (4)	C(4)-C(5)-C(10)	119.4 (4)
C(6)-C(5)-C(10)	118.7 (4)	C(5)-C(6)-C(7)	123.6 (4)
C(6)-C(7)-C(8)	118.4 (4)	C(6)-C(7)-O(13)	127.9 (4)
C(8)-C(7)-O(13)	113.6 (4)	C(7)-C(8)-C(9)	118.1 (4)
C(7)-C(8)-O(15)	116.0 (4)	C(9)-C(8)-O(15)	125.9 (4)
C(8)-C(9)-C(10)	123.6 (4)	C(1)-C(10)-C(5)	121.8 (3)
C(1)-C(10)-C(9)	120.6 (4)	C(5)-C(10)-C(9)	117.6 (4)
N(2)-C(11)-O(12)	123.7 (4)	C(7)-O(13)-C(14)	117.2 (4)
C(1)-C(16)-C(17)	116.7 (4)	C(16)-C(17)-C(18)	124.0 (4)
C(16)-C(17)-C(22)	120.7 (4)	C(18)-C(17)-C(22)	115.3 (4)
C(17)-C(18)-C(19)	125.4 (4)	C(18)-C(19)-C(20)	117.8 (4)
C(18)-C(19)-O(23)	121.4 (5)	C(20)-C(19)-O(23)	120.7 (4)
C(19)-C(20)-C(21)	118.6 (4)	C(19)-C(20)-O(24)	114.0 (4)
C(21)-C(20)-O(24)	127.4 (5)	C(20)-C(21)-C(22)	121.7 (4)
C(17)-C(22)-C(21)	121.1 (4)	Br-C(22)-C(17)	116.4 (4)
Br-C(22)-C(21)	120.1 (3)	C(20)-O(24)-C(25)	116.4 (4)

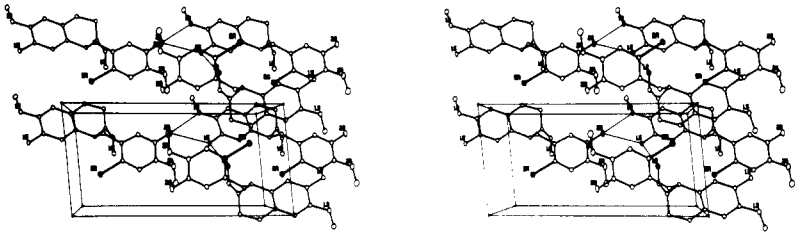

Figure 2. ORTEP[12] stereodrawing showing packing and hydrogen bonds. The oxygen atoms are labeled with the numbers of Figure 1.

distances are 2.400 and 2.342 Å, respectively.

The crystal conformation and bond lengths of **2** are shown in the PLUTO[11] drawing given in Figure 1. The conformation observed in the crystal has some short interatomic nonbonded contracts, but there is no obvious stereochemical barrier to rotation of the formyl group. In solution the situation may be rather different. A CAMSEQ[12] calculation indicates that completely free rotation about the C(1)–C(16) and C(16)–C(17) bonds is not possible since rotation produces contacts with the formyl group in its present conformation although it is possible to turn the bromobenzyl moiety over by a cooperative rotation about both bonds and there are many possible conformations with approximately equal energies. On the average, the randomly positioned bromobenzyl moiety could act as a barrier to rotation of the formyl group since, conversely, rotation of the formyl group to positions between the cis and trans configurations would bring it into contact with many of the otherwise energetically equivalent conformations of the bromobenzyl group.

The isolation of only one conformer in the solid state is probably a consequence of a lower energy for the observed crystal conformation caused by the fairly extensive hydrogen bonding and packing forces between the approximately parallel aromatic moieties (see ORTEP[13] drawing, Figure 2). Calculations on the trans rotamer indicate that, while an O(12)···O(15) intermolecular hydrogen bond might be formed by similarly packed molecules, O(12) would be in a position close to O(13) and C(7) (to which it cannot form hydrogen bonds), which would impede the formation of the other intermolecular bonds. Thus, either a different form of packing would be required or else the formyl group would have to rotate out of the presumably energetically favorable C(11), O(12), N(2), C(1), C(3) plane.

Experimental Section

Melting points were determined in open capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 MC instrument, using the solvents and concentrations specified.

NMR spectra were determined with a JEOL 100-MHz spectrometer and $(CH_3)_4Si$ as the internal reference. Mass spectra were obtained with a Perkin-Elmer RMU-6E spectrometer at 70 eV. Silica gel 60 for chromatography was purchased from Merck and Co., Inc. IR spectra were obtained with a Beckman IR 4230 instrument. Combustion analyses were performed by the Section on Microanalytical Services and Instrumentation of this Institute.

(*S*)-(+)-6′-Bromo-*N*-formyl-*N*-norreticuline (2). Analogous to the conversion of racemic *N*-formyl-*N*-norreticuline,[2] a mixture of 2.26 g (6.6 mmol) of (*S*)-(−)-*N*-norreticuline (**1**) and 44 mL of AcOH was heated to solution and the solution cooled rapidly to 25 °C. To the rapidly stirred solution was added dropwise 1.06 g (6.65 mmol) of Br_2 in 22 mL of AcOH during 20 min. The mixture was stirred an additional 40 min and evaporated to a foam, which was dried in vacuo for 1 h. The foam was dissolved in 4 mL of hot *n*-butyronitrile. After cooling to 70 °C, 3 mL of $CHCl_3$ was added and 1.5 h later the crystalline material was filtered, washed with 2 mL of *n*-butyronitrile (5 °C), and dried in vacuo to afford 541 mg (19%) of **2**,[14] mp 187–189 °C. The foam from the filtrate and washings was dissolved in 2.5 mL of *n*-butyronitrile and 2 mL of $CHCl_3$ and stored overnight at room temperature. The precipitate was filtered, stirred for 5 min in 2 mL of methanol (0 °C), filtered again, washed with 2 mL methanol (0 °C), and dried in vacuo to afford an additional 1.096 g (39%) of **2**,[14] mp 189–191 °C. The residue resulting from the filtrate and washings was dissolved in 2 mL of chloroform and the solution was stored overnight at 8 °C. The precipitate was

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(13) Johnson, C. K. ORTEP, ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN, 1965.
(14) This material consisted practically of only the cis rotamer. TLC analysis on silica gel GF [Analtech, Inc.; $CHCl_3$–CH_3OH (15:1) with I_2 development] showed only traces of trans rotamer in the form of a weak, slightly faster running spot (R_f 0.27) compared to that (R_f 0.24) of the cis isomer.

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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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

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