(52) Wolf, R. A. Unpublished results.
(53) Scheppele, S. E.; Grizzle, P. L.; Miller, D. W. *J. Am. Chem. Soc.* **1975**, *97*, 6165.
(54) Hildebrand, J. H.; Prausnitz, J. M.; Scott, R. L. "Regular and Related Solutions", Van Nostrand-Reinhold: Princeton, N.J., 1970; pp 207–215.
(55) Sanderson, J. R.; Story, P. R. *J. Org. Chem.* **1974**, *39*, 3463.
(56) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 125.
(57) Pryor, W. A.; Smith, K. *J. Am. Chem. Soc.* **1970**, *92*, 2731.
(58) Trachtman, M.; Miller, J. G. *J. Am. Chem. Soc.* **1962**, *84*, 4928.
(59) Bartlett, P. D.; Lorand, J. P. *J. Am. Chem. Soc.* **1966**, *88*, 3294.
(60) Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 2915.
(61) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274.
(62) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948.
(63) (a) Koenig, T.; Wielesek, R. A.; Huntington, J. G. *Tetrahedron Lett.* **1974**, 2283. (b) Koenig, T. Personal communication.
(64) Shelton, J. R.; Uzelmeier, C. W. *J. Am. Chem. Soc.* **1966**, *88*, 5222.
(65) McDonald, R. N.; Reitz, R. R. *J. Am. Chem. Soc.* **1976**, *98*, 8144.
(66) Shono, T.; Nishiguchi, I. *Tetrahedron* **1974**, *30*, 2183.
(67) Stefani, A. P.; Chuang, L.-Y.; Todd, H. E. *J. Am. Chem. Soc.* **1970**, *92*, 4168.
(68) Fort, R. C., Jr.; Hiti, J. *J. Org. Chem.* **1977**, *42*, 3968.
(69) Ernst, J. A.; Thankachan, C.; Tidwell, T. T. *J. Org. Chem.* **1974**, *39*, 3614.
(70) Timberlake, J. W.; Garner, A. W. *J. Org. Chem.* **1976**, *41*, 1666.
(71) Friedman, R. L.; Lewis, R. N.; Pastorino, R. L. *Mod. Plast.* **1971**, 66.
(72) Garner, A. W.; Timberlake, T. W.; Engel, P. S.; Melaugh, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 7377.
(73) (a) Duismann, W.; Rüchardt, C. *Tetrahedron Lett.* **1974**, 4517. (b) *Chem. Ber.* **1973**, *106*, 1083.
(74) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1976**, *9*, 13.
(75) Porter, N. A.; Dubay, G. R.; Green, J. G. *J. Am. Chem. Soc.* **1978**, 100, 920, and references cited therein.
(76) Engle, P. S.; Bishop, D. J. *J. Am. Chem. Soc.* **1975**, 97, 6754.
(77) Nozaki, K.; Bartlett, P. D. *J. Am. Chem. Soc.* **1946**, *68*, 1686.
(78) Tang, F.; Huyser, E. S. *J. Org. Chem.* **1978**, *43*, 1016.
(79) Russell, G. A. in ref 12, p 312.
(80) (a) Kozuka, S.; Lewis, E. S. *J. Am. Chem. Soc.* **1976**, *98*, 2254. (b) Lewis, E. S.; Ogino, D. *ibid.* **1976**, *98*, 2264.
(81) Milas, N. A.; Golubovic, A. *J. Am. Chem. Soc.* **1958**, *80*, 5994.
(82) Rüchardt, C.; Schwarzer, H. *Chem. Ber.* **1966**, *99*, 1861.
(83) Pryor, W. A.; Kneipp, K. G. *J. Am. Chem. Soc.* **1971**, *93*, 5584.
(84) We thank Dr. Sal Rand of the Texaco Research Center, Beacon, N.Y., for taking the 100-MHz spectra for us.
(85) Koenig, T.; Wolf, R. *J. Am. Chem. Soc.* **1967**, *89*, 2948.
(86) "The Aldrich Catalog-Handbook of Organic and Biochemicals", Aldrich Chemical Co., Inc.: Milwaukee, Wis., 1977–1978.
(87) Gassman, P. G.; Heckert, D. C. *Tetrahedron* **1965**, *21*, 2725.
(88) Pratt, D. G.; Rothstein, E. *J. Chem. Soc. C* **1968**, 2548.
(89) Atkinson, J. G.; Csakvary, J. J.; Herbert, G. T.; Stuart, R. S. *J. Am. Chem. Soc.* **1968**, *90*, 498.
(90) Vogel, A. I. "A Textbook of Practical Organic Chemistry", Longman: London, 1956; p 859.
(91) Abell, P. I.; Tien, R. *J. Org. Chem.* **1965**, *30*, 4212.
(92) Haworth, E.; Perkin, W. H. *J. Chem. Soc.* **1894**, *65*, 86.
(93) Walker, H. G.; Hauser, C. R. *J. Am. Chem. Soc.* **1946**, *68*, 1386.
(94) Simmons, H. E.; Blanchard, E. P.; Smith, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 134.
(95) Cox, E. F.; Caserio, M. C.; Silver, M. S.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 2719.
(96) Reference 86, p 211.
(97) Reference 86, p 222.
(98) Reference 86, p 215.

Epimerization and Isomerization in C_{20} Diterpenoid Alkaloids. Crystal and Molecular Structures of Atisinium Chloride, Dihydroatisine, Isoatisine, and Veatchine[1]

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Abstract: The solid-state conformation of four C_{20} diterpenoid alkaloids has been determined by X-ray crystallography. Atisinium chloride (orthorhombic, $P2_12_12_1$, a = 14.340, b = 18.180, c = 7.709 Å, R = 0.038 for 2007 observed reflections) is shown to have restricted access to both sides of the iminium double bond. Dihydroatisine (orthorhombic, $P2_12_12_1$, a = 13.004, b = 18.939, c = 7.840 Å, R = 0.055 for 1651 observed reflections) is shown to have a chair conformation for ring E, thus giving a basis for assignment of all ^{1}H and ^{13}C NMR resonances, and showing that boat-chair conformational isomerism of ring E is unlikely. Isoatisine (orthorhombic, $P2_12_12_1$, a = 13.212, b = 13.661, c = 10.403 Å, R = 0.048 for 1945 observed reflections) shows that the oxazolidine ring F closes exclusively in the endo configuration when closure is in the iso form. This result confirms a ^{13}C NMR study that isoatisine does not exist as a pair of epimers. Furthermore, it indicates that the doubled signal of the C(4) methyl group in isoatisine is attributable neither to a mixture of C(19) epimers, as was suggested in the case of atisine, nor to a mixture of the chair and boat conformers of the piperidine ring E. Veatchine (orthorhombic, $P2_12_12_1$, a = 9.934, b = 21.581, c = 8.674 Å, R = 0.050 for 1614 observed reflections) reveals a crystal structure which is disordered between C(20) epimers, showing that the normal closure of the oxazolidine ring can take place on either side of the iminium double bond, in agreement with the observed ^{13}C NMR data. The absolute configuration of atisinium chloride is shown to be 4*S*,5*S*,8*R*,10*R*,12*R*,15*S* by the *R*-ratio test. By analogy, the absolute configuration of dihydroatisine must be 4*S*,5*S*,8*R*,10*R*,12*R*,15*S*, and that of isoatisine must be 4*S*,5*S*,8*R*,10*R*,12*R*,15*S*,19*S*. The absolute configuration of veatchine must be 4*S*,5*S*,8*R*,10*R*,13*R*,15*R*,20*SR*, with the *SR* indicating a predominance of the 20*S* epimer. A similar configuration at C(20) is postulated for atisine on the basis of spectral data. The *S*:*R* ratio in veatchine is approximately 60:40, based on measurements of the diffracted intensity for sensitive reflections, which is in substantial agreement with the ratio found by integrating the C(4) methyl resonance in the ^{1}H NMR spectra of the two different sets of ^{13}C chemical shifts for the carbon atoms of the oxazolidine ring, piperidine ring, and C(4) methyl group.

Introduction

The C_{20} diterpenoid alkaloids isolated from various *Aconitum* and *Garrya* species (principally *A. heterophyllum* Wall, *G. veatchii* Kellogg, and *G. lauifolia* Hartw.) have been the subjects of extensive chemical investigation.[2-4] The molecular structure and stereochemistry of atisine (**1**) and several related alkaloids were initially established by classical degradative and synthetic methods.[2-4] Atisine (**1**), an amorphous base (pK_a = 12.8), undergoes a facile isomerization of the oxazolidine ring F (see Experimental Section for ring definitions) from its "normal" position (closed on C(20)) to the "iso" position (closed on C(19)) of isoatisine (**2**) by treatment with methanolic alkali or even by simple refluxing in hydroxylic solvents.[5] The path of this isomerization presumably goes through the ternary iminium form (**3**), which tautomerizes to the isoiminium form (**4**). The isomerization can be reversed by refluxing

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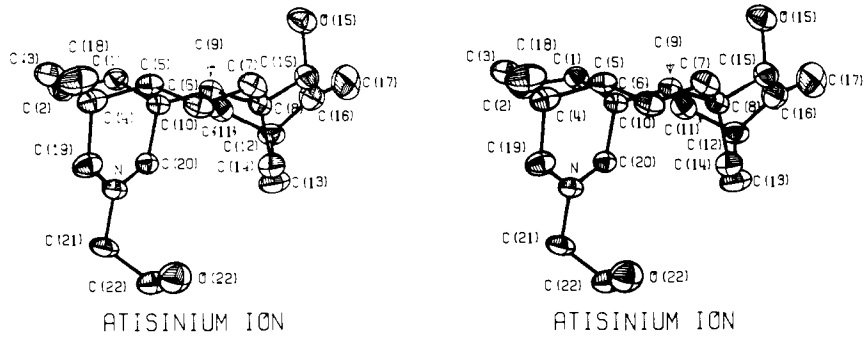
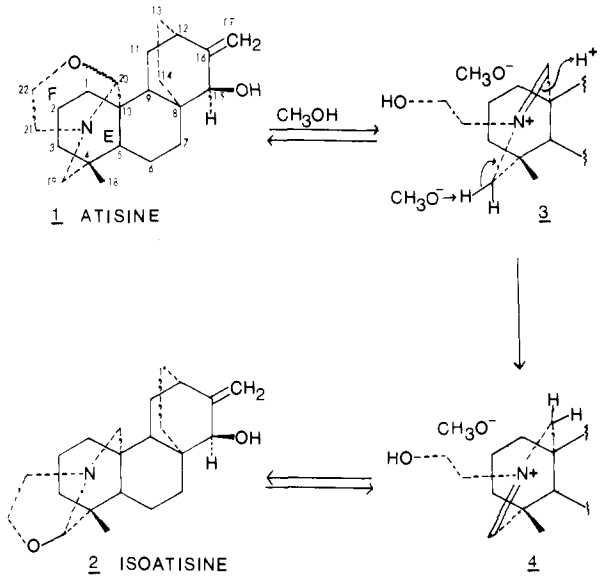
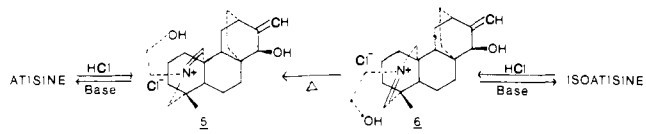


Figure 1. A stereoscopic drawing of the atisinium ion.



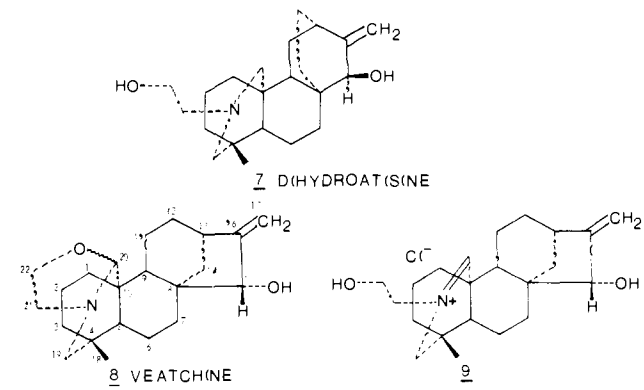
isoatisinium chloride (**6**) in such solvents as DMA, DMF, DEF, Me_2SO, and high-boiling alcohols.[6] Since the procedure



for the isolation of atisine involves its purification as atisinium chloride, the stereochemistry of atisine at the iminium carbon, C(20), must therefore be ambiguous. Early work assumed, without experimental evidence, a β configuration for the hydrogen attached to C(20).[7] The present work shows that this assumption is, at best, only partially true.

The inconclusive knowledge of the stereochemistry of atisine at C(20) has led to differing viewpoints concerning the interpretation of the doubling of certain peaks in the ^{1}H NMR spectra. An early hypothesis involved an equilibrium between conformers of atisine in which ring E existed in either a chair or boat form.[8] Pradhan and Girijavallabhan reported that the doubled C(4) methyl resonance coalesced to a broadened singlet in certain deuterated solvents, concluding that deuterium exchange occurred at C(20) in atisine. They explained these observations by postulating a facile interconversion of epimers in solution through a zwitterionic intermediate.[9] This interpretation is inconsistent with the later observation that deuterium exchange does not occur.[10] When the ^{13}C NMR spectrum of atisine was taken in nonionic solvents such as toluene, chloroform, and acetone, the ratio of C(20) epimers remained constant.[11] Consequently we concluded that these epimers do not exist in equilibrium with each other in *nonionic* solvents.[11] Recently we have explained the doubling of the C(4) methyl singlets and the C(20)-proton signals in the ^{1}H NMR spectra of atisine, veatchine, and related alkaloids by comparison with their ^{13}C NMR spectra.[12]

We undertook the resolution of these various findings by means of the series of crystal structures reported here. First, the absolute configuration of the atisane skeleton was confirmed by the structure determination of atisinium chloride (**5**). Based on the solid-state conformation of ring E in dihydroatisine (**7**), the correct assignments of the ^{13}C NMR resonances were established for this conformationally mobile part of the molecule.[12] The hypothesis of chair–boat conformational equilibrium can therefore be rejected. Finally, we sought to establish the favored closures for both the normal and isooxazolidine rings. The structure of isoatisine (**2**) showed clearly that closure to C(19) in an endo configuration is favored. On the other hand, the crystal structure of veatchine (**8**) surpris-



ingly showed that *both epimers existed in the unit cell in a disordered relationship.* Closure of the oxazolidine ring to C(20) in an exo configuration is slightly, but significantly, favored. This result agrees with the ^{13}C NMR data reported for veatchine.

The C(4) methyl resonance appears, as noted above, as an unequal doublet in the ^{1}H NMR spectra of both veatchine and isoatisine. The doubling persists in the ^{13}C NMR spectrum *only in the case of veatchine.* In combination with our crystal structure results, these observations show that veatchine exists in solution as a mixture of epimers. The same cannot be said for isoatisine, for which the doubling of the C(4) methyl singlet must be attributed to the conformational flexibility of the oxazolidine ring. This conclusion is supported by comparing the ^{1}H NMR spectrum of α-oxoisoatisine, in which the amide >C=O group is at C(21), with that of isoatisine. The ^{1}H NMR spectrum of α-oxoisoatisine shows only one sharp singlet for the C(4)-CH_3 group.[8]

Molecular Structure and Conformation

Except for the question of the conformation of rings E and F, the chemical connectivity has been previously established for atisinium chloride (**5**), dihydroatisine (**7**), veatchine (**8**),

Table I. Interatomic Distances (Å) (Estimated Standard Deviations in Parentheses)

atoms	interatomic distance: atisinium chloride	dihydro-atisine	isoatisine	veatchine	atoms	interatomic distance: atisinium chloride	dihydro-atisine	isoatisine	veatchine
C(1)-C(2)	1.528 (3)	1.533 (5)	1.533 (4)	1.523 (6)	C(15)-H(15b)				0.89 (4)
C(1)-C(10)	1.563 (3)	1.551 (5)	1.544 (3)	1.545 (5)	C(16)-C(17)	1.314 (4)	1.324 (7)	1.313 (4)	1.331 (6)
C(1)-H(1a)	0.99 (3)	0.98 (3)	0.99 (2)	1.06 (4)	C(17)-H(171)	0.95 (4)	0.91 (9)	0.92 (3)	0.92 (4)
C(1)-H(1b)	0.99 (2)	1.02 (3)	1.03 (3)	0.89 (4)	C(17)-H(172)	1.00 (3)	0.99 (4)	0.99 (4)	0.93 (5)
C(2)-C(3)	1.513 (4)	1.526 (6)	1.526 (4)	1.527 (6)	C(18)-H(181)	0.99 (3)	0.95 (3)	0.95 (3)	1.14 (5)
C(2)-H(2a)	1.00 (3)	1.00 (4)	1.06 (3)	1.00 (5)	C(18)-H(182)	0.96 (4)	1.08 (5)	1.06 (3)	0.85 (5)
C(2)-H(2b)	0.98 (3)	0.93 (4)	1.16 (3)	0.93 (4)	C(18)-H(183)	0.99 (4)	1.05 (6)	0.86 (3)	0.82 (5)
C(3)-C(4)	1.543 (3)	1.534 (5)	1.546 (4)	1.535 (5)	C(19)-N	1.473 (2)	1.464 (5)	1.440 (3)	1.462 (5)
C(3)-H(3a)	1.06 (3)	1.03 (3)	1.07 (4)	0.89 (4)	C(19)-O(22)			1.437 (3)	
C(3)-H(3b)	1.01 (3)	0.98 (4)	1.01 (3)	1.09 (4)	C(19)-H(191)	0.98 (3)	1.14 (4)	1.20 (2)	0.95 (4)
C(4)-C(5)	1.544 (3)	1.537 (5)	1.552 (3)	1.555 (5)	C(19)-H(192)	1.03 (3)	1.10 (4)		0.94 (4)
C(4)-C(18)	1.536 (4)	1.537 (6)	1.532 (4)	1.540 (6)	C(20)-N	1.293 (3)	1.469 (4)	1.477 (3)	1.459 (5)
C(4)-C(19)	1.530 (2)	1.543 (5)	1.525 (4)	1.523 (5)	C(20)-O(22ma)				1.311 (6)
C(5)-C(6)	1.530 (3)	1.533 (5)	1.529 (3)	1.520 (5)	C(20)-O(22mi)				1.254 (7)
C(5)-C(10)	1.541 (3)	1.547 (4)	1.546 (3)	1.558 (5)	C(20)-H(20)	0.97 (2)			1.254 (7)
C(5)-H(5b)	0.99 (2)	1.02 (4)	0.95 (3)	1.01 (4)	C(20)-H(201)		1.02 (4)	1.00 (3)	
C(6)-C(7)	1.521 (3)	1.529 (5)	1.522 (4)	1.514 (5)	C(20)-H(202)		1.06 (4)	1.02 (3)	
C(6)-H(6a)	0.98 (2)	1.09 (4)	0.94 (2)	1.01 (4)	C(21)-N	1.492 (2)	1.547 (8)	1.466 (4)	1.451 (8)
C(6)-H(6b)	0.98 (2)	0.99 (4)	1.02 (3)	0.91 (4)	C(21)-C(22)	1.511 (3)	1.547 (8)	1.530 (5)	
C(7)-C(8)	1.521 (3)	1.530 (5)	1.533 (3)	1.528 (5)	C(21)-C(22ma)				1.451 (8)
C(7)-H(7a)	1.03 (3)	0.97 (3)	1.00 (2)	0.97 (3)	C(21)-C(22mi)				1.40 (1)
C(7)-H(7b)	1.00 (3)	1.04 (3)	0.98 (3)	0.92 (4)	C(21)-H(211)	1.05 (3)	1.19 (5)	0.96 (4)	
C(8)-C(9)	1.541 (3)	1.550 (4)	1.550 (3)	1.551 (5)	C(21)-H(212)	1.05 (3)	1.09 (6)	1.12 (4)	
C(8)-C(14)	1.551 (2)	1.539 (5)	1.543 (3)	1.568 (5)	C(21)-H(21d)				0.70 (4)
C(8)-C(15)	1.552 (3)	1.548 (5)	1.561 (3)	1.556 (5)	C(22)-O(22)	1.409 (3)		1.427 (4)	
C(9)-C(10)	1.551 (3)	1.553 (4)	1.559 (3)	1.563 (5)	C(22)-O(22a)		1.263 (9)		
C(9)-C(11)	1.557 (3)	1.555 (5)	1.557 (3)	1.563 (5)	C(22)-O(22b)		1.210 (12)		
C(9)-H(9b)	1.02 (2)	0.91 (3)	0.99 (2)	0.98 (3)	C(22)-O(22c)		1.270 (21)		
C(10)-C(20)	1.495 (2)	1.539 (4)	1.547 (3)	1.515 (5)	C(22)-H(221)	1.12 (2)		1.07 (4)	
C(11)-C(12)	1.532 (3)	1.541 (5)	1.534 (3)	1.523 (6)	C(22)-H(222)	1.00 (3)		1.14 (4)	
C(11)-H(11a)	1.05 (3)	1.01 (4)	1.02 (3)	1.16 (5)	C(22ma)-O(22ma)				1.450 (8)
C(11)-H(11b)	1.05 (3)	1.08 (4)	1.02 (2)	1.00 (5)	C(22ma)-H(221d)				1.14 (5)
C(12)-C(13)	1.531 (4)	1.530 (6)	1.530 (4)	1.530 (6)	C(22ma)-H(222d)				1.04 (6)
C(12)-C(16)	1.501 (3)	1.496 (5)	1.509 (3)		C(22ma)-C(22mi)				1.288 (13)[a]
C(12)-H(12a)				1.04 (5)	C(22mi)-O(22mi)				1.44 (1)
C(12)-H(12b)	0.94 (3)	1.08 (4)	0.98 (3)	0.98 (4)	C(22mi)-H(221d)				1.27 (5)
C(13)-C(14)	1.535 (4)	1.529 (6)	1.541 (3)	1.523 (6)	C(22mi)-H(223d)				1.05 (6)
C(13)-C(16)				1.508 (5)	O(15)-H(15OH)	0.85 (4)		0.83 (3)	0.84 (6)
C(13)-H(13a)	0.96 (3)	0.97 (4)	0.93 (3)		O(22)-H(22OH)	1.01 (5)			
C(13)-H(13b)	1.07 (3)	1.02 (5)	1.07 (3)	0.93 (4)	O(22ma)-O(22mi)				1.532 (8)[a]
C(14)-H(14a)	1.07 (2)	0.98 (4)	0.94 (3)	0.94 (3)					
C(14)-H(14b)	0.92 (3)	1.05 (4)	0.88 (3)	1.04 (4)					
C(15)-C(16)	1.523 (4)	1.507 (5)	1.517 (3)	1.521 (6)					
C(15)-O(15)	1.425 (3)	1.446 (4)	1.421 (3)	1.421 (5)					
C(15)-H(15a)	1.04 (3)	1.03 (3)	1.01 (3)						

[a] Nonbonding distance between corresponding atoms of 20*R* and 20*S* epimers.

and isoatisine (**2**).[2-4,13] Our work confirms the earlier conclusions[14,15] and, in particular, shows that the hydroxyl group at C(15) has a β orientation in the atisines, while it is α in veatchine (**8**). Bond lengths and angles are given in Tables I and II for all four structures. Figures 1-4 show stereoscopic drawings[16] of the molecules of the atisinium ion (**5**, Figure 1), veatchine (**8**, Figure 2), isoatisine (**2**, Figure 3), and dihydroatisine (**7**, Figure 4).

The torsion angles for the various rings in all four structures are shown in Table III. Ring E is found to adopt a chair conformation in dihydroatisine, isoatisine, and veatchine. This lends additional support to the interpretation of the ^{1}H NMR spectrum of atisine that the earlier postulate of conformational isomerism in atisine[8] (involving an equilibrium between chair and boat conformations of ring E) is incorrect. The ternary iminium structure of atisinium chloride forces ring E to assume a flattened chair conformation. It is also interesting to observe that ring E is slightly flattened at the fusion to ring F in isoatisine, but not in veatchine.

Rings A and B have essentially identical chair geometries in all four compounds. Ring B differs slightly, but significantly, from an ideal geometry by being flattened along the C(8)-C(9) edge. The fact that this bond is also the point of fusion of ring B to ring C and the bicyclo[2.2.2]octane fragment suggests that this bond acts as a "hinge" in transferring steric effects from one end of the molecule to the other. The torsion angles of the bicyclo[2.2.2]octane system deviate from their ideal values more in isoatisine than in dihydroatisine or atisinium chloride ($\bar{\Delta}$ = 2.94° for atisinium chloride, 4.72° for dihydroatisine, and 11.14° for isoatisine; $\bar{\Delta}$ is the average absolute deviation of the torsion angles from the ideal values of 0, 60, or −60°). However, interactions between eclipsed hydrogens in an ideal [2.2.2] system support an expectation that the minimum energy conformation of this moiety should be slightly skewed. Molecular mechanics calculations have shown that a skewed model of bicyclo[2.2.2]octane is approximately 0.08 kcal/mol lower in energy than the eclipsed (D_{3h}) conformation.[17] The observation that ring E is more distorted in isoatisine than in either dihydroatisine or veatchine suggests that the iso closure of the oxazolidine ring allows ring E to absorb

Table II. Bond Angles (deg) (Estimated Standard Deviations in Parentheses)

atoms	angle			
	atisinium chloride	dihydroatisine	isoatisine	veatchine
C(2)-C(1)-C(10)	112.5 (2)	115.5 (3)	116.0 (2)	116.4 (3)
C(1)-C(2)-C(3)	112.1 (2)	112.4 (3)	110.5 (2)	112.7 (3)
C(2)-C(3)-C(4)	114.1 (2)	114.4 (3)	114.7 (2)	116.3 (3)
C(3)-C(4)-C(5)	109.4 (2)	108.7 (3)	108.0 (2)	108.0 (3)
C(3)-C(4)-C(18)	108.0 (2)	107.5 (3)	108.2 (2)	107.5 (3)
C(3)-C(4)-C(19)	111.0 (2)	111.8 (3)	108.0 (2)	112.8 (3)
C(5)-C(4)-C(18)	111.7 (2)	112.4 (3)	111.6 (2)	110.8 (3)
C(5)-C(4)-C(19)	109.2 (1)	109.5 (3)	110.9 (2)	109.0 (3)
C(18)-C(4)-C(19)	107.5 (2)	106.9 (3)	110.0 (2)	108.8 (3)
C(4)-C(5)-C(6)	114.4 (2)	115.9 (3)	116.5 (2)	115.8 (3)
C(4)-C(5)-C(10)	108.8 (1)	108.7 (3)	109.4 (2)	109.6 (3)
C(6)-C(5)-C(10)	110.3 (1)	112.1 (3)	111.4 (2)	112.1 (3)
C(5)-C(6)-C(7)	111.5 (2)	110.8 (3)	110.5 (2)	111.3 (3)
C(6)-C(7)-C(8)	113.1 (2)	114.0 (3)	114.0 (2)	113.2 (3)
C(7)-C(8)-C(9)	110.8 (1)	110.4 (3)	112.4 (2)	111.2 (3)
C(7)-C(8)-C(14)	110.6 (2)	111.5 (3)	111.7 (2)	113.8 (3)
C(7)-C(8)-C(15)	111.1 (2)	110.5 (3)	109.0 (2)	110.8 (3)
C(9)-C(8)-C(14)	111.1 (1)	113.0 (3)	111.9 (2)	112.3 (3)
C(9)-C(8)-C(15)	107.1 (2)	107.8 (3)	106.2 (2)	109.1 (3)
C(14)-C(8)-C(15)	105.9 (2)	103.4 (3)	105.3 (2)	98.9 (3)
C(8)-C(9)-C(10)	115.1 (2)	117.9 (3)	118.9 (2)	118.6 (3)
C(8)-C(9)-C(11)	109.5 (1)	109.1 (3)	108.5 (2)	111.5 (3)
C(10)-C(9)-C(11)	114.9 (1)	115.2 (3)	114.5 (2)	115.0 (3)
C(1)-C(10)-C(5)	110.1 (2)	108.7 (2)	109.2 (2)	107.4 (3)
C(1)-C(10)-C(9)	108.0 (2)	106.8 (3)	106.1 (2)	107.3 (3)
C(1)-C(10)-C(20)	104.5 (2)	110.6 (3)	110.9 (2)	109.9 (3)
C(5)-C(10)-C(9)	111.1 (1)	109.7 (2)	109.2 (2)	109.1 (3)
C(5)-C(10)-C(20)	109.7 (2)	108.8 (3)	107.9 (2)	107.5 (3)
C(9)-C(10)-C(20)	113.3 (1)	112.2 (2)	113.4 (2)	115.3 (3)
C(9)-C(11)-C(12)	110.6 (2)	110.6 (3)	109.8 (2)	115.3 (3)
C(11)-C(12)-C(13)	108.4 (2)	108.1 (3)	108.4 (2)	111.0 (3)
C(11)-C(12)-C(16)	108.9 (2)	107.9 (3)	108.6 (2)	
C(13)-C(12)-C(16)	109.1 (2)	109.8 (3)	108.4 (2)	
C(12)-C(13)-C(14)	109.4 (2)	109.2 (3)	108.9 (2)	109.2 (3)
C(12)-C(13)-C(16)				110.0 (3)
C(14)-C(13)-C(16)				102.6 (3)
C(8)-C(14)-C(13)	111.3 (2)	111.5 (3)	111.5 (2)	101.3 (3)
C(8)-C(15)-C(16)	109.5 (2)	109.6 (3)	108.6 (2)	104.8 (3)
C(8)-C(15)-O(15)	114.1 (2)	112.5 (3)	114.7 (2)	108.9 (3)
C(16)-C(15)-O(15)	107.2 (2)	109.6 (3)	112.3 (2)	111.3 (3)
C(12)-C(16)-C(15)	112.3 (2)	112.7 (3)	112.3 (2)	
C(12)-C(16)-C(17)	124.5 (3)	123.5 (4)	124.4 (2)	
C(13)-C(16)-C(15)				107.8 (3)
C(13)-C(16)-C(17)				127.5 (4)
C(15)-C(16)-C(17)	123.2 (3)	123.8 (4)	123.2 (2)	124.7 (4)
C(4)-C(19)-N	114.1 (2)	113.9 (3)	116.1 (2)	110.7 (3)
C(4)-C(19)-O(22)			112.8 (2)	
N-C(19)-O(22)			107.0 (2)	
C(10)-C(20)-N	123.2 (2)	113.7 (2)	112.8 (2)	122.8 (4)
C(10)-C(20)-O(22ma)				122.8 (4)
C(10)-C(20)-O(22mi)				124.9 (4)
N-C(20)-O(22ma)				104.5 (3)
N-C(20)-O(22mi)				107.9 (4)
C(22)-C(21)-N	111.3 (1)	111.6 (3)	102.0 (2)	
C(22ma)-C(21)-N				102.2 (4)
C(22mi)-C(21)-N				105.8 (5)
C(21)-C(22)-O(22)	113.1 (1)		105.5 (2)	
C(21)-C(21)-O(22a)		115.5 (6)		
C(21)-C(22)-O(22b)		121.3 (7)		
C(21)-C(22)-O(22c)		100.0 (10)		
O(22a)-C(22)-O(22b)		100.6 (7)		
O(22a)-C(22)-O(22c)		107.6 (10)		
O(22b)-C(22)-O(22c)		111.7 (11)		
C(21)-C(22ma)-O(22ma)				105.9 (5)
C(21)-C(22mi)-O(22mi)				105.9 (7)
C(19)-N-C(20)	124.2 (1)	112.0 (3)	117.2 (2)	113.1 (3)
C(19)-N-C(21)	116.2 (2)	110.5 (3)	102.5 (2)	115.1 (4)
C(20)-N-C(21)	119.5 (2)	108.7 (3)	111.8 (2)	101.1 (3)
C(19)-O(22)-C(22)			107.2 (2)	
C(20)-O(22ma)-C(22ma)				107.6 (4)
C(20)-O(22mi)-C(22mi)				108.9 (6)

Table III. Torsion Angles (deg) (Estimated Standard Deviations in Parentheses)

atoms	angle			
	atisinium chloride	dihydroatisine	isoatisine	veatchine
		Ring A		
C(1)-C(2)-C(3)-C(4)	−49.9 (3)	−44.9 (4)	−48.8 (3)	−42.0 (5)
C(2)-C(3)-C(4)-C(5)	55.9 (2)	56.5 (4)	57.8 (3)	52.6 (4)
C(3)-C(4)-C(5)-C(10)	−60.3 (2)	−64.5 (3)	−62.1 (2)	−62.9 (4)
C(4)-C(5)-C(10)-C(1)	60.6 (2)	61.9 (3)	59.7 (2)	62.8 (3)
C(5)-C(10)-C(1)-C(2)	−55.1 (2)	−51.6 (4)	−52.5 (3)	−52.7 (4)
C(10)-C(1)-C(2)-C(3)	49.0 (3)	42.9 (4)	46.2 (3)	42.3 (5)
		Ring B		
C(5)-C(6)-C(7)-C(8)	−57.7 (2)	−57.0 (4)	−56.6 (2)	−58.7 (4)
C(6)-C(7)-C(8)-C(9)	51.0 (2)	48.7 (4)	43.0 (3)	47.7 (4)
C(7)-C(8)-C(9)-C(10)	−47.6 (2)	−44.7 (4)	−37.3 (2)	−41.7 (4)
C(8)-C(9)-C(10)-C(5)	49.7 (2)	46.7 (3)	43.0 (2)	43.3 (4)
C(9)-C(10)-C(5)-C(6)	−53.5 (2)	−52.1 (3)	−54.3 (2)	−51.0 (4)
C(10)-C(5)-C(6)-C(7)	58.2 (2)	58.5 (4)	63.0 (2)	60.7 (4)
		Ring C		
C(8)-C(9)-C(11)-C(12)	−1.0 (2)	−3.1 (4)	−18.7 (2)	37.4 (4)
C(9)-C(11)-C(12)-C(13)	60.7 (3)	62.0 (4)	71.0 (2)	−43.6 (4)
C(11)-C(12)-C(13)-C(14)	−63.4 (3)	−64.7 (4)	−53.6 (2)	63.7 (4)
C(12)-C(13)-C(14)-C(8)	6.5 (3)	8.6 (4)	−9.4 (3)	−72.5 (4)
C(13)-C(14)-C(8)-C(9)	53.1 (2)	50.8 (4)	61.3 (2)	66.6 (3)
C(14)-C(8)-C(9)-C(11)	−55.4 (2)	−53.0 (4)	−44.0 (2)	−50.0 (4)
		Ring D		
C(8)-C(15)-C(16)-C(12)	2.4 (3)	−2.7 (4)	−14.0 (3)	
C(15)-C(16)-C(12)-C(13)	−60.7 (3)	−56.6 (4)	−50.9 (3)	
C(16)-C(12)-C(13)-C(14)	54.9 (3)	52.7 (4)	64.0 (2)	
C(12)-C(13)-C(14)-C(8)	6.5 (3)	8.6 (4)	−9.4 (3)	
C(13)-C(14)-C(8)-C(15)	−62.8 (2)	−65.3 (3)	−53.5 (2)	
C(14)-C(8)-C(15)-C(16)	57.4 (2)	61.8 (3)	67.0 (2)	
C(8)-C(15)-C(16)-C(13)				−8.4 (4)
C(15)-C(16)-C(13)-C(14)				−22.2 (4)
C(16)-C(13)-C(14)-C(8)				44.1 (3)
C(13)-C(14)-C(8)-C(15)				−48.3 (3)
C(14)-C(8)-C(15)-C(16)				34.5 (3)
		Ring C/D		
C(8)-C(9)-C(11)-C(12)	−1.0 (2)	−3.1 (4)	−18.7 (2)	
C(9)-C(11)-C(12)-C(16)	−57.7 (2)	−56.7 (4)	−46.4 (2)	
C(11)-C(12)-C(16)-C(15)	57.3 (3)	60.9 (4)	66.6 (2)	
C(12)-C(16)-C(15)-C(8)	2.4 (3)	−2.7 (4)	−14.0 (3)	
C(16)-C(15)-C(8)-C(9)	−61.1 (2)	−58.0 (3)	−51.7 (2)	−82.9 (3)
C(15)-C(8)-C(9)-C(11)	59.7 (2)	60.5 (3)	70.3 (2)	58.5 (4)
C(8)-C(9)-C(11)-C(12)				37.4 (4)
C(9)-C(11)-C(12)-C(13)				−43.6 (4)
C(11)-C(12)-C(13)-C(16)				−48.1 (4)
C(12)-C(13)-C(16)-C(15)				93.8 (4)
C(13)-C(16)-C(15)-C(8)				−8.4 (4)
		Ring E		
N-C(19)-C(4)-C(5)	−39.7 (2)	−55.1 (4)	−45.3 (3)	−58.6 (4)
C(19)-C(4)-C(5)-C(10)	61.3 (2)	57.7 (3)	55.9 (2)	59.9 (4)
C(4)-C(5)-C(10)-C(20)	−53.7 (2)	−58.4 (3)	−60.8 (2)	−55.4 (4)
C(5)-C(10)-C(20)-N	26.8 (3)	56.9 (3)	55.7 (2)	53.2 (4)
C(10)-C(20)-N-C(19)	−5.3 (3)	−53.1 (4)	−46.3 (3)	−54.1 (4)
C(20)-N-C(19)-C(4)	12.1 (3)	52.0 (4)	41.1 (3)	55.3 (4)
		N-Hydroxyethyl Side Chain		
C(10)-C(20)-N-C(21)	177.2 (2)	−175.5 (3)		
C(20)-N-C(21)-C(22)	70.0 (2)	−156.7 (4)		
N-C(21)-C(22)-O(22)	52.2 (2)			
N-C(21)-C(22)-O(22a)		54.8 (6)		
N-C(21)-C(22)-O(22b)		−67.0 (9)		
N-C(21)-C(22)-O(22c)		169.9 (10)		
C(4)-C(19)-N-C(21)	−170.3 (2)	173.4 (3)		
C(19)-N-C(21)-C(22)	−107.5 (2)	79.9 (5)		
		Ring F (Oxazolidine Ring)		
N-C(21)-C(22)-O(22)			27.4 (3)	
C(21)-C(22)-O(22)-C(19)			−5.3 (3)	
C(22)-O(22)-C(19)-N			−19.4 (3)	
O(22)-C(19)-N-C(21)			36.9 (3)	
C(19)-N-C(21)-C(22)			−38.4 (3)	

Table III (*Continued*)

atoms	angle: atisinium chloride	dihydroatisine	isoatisine	veatchine
N-C(21)-C(22ma)-O(22ma)				15.1 (5)
C(21)-C(22ma)-O(22ma)-C(20)				12.6 (6)
C(22ma)-O(22ma)-C(20)-N				−35.3 (5)
O(22ma)-C(20)-N-C(21)				44.2 (4)
C(20)-N-C(21)-C(22ma)				−34.4 (4)
N-C(21)-C(22mi)-O(22mi)				−4.6 (8)
C(21)-C(22mi)-O(22mi)-C(20)				−16.6 (9)
C(22mi)-O(22mi)-C(20)-N				31.2 (7)
O(22mi)-C(20)-N-C(21)				−32.5 (5)
C(20)-N-C(21)-C(22mi)				20.9 (6)
	Skew of Bicyclo[2.2.2]octane System			
O(15)-C(15)-C(16)-C(17)	57.4 (3)	53.6 (5)	34.9 (3)	
C(9)-C(8) . . . C(12)-C(11)	−.5 (1)	−1.8 (2)	−11.2 (1)	
C(14)-C(8) . . . C(12)-C(13)	3.8 (2)	5.1 (2)	−5.5 (2)	
C(15)-C(8) . . . C(12)-C(16)	1.4 (2)	−1.5 (2)	−8.1 (2)	

the conformational strain of the molecule in isoatisine, while the bicyclooctane moiety does so when the oxazolidine ring is either closed in the normal position or opened. Special attention should be paid to the "torsion" angles involving the nonbonded, bridgehead atoms C(8) and C(12) in atisinium chloride, dihydroatisine, and isoatisine. These values show that the bicyclo[2.2.2]octane system in isoatisine differs from that in the other two cases by a rotation of −9.4° around the C(8)···C(12) axis, which is quite close to the value of ±7.0° found in the molecular mechanics minimization.[17] Both values differ significantly from those of Ermer and Dunitz,[18] who found that the bicyclo[2.2.2]octane fragment in bicyclo[2.2.2]octane-1,4-dicarboxylic acid showed D_{3h} symmetry within one standard deviation.

The oxazolidine ring F differs significantly in conformation in the structures of veatchine and isoatisine; from the values in Table III, it can be seen that it assumes an N-flap envelope conformation in isoatisine. An envelope conformation with C(20) at the flap is found for the minor epimer in veatchine, while a twist conformation is found for the major epimer. These differences do not appear to be sufficiently large that they can be solely responsible for the greater stability of the iso form relative to the normal form. Indeed, it must be noted that the C(20)-O(22ma) and C(20)-O(22mi) bond lengths in veatchine are both much shorter (and presumably stronger) than expected for a C-O single bond, while the corresponding bond in isoatisine is of normal length. The disorder at the oxazolidine oxygen may have resulted in some *apparent* shortening of the C-O bonds due to thermal motion. The magnitude of such shortening may be estimated to be 0.08–0.13 Å from a comparison of the C(21)-C(22) bond length in isoatisine with equivalent distances in veatchine. This estimate must be taken as an upper limit, since C(22)-O(22) in isoatisine does not differ significantly from the corresponding bond lengths in veatchine.

Intermolecular Interactions and Crystal Packing

In each of the structures reported here, the possibilities for hydrogen bonding are limited by the small number of potential donor and acceptor atoms. In the case of atisinium chloride, it is not surprising that the packing is determined by the interactions of the positive N atom with the Cl^- ion (N···Cl′ = 3.886 (2), N···Cl″ = 3.924 (2) Å; ′ = $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$, ″ = $x - \frac{1}{2}, \frac{1}{2} - y, -z$). In addition, the chloride ion accepts hydrogen bonds from both hydroxyl groups (O(15)···Cl = 3.247 (2), H(15OH)···Cl = 2.43 (4), and O(22)···Cl‴ = 3.131 (2), H(22OH)···Cl‴ = 2.13 (5) Å; ‴ = $x - \frac{1}{2}, \frac{1}{2} - y, 1 - z$). The structure of veatchine reveals only a single hydrogen bonding interaction between the nitrogen as acceptor and the 15β-hydroxyl group as donor (O(15)···N′ = 3.048 (4), H(15OH)···N′ = 2.27 (6) Å; ′ = $x - 1, y, z$). Unexpectedly, the nitrogen atom of isoatisine is not involved in any close intermolecular encounters (i.e., less than 3.6 Å). However, the oxazolidine ring oxygen is the acceptor in a hydrogen bond with the 15α-hydroxyl group (O(15)···O(22)′ = 2.992 (3), H(15OH)···O(22)′ = 2.29 (4) Å; ′ = $x + \frac{1}{2}, \frac{3}{2} - y, 1 - z$). This stands in contrast to veatchine, in which neither of the disordered oxazolidine oxygens particpates in any hydrogen bonding; packing forces, therefore, cannot account for the disorder observed in veatchine.

Because of the disorder found in the crystal of dihydroatisine, it proved impossible to locate the hydrogen of either hydroxyl group. Donor-acceptor relationships, therefore, cannot be resolved. The difference maps showed evidence that the hydroxyl group of the N-β-hydroxyethyl side chain can rotate freely, principally occupying the three positions included in the refinement with partial site occupancy. The three positions correspond to conformations in which the 22-hydroxyl group is either + synclinal, − synclinal, or trans to the nitrogen atom. In the first two positions, the intermolecular distance to O(15)′ is sufficiently short to imply hydrogen bonding (O(22a)···O(15)′ = 2.798 (7), O(22b)···O(15)′ = 2.805 (10) Å; ′ = $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$). In the third, the distance to N is too great to suggest hydrogen bonding (O(22c)···N″ = 3.25 (2) Å; ″ = $\frac{1}{2} - x, 1 - y, z + \frac{1}{2}$), but those to other disordered hydroxyl groups are not (O(22c)···O(22a)″ = 2.82 (2), O(22c)···O(22b)″ = 2.68 (1) Å). It would appear to be possible for the conformation of one hydroxyethyl group to influence that of its neighbor, leading to short-range ordering. However, no evidence for the doubling of the unit cell volume which would then be necessary was found.

Absolute Configuration of C_{20} Diterpenoid Alkaloids

The stereochemistry of the C_{20} diterpenoid alkaloids from *Garrya* and *Aconitum* species has been indicated from chemical correlation and optical rotatory dispersion studies.[7] Our work confirms these earlier conclusions. On the basis of Hamilton's test[19] ($R = 0.038$, $R_w = 0.037$ for the given enantiomorph, $R = 0.055$, $R_w = 0.064$ for the opposite) applied to the data for atisinium chloride, the absolute configuration of the atisinium ion is 4*S*,5*S*,8*R*,10*R*,12*R*,15*S*; because of the unsaturation at C(20), no direct evidence can be obtained from this structure for the configuration of this center in atisine. An indirect argument is presented below.

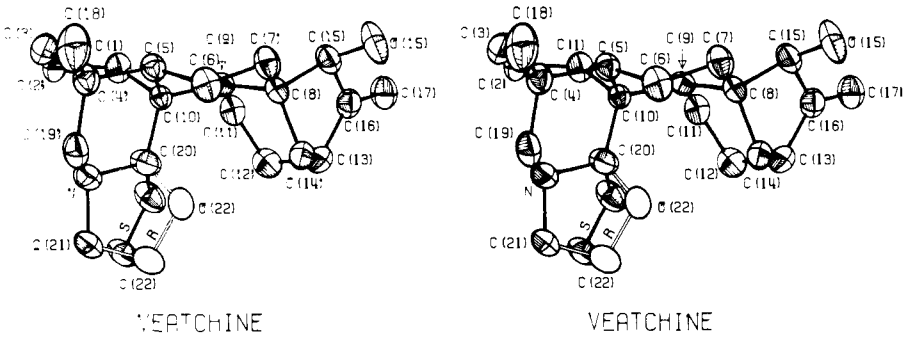


Figure 2. A stereoscopic drawing of veatchine. The disordered atoms of the minor epimer are shown as open circles.

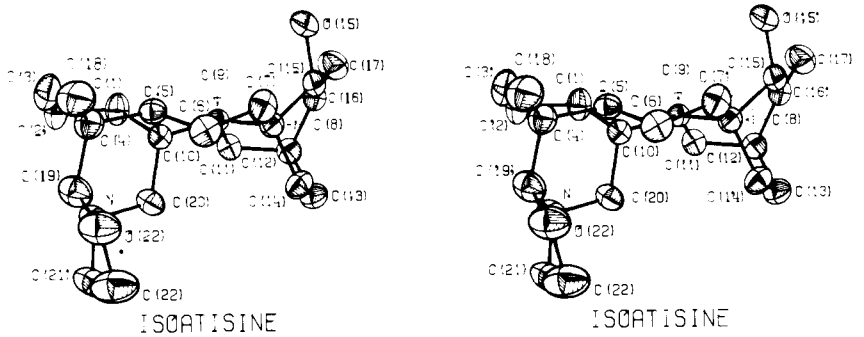


Figure 3. A stereoscopic drawing of isoatisine.

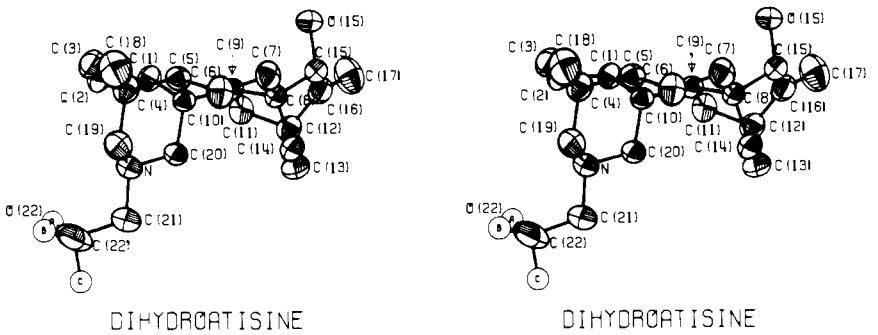


Figure 4. A stereoscopic drawing of dihydroatisine.

The reduction of atisinium chloride, atisine, and isoatisine to dihydroatisine can be accomplished under mild conditions, which makes the inversion of all chiral centers impossible.[13] The absolute configuration of dihydroatisine must therefore be 4*S*,5*S*,8*R*,10*R*,12*R*,15*S*.

Isomerization of atisine (**1**) to isoatisine (**2**) takes place with ease at room temperature in protic solvents.[5b] Hence its absolute configuration must be 4*S*,5*S*,8*R*,10*R*,12*R*,15*S*,19*S*. The first six of these centers may be assigned by analogy with atisine. From the lack of any evidence for disorder in the oxazolidine ring either in the present work or in the NMR investigations,[8,12] the configuration of C(19) may be assigned by using the other six as internal reference points.

The *Garrya* alkaloids (e.g., veatchine) have been related to the C_{20} diterpenoid alkaloids from *Aconitum* species (e.g., atisine) by conversion to a common intermediate.[15] Retaining the absolute configuration of the atisane skeleton given above, the absolute configuration of veatchine can be assigned as 4*S*,5*S*,8*R*,10*R*,13*R*,15*R*,20*SR*. The designation of the absolute configuration of C(20) as "*SR*" was chosen to indicate (1) that, in any given sample of veatchine, both epimers exist, and (2) that the 20*S* (exo configuration of the oxazolidine ring) epimer predominates. Since veatchine and atisine both show similar doubling of the C(4) methyl singlet in their ^1H and ^{13}C NMR spectra,[8] we believe that the absolute configuration of C(20) in atisine may also be assigned as *SR*.

All positional parameters, torsion angles, and perspective drawings refer to the molecules in the absolute configuration specified above.

Occurrence of Disorder between Epimers

In a crystal structure determination, it is well recognized that the resulting molecular structure represents, in actuality, a time and space average of the "true" molecular structure. A somewhat less well recognized assumption is that the *same entity*—either a molecule or ions in a fixed ratio—is packed together to make the crystal. Disorder between similar moieties is commonly found in mineral structures, e.g., substitution of aluminum for silicon in complex silicates. Such instances are less common in organic structures, where the crystallizing entity is usually a single more complex molecule. In these cases, disorder is often limited to partial site occupancy of a molecule of a solvent of crystallization. Instances in which one crystallographic site is occupied by two *different* molecules on a disordered basis are much more rare. However, it would be expected that a basic principle may be applied equally to any structure, organic or inorganic: entities which are similar in their capability to form bonds (ionic, covalent, or hydrogen)

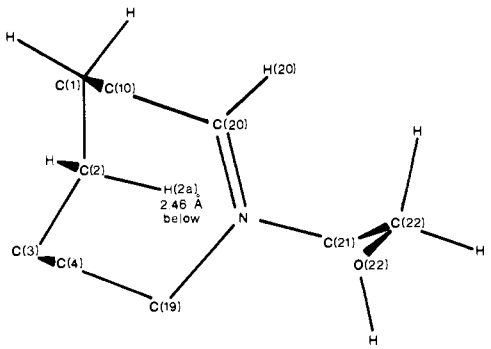


Figure 5. The pro-*S* side of the C(20)–N bond in atisinium chloride.

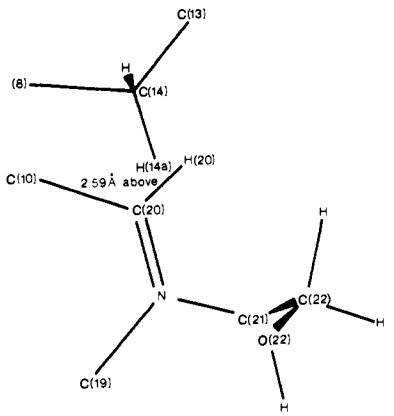


Figure 6. The pro-*R* side of the C(20)–N bond in atisinium chloride.

to other components of the crystal structure may be expected to be interchangeable with each other.

That this is the case with the molecules of veatchine and atisine may be readily seen by inspection of molecular models. The change of the oxazolidine ring from the favored exo fusion (20*S*) to endo (20*R*) involves only the movement of C(22) and O(22), plus a rotation of +55° around the N–C(21) bond. There is no perceptible change in either the accessibility or orientation of the nitrogen atom for hydrogen bonding. Neither does the movement of the two atoms have a major effect upon the overall dimensions of the molecule. It is not surprising, then, that the two epimers can occupy the same unit cell. The few similar cases which can be found in the literature generally involved disorder between α and β anomers in mono- and disaccharides: *N*-acetyl-α-D-glucosamine,[20] α-lactose,[21] and α-melibiose.[22] In each of these cases, the anomeric hydroxyl group could participate equally well in the hydrogen bonding scheme in either the α or β position, thus tending to stabilize the disordered structure. This is not analogous to the situation in veatchine, where O(22) is not involved in hydrogen bonding.

None of our experimental measurements supports an alternate hypothesis of veatchine being truly monoclinic, $P2_1$, $Z = 4$, with the asymmetric unit containing one each 20*S* and 20*R* molecule. All reflections required to be systematically absent by the space group $P2_12_12_1$ were measured, and no significant diffracted intensity was found in any case. Therefore, we conclude that the unit cell of veatchine contains four symmetrically related 20*S* molecules, with approximately 40% of the sites randomly substituted with 20*R* molecules. That this model must apply to the bulk sample of veatchine, as well as to the single crystal selected for data collection, is supported by the examination of reflections, which were particularly sensitive to variation of the proportion of the two epimers for several crystals. A partial set of data, collected from three additional crystals, supported similar epimeric ratios.

A somewhat similar instance is found in the structure of racemic 2-*exo*-norbornanol *p*-toluenesulfonate, which shows disorder between enantiomeric molecules.[23] Following the nomenclature used by Altona and Sundaralingam,[23] we describe the crystal structure of veatchine as exhibiting *epimeric disorder*.

Re-formation of the Oxazolidine Ring

The fact that the oxazolidine ring F closes in two different configurations in the regeneration of veatchine (**8**) from veatchinium chloride (**9**) (and, presumably, in atisine as well) suggests the existence of unusual constraints on the mechanism of ring closure. In Figures 5 and 6 we show the projection on the plane of the N–C(20) double bond of atisinium chloride (defined by N, C(20), C(10), C(19), C(21), and H(20)) of the nearby atoms on either side of the plane. We have arbitrarily defined the side of this plane toward C(1) as "above" the plane; since closure of the O(22) to this side of the plane leads to an *S* configuration at C(20), we also refer to this as the "pro-20*S*" side of the plane.

A comparison of Figures 5 and 6 suggests that access to the pro-20*R* side of the plane is sterically hindered, especially by H(14), which is situated almost directly over C(20). Calculations of the "congestion"[24] around the iminium bond showed, surprisingly, that access to the pro-20*S* side of the bond was almost equally restricted by H(2). Wipke and Gund noted the lack of discrimination in such cases, and have attributed it to the predominance of approach pathways which were not perpendicular to the plane of the double bond.[24a] The existence of such pathways is not unexpected, especially in cases of ring closure, where geometric constraints limit the possible approaches.

It should be noted that the closure of the *N*-hydroxyethyl group in the ternary iminium structures is an example of a 5-endo-trig ring closure, following Baldwin's notation.[25] Following Baldwin's rules, this type of ring closure is *disfavored;* this is not to say, of course, that it is impossible, only that it "may not compete effectively with alternative favored ring closures or other reaction pathways".[25a] Such ring closures have been reported, but the proposed mechanism involved an intermediate in which a tautomeric shift has taken place, thus allowing the ring closure to be of the more favored 5-exo-trig type.[25b] Such a mechanism could not exist for a normal closure in the atisines, where C(10) is bonded to four other carbons, nor for the iso closure, where the same is true of C(4), since no electronic structure can be drawn with a C(20)–C(10) or a C(19)–C(4) double bond. Indeed, no possible mechanism which involves a tautomeric shift of the iminium double bond between its normal and iso forms can be accepted, for such a process would necessarily be accompanied by a rapid exchange of the hydrogens on C(19) and C(20) with deuterium in D_2O. Such an exchange has been shown not to occur by recent work in our laboratory,[10-12] in contrast to older observations.[9a]

Experimental Section

Atisinium chloride (**5**) was obtained from a reference sample reserved during the extraction of atisine from the roots of *A. heterophyllum* Wall. Clear, tabular crystals were grown from 95% ethanol [mp 325–326 °C (lit. 329–331 °C), $[\alpha]^{23}_D$ +22.6° (*c* 4.9 mg/mL, 95% EtOH), (lit. +25.0°, *c* 1.0)].[13] Dihydroatisine (7) was prepared by reduction of isoatisine with $NaBH_4$, and recrystallized from acetone [mp 159–161 °C (lit. 159–161 °C[13])]. Isoatisine (**2**) was isolated from the mother liquors remaining from the extraction of atisine, and recrystallized from acetone [mp 150–152 °C (lit. 149.5–152 °C[13])].

Veatchine (**8**) was obtained from a reference sample kept during its isolation from the bark of *G. veatchii* Kellogg.[15] Clear, prismatic crystals were obtained from hot acetone [mp 122–126 °C (lit. 125.5–128.5 °C)].

The crystals were mounted on fine glass fibers with epoxy glue in

Table IV. Fractional Atomic Positional Parameters ($\times 10^4$) (Estimated Standard Deviations in Parentheses)

atom	X	Y	Z
	A. Atisinium Chloride		
Cl	6761.3 (6)	0894.8 (5)	1623.9 (12)
C(1)	4369 (2)	3714 (1)	−0237 (3)
C(2)	4487 (2)	4458 (1)	0658 (4)
C(3)	5017 (2)	4394 (1)	2349 (4)
C(4)	4643 (1)	3792 (1)	3576 (3)
C(5)	4637 (1)	3046 (1)	2619 (3)
C(6)	4346 (1)	2392 (1)	3745 (3)
C(7)	4377 (2)	1675 (1)	2730 (3)
C(8)	3762 (1)	1684 (1)	1122 (3)
C(9)	3962 (1)	2370 (1)	0008 (3)
C(10)	3997 (1)	3107 (1)	1020 (3)
C(11)	3309 (2)	2371 (1)	−1605 (3)
C(12)	2685 (2)	1687 (1)	−1609 (3)
C(13)	2085 (2)	1698 (2)	0033 (4)
C(14)	2717 (1)	1643 (1)	1634 (3)
C(15)	3948 (2)	1001 (1)	−0035 (3)
C(16)	3291 (2)	1014 (1)	−1587 (3)
C(17)	3272 (3)	0495 (2)	−2772 (5)
C(18)	5271 (2)	3773 (2)	5190 (4)
C(19)	3653 (1)	3972 (1)	4183 (3)
C(20)	3056 (1)	3377 (1)	1562 (3)
C(21)	1963 (1)	4053 (1)	3317 (3)
C(22)	1331 (1)	3433 (1)	3884 (3)
N	2921 (1)	3780 (1)	2921 (2)
O(15)	4874 (1)	0959 (1)	−0697 (2)
O(22)	1709 (1)	0310 (1)	5245 (2)
H(1a)	3952 (20)	3739 (15)	−1252 (39)
H(1b)	4960 (16)	3521 (12)	−0730 (32)
H(2a)	3848 (19)	4673 (14)	0785 (37)
H(2b)	4840 (22)	4786 (18)	−0098 (45)
H(3a)	4997 (21)	4910 (16)	2988 (44)
H(3b)	5693 (18)	4317 (14)	2037 (36)
H(5b)	5288 (15)	2977 (13)	2205 (32)
H(6a)	3707 (16)	2462 (12)	4163 (29)
H(6b)	4748 (16)	2370 (13)	4775 (30)
H(7a)	4145 (18)	1230 (15)	3443 (39)
H(7b)	5031 (21)	1573 (14)	2334 (37)
H(9b)	4636 (15)	2307 (11)	−0392 (28)
H(11a)	2884 (23)	2843 (17)	−1544 (45)
H(11b)	3673 (20)	2346 (14)	−2788 (36)
H(12b)	2294 (18)	1716 (13)	−2579 (34)
H(13a)	1702 (22)	2130 (16)	0077 (42)
H(13b)	1640 (21)	1225 (19)	0022 (42)
H(14a)	2573 (17)	2048 (13)	2598 (33)
H(14b)	2625 (19)	1195 (15)	2175 (38)
H(15a)	3816 (19)	0555 (15)	0782 (37)
H(171)	2877 (28)	0534 (22)	−3756 (57)
H(172)	3697 (22)	0060 (16)	−2639 (46)
H(181)	5927 (21)	3697 (18)	4831 (39)
H(182)	5048 (25)	3421 (18)	6019 (54)
H(183)	5240 (25)	4250 (19)	5814 (49)
H(191)	3551 (18)	4496 (15)	4380 (38)
H(192)	3509 (21)	3709 (18)	5333 (42)
H(20)	2507 (16)	3318 (13)	0830 (34)
H(211)	2092 (22)	4450 (17)	4284 (44)
H(212)	1680 (19)	4307 (15)	2220 (39)
H(221)	1092 (12)	3046 (9)	2836 (24)
H(222)	0723 (21)	3668 (16)	4184 (41)
H(15OH)	5278 (25)	0931 (19)	0099 (48)
H(22OH)	1637 (29)	3330 (23)	6313 (63)
	B. Dihydroatisine		
C(1)	5302 (3)	4067 (2)	0645 (5)
C(2)	5519 (3)	4757 (2)	1599 (5)
C(3)	6191 (3)	4645 (2)	3173 (5)
C(4)	5876 (3)	4014 (2)	4282 (5)
C(5)	5876 (2)	3346 (2)	3169 (4)
C(6)	5795 (3)	2643 (2)	4128 (5)
C(7)	5882 (3)	2020 (2)	2896 (5)
C(8)	5082 (2)	2027 (2)	1466 (4)
C(9)	5041 (2)	2763 (2)	0610 (4)
C(10)	5036 (2)	3423 (2)	1785 (4)
C(11)	4205 (3)	2758 (2)	−0807 (5)
C(12)	3727 (3)	2017 (2)	−0982 (5)
C(13)	3207 (3)	1831 (2)	0710 (6)
C(14)	4025 (3)	1773 (2)	2104 (5)
C(15)	5362 (3)	1480 (2)	0074 (5)
C(16)	4578 (3)	1506 (2)	−1337 (5)
C(17)	4629 (5)	1117 (3)	−2738 (7)
C(18)	6644 (3)	3967 (2)	5766 (6)
C(19)	4801 (3)	4118 (2)	5076 (5)
C(20)	3990 (2)	3531 (2)	2667 (4)
C(21)	2957 (3)	4157 (2)	4694 (7)
C(22)	2689 (4)	4908 (4)	5334 (9)
N	3966 (2)	4141 (1)	3825 (4)
O(15)	6379 (2)	1593 (1)	−0622 (4)
O(22a)[a]	2711 (5)	5387 (3)	4215 (8)
O(22b)[a]	3176 (7)	5186 (5)	6464 (13)
O(22c)[a]	1756 (15)	4816 (10)	5758 (26)
H(1a)	4751 (25)	4156 (17)	−0179 (43)
H(1b)	5937 (25)	3939 (18)	−0062 (42)
H(2a)	4844 (34)	4978 (23)	1911 (56)
H(2b)	5789 (31)	5086 (20)	0841 (49)
H(3a)	6227 (25)	5099 (17)	3905 (42)
H(3b)	6902 (28)	4548 (18)	2847 (45)
H(5b)	6545 (28)	3296 (19)	2500 (46)
H(6a)	5059 (28)	2535 (20)	4749 (50)
H(6b)	6352 (27)	2634 (19)	4991 (50)
H(7a)	5829 (26)	1576 (17)	3500 (45)
H(7b)	6574 (27)	2037 (18)	2222 (45)
H(9b)	5655 (24)	2774 (16)	0045 (42)
H(11a)	3653 (31)	3107 (20)	−0470 (53)
H(11b)	4556 (27)	2849 (19)	−2037 (50)
H(12b)	3253 (34)	2060 (22)	−2104 (56)
H(13a)	2678 (28)	2181 (19)	0952 (47)
H(13b)	2827 (34)	1364 (24)	0556 (61)
H(14a)	3834 (27)	2042 (19)	3127 (47)
H(14b)	4148 (28)	1242 (20)	2413 (44)
H(15a)	5445 (27)	0991 (18)	0640 (46)
H(171)	4394 (58)	1383 (46)	−3618 (20)
H(172)	5201 (28)	0776 (19)	−2807 (46)
H(181)	7293 (26)	3830 (19)	5313 (47)
H(182)	6505 (38)	3511 (26)	6568 (68)
H(183)	6675 (46)	4447 (32)	6443 (80)
H(191)	4579 (29)	3666 (20)	5961 (57)
H(192)	4759 (28)	4603 (20)	5855 (53)
H(201)	3440 (33)	3612 (21)	1767 (53)
H(202)	3799 (27)	3085 (18)	3430 (46)
H(211)	3064 (38)	3699 (26)	5715 (68)
H(212)	2378 (44)	3920 (32)	3874 (84)
	C. Veatchine		
C(1)	5068 (4)	7844 (2)	2367 (5)
C(2)	6439 (4)	7778 (2)	3134 (5)
C(3)	6441 (4)	8002 (2)	4805 (5)
C(4)	5674 (3)	8605 (2)	5132 (4)
C(5)	4227 (3)	8535 (2)	4471 (4)
C(6)	3230 (4)	9035 (2)	4939 (4)
C(7)	1819 (4)	8878 (2)	4411 (5)
C(8)	1706 (3)	8794 (2)	2667 (4)
C(9)	2839 (3)	8368 (2)	2044 (4)
C(10)	4296 (3)	8452 (1)	2689 (4)
C(11)	2746 (4)	8290 (2)	0255 (4)
C(12)	2320 (4)	8868 (2)	−0627 (4)
C(13)	1147 (4)	9194 (2)	0177 (5)
C(14)	1607 (3)	9420 (2)	1755 (5)
C(15)	0315 (3)	8514 (2)	2225 (5)
C(16)	0067 (4)	8730 (2)	0580 (5)
C(17)	−0930 (4)	8531 (2)	−0314 (5)
C(18)	5636 (4)	8694 (3)	6893 (5)
C(19)	6339 (3)	9170 (2)	4405 (5)
C(20)	5071 (4)	8997 (2)	2039 (5)
C(21)	6815 (4)	9670 (2)	1893 (6)
C(22ma)[a]	6238 (7)	9572 (3)	0375 (8)
C(22mi)[a]	5634 (9)	9938 (5)	1323 (13)

Table IV (*Continued*)

atom	*X*	*Y*	*Z*
O(15)	−0678 (2)	8749 (2)	3247 (4)
O(22ma)[a]	5261 (4)	9078 (2)	0557 (5)
O(22mi)[a]	4566 (5)	9512 (3)	1706 (8)
N	6389 (3)	9108 (1)	2728 (4)
H(1a)	5212 (40)	7833 (18)	1157 (45)
H(1b)	4623 (42)	7514 (18)	2729 (48)
H(2a)	6973 (46)	8100 (21)	2575 (51)
H(2b)	6682 (41)	7361 (19)	3190 (49)
H(3a)	7296 (35)	8037 (18)	5114 (43)
H(3b)	5907 (41)	7645 (19)	5449 (47)
H(5b)	3898 (39)	8123 (18)	4867 (46)
H(6a)	3479 (35)	9434 (17)	4387 (42)
H(6b)	3173 (37)	9076 (17)	5977 (43)
H(7a)	1148 (32)	9177 (16)	4724 (38)
H(7b)	1660 (38)	8504 (18)	4897 (44)
H(9b)	2623 (32)	7961 (16)	2484 (39)
H(11a)	3782 (46)	8119 (21)	−0186 (54)
H(11b)	2106 (45)	7945 (22)	0032 (54)
H(12a)	3091 (46)	9186 (21)	−7096 (52)
H(12b)	2190 (37)	8719 (17)	−1688 (48)
H(13b)	0819 (44)	9492 (21)	−0493 (50)
H(14a)	2435 (33)	9629 (16)	1781 (40)
H(14b)	0888 (39)	9703 (20)	2275 (46)
H(15b)	0285 (45)	8100 (20)	2271 (52)
H(171)	−1093 (39)	8705 (18)	−1269 (46)
H(172)	−1549 (46)	8248 (22)	0062 (57)
H(181)	4943 (50)	8324 (21)	7386 (56)
H(182)	6441 (47)	8650 (22)	7221 (52)
H(183)	5391 (47)	9045 (22)	7120 (55)
H(191)	5921 (35)	9547 (17)	4706 (41)
H(192)	7174 (43)	9244 (21)	4877 (51)
H(15OH)	−1433 (56)	8796 (25)	2841 (63)
H(21d)	7501 (44)	9718 (23)	2050 (54)
H(221d)	5629 (52)	9969 (24)	−0140 (60)
H(222d)	6907 (65)	9412 (29)	−0454 (72)
H(223d)	5787 (55)	10237 (27)	2259 (68)
	D. Isoatisine		
C(1)	1439 (2)	6218 (2)	4553 (2)
C(2)	1271 (2)	6239 (2)	3095 (3)
C(3)	0648 (2)	7134 (2)	2715 (3)
C(4)	−0321 (2)	7291 (2)	3521 (2)
C(5)	−0006 (1)	7380 (1)	4953 (2)
C(6)	−0829 (2)	7705 (2)	5894 (2)
C(7)	−0374 (2)	7923 (2)	7207 (2)
C(8)	0211 (2)	7063 (1)	7794 (2)
C(9)	0892 (1)	6538 (1)	6794 (2)
C(10)	0496 (1)	6415 (1)	5391 (2)
C(11)	1310 (2)	5583 (1)	7413 (2)
C(12)	1221 (2)	5642 (2)	8881 (2)
C(13)	0101 (2)	5563 (2)	9243 (2)
C(14)	−0498 (2)	6342 (2)	8491 (2)
C(15)	0937 (2)	7461 (1)	8856 (2)
C(16)	1606 (2)	6628 (2)	9313 (2)
C(17)	2449 (2)	6764 (2)	9959 (3)
C(18)	−0844 (2)	8223 (2)	3041 (3)
C(19)	−1009 (2)	6409 (2)	3315 (3)
C(20)	−0289 (2)	5583 (1)	5242 (2)
C(21)	−1622 (2)	4920 (2)	3878 (3)
C(22)	−2442 (2)	5684 (3)	4149 (4)
N	−0697 (2)	5512 (1)	3924 (2)
O(15)	1507 (1)	8300 (1)	8493 (2)
O(22)	−2036 (1)	6590 (1)	3704 (2)
H(1a)	1696 (18)	5572 (18)	4845 (24)
H(1b)	1891 (23)	6809 (22)	4785 (29)
H(2a)	0903 (22)	5574 (19)	2836 (29)
H(2b)	2072 (23)	6311 (23)	2646 (31)
H(3a)	0436 (27)	7147 (26)	1721 (36)
H(3b)	1049 (27)	7751 (24)	2875 (33)
H(5b)	0502 (19)	7871 (19)	5013 (26)
H(6a)	−1346 (18)	7236 (17)	5941 (23)
H(6b)	−1168 (25)	8333 (24)	5586 (35)
H(7a)	0081 (19)	8501 (18)	7120 (23)
H(7b)	−0854 (22)	8141 (19)	7862 (27)
H(9b)	1472 (18)	6993 (17)	6729 (24)
H(11a)	0934 (21)	4995 (19)	7050 (27)
H(11b)	2066 (18)	5526 (18)	7203 (25)
H(12b)	1570 (18)	5072 (18)	9241 (25)
H(13a)	−0117 (21)	4931 (22)	9081 (29)
H(13b)	0029 (21)	5641 (20)	10265 (29)
H(14a)	−0926 (20)	6029 (18)	7899 (26)
H(14b)	−0924 (24)	6651 (23)	8995 (33)
H(15a)	0511 (23)	7655 (23)	9614 (32)
H(171)	2632 (23)	7407 (23)	10105 (32)
H(172)	2914 (26)	6209 (26)	10117 (38)
H(181)	−1026 (23)	8178 (19)	2157 (28)
H(182)	−1572 (26)	8307 (24)	3447 (34)
H(183)	−0452 (25)	8718 (24)	3153 (34)
H(191)	−1568 (14)	6255 (13)	2425 (18)
H(201)	0045 (18)	4933 (19)	5366 (26)
H(202)	−0894 (18)	5691 (18)	5831 (25)
H(211)	−1605 (29)	4398 (28)	4491 (40)
H(212)	−1756 (28)	4879 (24)	2812 (34)
H(221)	−3169 (27)	5504 (26)	3763 (37)
H(222)	−2732 (29)	5813 (28)	5162 (42)
H(15OH)	2031 (26)	8118 (24)	8114 (35)

E. Site Occupancy of Disordered Atoms

atom	site occupancy
1. Dihydroatisine	
O(22a)	0.425 (6)
O(22b)	0.270 (6)
O(22c)	0.128 (6)
2. Veatchine	
C(22ma)	0.60 (2)
C(22mi)	0.44 (2)
O(22ma)	0.64 (1)
O(22mi)	0.49 (1)

[a] Disordered atom; see part E for site occupancy.

all cases, except for veatchine. In this case, the crystals, although stable when enclosed in a vial, became amorphous when exposed to air for several hours. It was suspected that the crystals might be hygroscopic, because the residue on a microscope slide showed the appearance of a liquid. However, the same behavior was observed when the crystals were exposed to air in a drying oven at 105 °C, well below the melting point of veatchine. For the X-ray studies, crystals of veatchine were enclosed in a capillary which was then sealed by heat. Under these conditions, no observable deterioration of the crystal occurred. It is of interest to note that garryine (the iso form of veatchine) is reported to exist as an amorphous solid which has a crystalline hydrate.[26]

The numbering scheme used to designate the atoms corresponds to the convention for the atisane skeleton, and is shown explicitly for atisine (**1**) Where a hydrogen atom can be clearly assigned either on α or β orientation, it is given the number of the carbon atom to which it is attached, with either "a" or "b", respectively, appended; otherwise an arbitrary digit is appended. The disordered oxygen atoms at O(22) of dihydroatisine are labeled O(22a), O(22b), and O(22c), based on their refined site occupancies. In the structure of veatchine the disordered C and O atoms of the oxazolidine ring were numbered C(22ma) and O(22ma) for the major contributor, and C(22mi) and O(22mi) for the minor contributor, respectively. Several atomic positions were found from difference maps which corresponded to geometrically reasonable locations for hydrogen atoms attached to C(21), C(22), or C(23), and which proved to be stable to refinement. These atoms are indicated by a "d" appended to the atom number. We make no claim for the accuracy of these atomic positions, but include them in the tables for completeness.

Table V. Crystal Data, Data Collection Parameters, and Refinement Results

	atisinium chloride	dihydroatisine	isoatisine	veatchine
cell dimensions				
a, Å	14.340 (1)	13.004 (2)	13.212 (1)	9.934 (3)
b, Å	18.180 (2)	18.939 (4)	13.661 (1)	21.581 (8)
c, Å	7.709 (1)	7.840 (2)	10.403 (1)	8.674 (2)
V, Å^3	2009.7 (6)	1931 (1)	1877 (5)	1860 (2)
space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Z	4	4	4	4
mol wt	379.972	345.527	343.511	343.511
density, g cm^{-3}				
obsd	1.256 (1)	1.189 (1)	1.208 (2)	1.239 (3)
calcd	1.256	1.188	1.215	1.227
method	flotation in chloroform–toluene	flotation in CCl_4–hexane	flotation in aqueous KI	flotation in chloroform–toluene
temp, °C	25	26	20	25
radiation	Cu Kα	Cu Kα	Cu Kα	Mo Kα
wavelength, Å	1.5418	1.5418	1.5418	0.710 69
$2\theta_{max}$	150.20°	150.32°	149.48	54.90
reflections				
measd	2377	2281	2197	2424
obsd	2007 (84.4%)	1651 (72.4%)	1945 (88.5%)	1614 (66.6%)
unobsd	370	630	252	810
final agreement				
R	0.038	0.055	0.048	0.050
R_w	0.037	0.068	0.064	0.079
av shift/esd	0.33	0.167	0.368	0.216
no. of unobsd reflections calculating greater than threshold	35 (9.5%)	95 (15.1%)	43 (17.1%)	122 (15.1%)
max in final difference electron density map, e Å^{-3}	0.20	0.31	0.23	0.27

The various rings of the atisane skeleton are referred to as ring A (carbons 1-5 and 10), B (carbons 5-10), C (carbons 8, 9, and 11-14), and D (carbons 8, 15, 16, and 12-14). In the alkaloid, an additional ring E is formed by N and carbons 19, 4, 5, 10, and 20. The fusion of rings C and D at carbons 8 and 12 forms a bicyclo[2.2.2.]octane moiety, with an additional ring made up of carbons 8, 9, 11, 12, 16, and 15. The nomenclature of veatchine is similar, except that the fusion of rings C and D occurs at carbons 8 and 13, making ring D a five-membered ring composed of carbons 8, 15, 16, 13, and 14, and forming a bicyclo[3.2.1]octane moiety.

Measurements of the integrated intensity of the diffraction maxima were made on an Enraf-Nonius CAD-4 diffractometer. The data were reduced to structure amplitudes using a locally written program. The structures were solved by direct methods using a multiple-solution technique (MULTAN).[27] All subsequent calculations were carried out on a CDC CYBER 70/74 computer using the programs of the X-RAY system.[28] The atomic scattering factors of Cromer and Mann[29] were used for C, N, O, and Cl, the latter two being corrected for anomalous dispersion in the atisinium chloride structure. The scattering factors for hydrogen were taken from Stewart, Davidson, and Simpson.[30] The least-squares refinements used a free-blocking large block diagonal approximation to the full matrix. The quantity minimized was $\Sigma(w|\Delta F|)^2$ where w is an empirically determined weight which gave no significant trend of $w\Delta F$ with respect to either sin θ or F. The crystal data and various parameters associated with the data collection and refinement are given in Table V. For the most part, the solution and refinement of each structure presented little difficulty. In two cases, problems of disorder occurred.

In the case of dihydroatisine, atoms C(22) and O(22)—the two terminal atoms of the *N*-β-hydroxyethyl side chain—did not refine to consistent positions in the earlier cycles of least-squares refinement. After most of the hydrogen atoms had been located, and weights applied to the observations, difference maps calculated from a model with C(22) and O(22) missing revealed a threefold disorder in the position of O(22). The final cycles of refinement varied the site occupancy of three partial oxygen atoms, O(22a), O(22b), and O(22c). Refinement of anisotropic thermal parameters for these three atoms proved unsuccessful, so all three were assigned a common overall, isotropic temperature factor.

The refinement of the structure of veatchine led to the interesting discovery of epimeric disorder discussed more extensively above. All but one of the nonhydrogen atoms were located from an *E* map based on the phases generated by MULTAN. The missing atom was the hydroxyl oxygen, O(15), which was readily located from a difference electron density map. An additional peak was found near O(22), and ignored in forming a molecule from all the atomic positions. In retrospect, this peak (no. 23 out of 30 searched for) provided an early indication of the disorder between the C(20) epimers.

Refinement of an ordered model consisting of 22 carbon, 2 oxygen, and 1 nitrogen atoms, all with anisotropic thermal parameters, converged at $R = 0.149$. A difference map was calculated to locate hydrogen atoms, and instead revealed two large peaks which corresponded to the disordered positions for C(22) and O(22). A difference map calculated on the assumption that these represented fully occupied atomic sites showed maxima at the original coordinates. The four atoms were thus treated as half-occupied sites in subsequent refinement. After all but three of the hydrogen atoms had been located (the missing hydrogens being bonded to C(21) and C(22), and thus presumably disordered themselves), the site occupancy was allowed to vary in the least-squares refinement. Regardless of the starting point, the refined values of the site occupancy converged to indicate the predominance of one epimer by approximately a 60:40 ratio. Based on the esd's from the least-squares refinement, this ratio is significantly different from 50:50; it is also in general agreement with the ratio found by integrating the doubled peaks in the NMR spectra of atisine and veatchine.[8]

Positional parameters and their esd's derived from the diagonal terms of the inverse least-squares matrix are given in Table IV for all atoms. Tables of isotropic and anisotropic thermal parameters and comparisons of observed and calculated structure factors are available as supplementary material (see paragraph at end of paper).

In order to establish the consistency of the ratio of the epimers in veatchine, a limited set of data was collected from three additional crystals. The reflections included in this partial set of data included 22 "sensitive" and 10 "insensitive" reflections, chosen on the basis of structure factor calculations on both the 20*S* (major epimer) and 20*R* (minor epimer) molecules.

The final coordinates for veatchine (see Table IV and the supplementary material) were used with appropriate modifications to the site occupancies. In both cases, the residual was substantially greater for the ordered model ($R_{20S} = 0.147$, $R_{20R} = 0.188$) than for the disordered model. A comparison of the structure amplitudes showed

that 66 of the 2424 observed reflections differed by at least 20σ. Furthermore, 22 of these reflections showed a relative difference in $|F_c|^2$ which was at least 40 times the relative standard deviation of the integrated intensity, showing that a change in $|F|^2$ of as little as 2.5% should be measurable. Similarly, 60 reflections were found to be statistically insensitive ($<3\sigma$) to variations in the site occupancies. The strongest ten of these reflections were selected for use as scaling reflections.

Structure factor calculations were made for these 32 reflections at epimeric ratios (expressed as the fraction of the minor epimer) of 0, 0.25, 0.50, 0.75, and 1.00. The "sensitive" reflections showed, without exception, a linear relationship between $|F_c|$ and the epimeric ratio. The "insensitive" reflections showed minor deviations from linearity, but the root mean square deviation from linearity was less than 1.5% in each case. The variation of $|F_c|$ with the epimeric ratio for all 32 reflections is shown in six graphs included in the supplementary material (see paragraph at end of paper).

Triplicate sets of integrated intensity measurements were made for all 32 reflections on three different crystals. Mo Kα radiation was used, and the scan range was set at $1.5 + 0.35 \tan\theta$ degrees. The scan speed was selected on the basis of a preliminary scan at 3°/min so that at least 10 000 net counts could be accumulated, giving a potential precision of 1% in the integrated intensity. The insensitive reflections were weaker, so their precision was slightly poorer, being as high as 3.7% in one case.

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Supplementary Material Available: A listing of anisotropic and isotropic thermal parameters, comparisons of observed and calculated structure amplitudes, and figures showing the variation of F_c with the epimeric ratio (91 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Portions of this work were presented at the summer 1976 Meeting of the American Crystallographic Association, Evanston, Ill, Abstract O7, the summer 1977 Meeting of the ACA, East Lansing, Mich., Abstract M1, and the 1977 Southeast Regional Meeting of the American Chemical Society, Abstract 361. A preliminary publication has also appeared: De Camp, W. H.; Pelletier, S. W. *Science* **1977**, *198*, 726.
(2) Wiesner, K.; Valenta, Z. *Prog. Chem. Org. Nat. Prod.* **1958**, *16*, 26, and references cited therein.
(3) Pelletier, S. W.; Keith, L.H. In "The Alkaloids", Vol. 12; Manske, R. H. F., Ed.; Academic Press: New York, N.Y., 1970; Chapter 2, and references cited therein.
(4) For a recent review of the chemistry of the C_{20} diterpenoid alkaloids, see Pelletier, S. W.; Page, S. W. *Int. Rev. Sci.: Org. Chem., Ser. Two*, **9**, (1976).
(5) (a) Jacobs, W. A.; Craig, L. C. *J. Biol. Chem.* **1943**, *147*, 567. (b) Pelletier, S. W.; Gopinath, K. W.; Kawazu, K. *Chem. Ind. (London)* **1966**, 28.
(6) Pelletier, S. W.; Kawazu, K.; Gopinath, K. W. *J. Am. Chem. Soc.* **1965**, *87*, 5229.
(7) Vorbrueggen, H.; Djerassi, C. *J. Am. Chem. Soc.* **1962**, *84*, 2990. This error has, unfortunately, been propagated in at least one standard reference work: Klyne, W.; Buckingham, J. "An Atlas of Stereochemistry", Oxford University Press: London, 1974.
(8) Pelletier, S. W.; Oeltmann, T. N. *Tetrahedron* **1968**, *24*, 2019.
(9) (a) Pradhan, S. K.; Girijavallabhan, V. M. *Chem. Commun.* **1970**, 644. (b) Pradhan, S. K. *Tetrahedron Lett.* **1978**, 263.
(10) Pelletier, S. W.; Mody, N. V. *Tetrahedron Lett.* **1977**, 1477.
(11) Mody, N. V.; Pelletier, S. W. *Tetrahedron*, **1978**, *34*, 2421.
(12) Pelletier, S. W.; Mody, N. V. *J. Am. Chem. Soc.* **1977**, *99*, 284.
(13) Pelletier, S. W.; Aneja, R.; Gopinath, K. W. *Phytochemistry* **1968**, *7*, 625.
(14) Pelletier, S. W.; Parthasarathy, P. C. *J. Am. Chem. Soc.* **1965**, *87*, 777.
(15) Pelletier, S. W.; Locke, D. M. *J. Am. Chem. Soc.* **1965**, *87*, 761.
(16) Johnson, C. K. ORTEP-II, ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1971.
(17) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127, and additional unpublished data.
(18) Ermer, O.; Dunitz, J. D. *Helv. Chim. Acta* **1969**, *52*, 1861.
(19) Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 502.
(20) Johnson, L. N. *Acta Crystallogr.* **1966**, *21*, 885.
(21) (a) Fries, D. C.; Rao, S. T.; Sundaralingam, M. *Acta Crystallogr., Sect. B* **1971**, *27*, 994. (b) Bugg, C. E. *J. Am. Chem. Soc.* **1973**, *95*, 908. (c) Cook, W. J.; Bugg, C. E. *Acta Crystallogr., Sect. B* **1973**, *29*, 907.
(22) Hirotsu, K.; Higuchi, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1240. Kanters, J. A.; Roelofsen, G.; Doesburg, H. M.; Koops, T. *Acta Crystallogr., Sect. B* **1976**, *32*, 2830. Gress, M. E.; Jeffrey, G. A.; Rohrer, D. C. American Crystallographic Association Meeting, Clemson, S.C., 1976, Abstract PB3.
(23) Altona, C.; Sundaralingam, M. *Acta Crystallogr., Sect. B* **1972**, *28*, 1806.
(24) (a) Wipke, W. T.; Gund, P. *J. Am. Chem. Soc.* **1974**, *96*, 299. (b) *ibid.* **1976**, *98*, 8107.
(25) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *ibid.* **1976**, 736. (c) Baldwin, J. E. *ibid.* **1976**, 738.
(26) Wiesner, K.; Figdor, S. K.; Bartlett, M. F.; Henderson, D. R. *Can. J. Chem.* **1952**, *30*, 608.
(27) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27*, 368.
(28) Stewart, J. M., Ed. "The X-RAY System—Version of 1976", Technical Report TR-446, Computer Science Center, University of Maryland, College Park, Md. Some of the early calculations were performed using the 1972 version of the X-RAY system.
(29) Cromer, D. T.; Mann, J. B. *Acta Crystallogr., Sect. A.* **1968**, *24*, 321.
(30) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.

Sirohydrochlorin.[1] Prosthetic Group of Sulfite and Nitrite Reductases and Its Role in the Biosynthesis of Vitamin B_{12}

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Abstract: Isolation of metabolites from cobalt-free incubations of *Propionibacterium shermanii* extracts has uncovered a new intermediate ($C_{42}H_{46}N_4O_{16}$) related to the corrin biosynthetic pathway whose physical properties are identical with those of sirohydrochlorin. Structural proposals utilizing ^{13}C NMR and ^1H NMR spectra for this compound, which is the prosthetic group of a number of six-electron reducing enzymes, are discussed and the intermediacy of sirohydrochlorin in corrin biosynthesis is demonstrated in a double-labeling experiment. On the basis of these findings the complete stereostructure (**7**) is proposed for sirohydrochlorin and hence siroheme, the novel iron-containing prosthetic group of *Escherichia coli* NADPH-sulfite reductase (EC 1.8.1.2) and of ferredoxin-nitrite reductase (EC 1.7.7.1) of spinach.

Recent work in these laboratories[2a-c] and independently at Cambridge[3] and Stuttgart[4] has confirmed the role of uro'gen III (**1**) in the biosynthesis of vitamin B_{12} (**2**) in whole cells of *Propionibacterium shermanii*, and of cobyrinic acid (**3**) in cell-free extracts of *P. shermanii* and *Clostridium tetanomorphum* as first suggested by ^{13}C-labeling experiments with the uro'gen I-IV mixed isomers.[5] It has also been shown[2d] that during the bioconversion of both uro'gen III (**1**) and the "ring

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