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Conformational Analysis of the Oxazolidine and Tetrahydro-1,3-oxazine Ring of C_{20}-Diterpenoid Alkaloid Derivatives[1]

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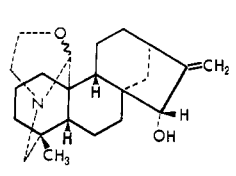
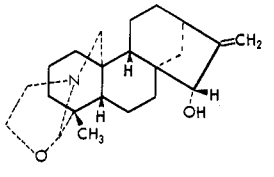
Chemical and spectral data about the behavior of the oxazolidine ring of atisine and veatchine in hydrogen-bonding and non-hydrogen-bonding solvents are presented. The steric effect of the C(16) methyl group on closure of the normal- and iso-type oxazolidine ring in various derivatives of atisine, veatchine, cuauchichicine, and garryfoline has been studied by ^{13}C NMR spectroscopy. The normal-type oxazolidine ring of veatchine-related derivatives closes from one side of the trigonal C(20) carbon to give a single C(20) epimer when the C(16) methyl group is in a β configuration. By contrast, the presence of the C(16) methyl group in an α configuration affords both C(20) epimers on ring closure. The iso-type oxazolidine ring closes from both sides of the trigonal C(19) carbon to give both epimers regardless of the conformation of the C(16) methyl group. Treatment of various imine derivatives with glycidol afforded the favored six-membered tetrahydro-1,3-oxazine derivatives exclusively, instead of the possible five-membered oxazolidine-ring-containing derivatives. The structure of one of the isomers of 22-hydroxyhomoveatchine acetate (**42**) was confirmed by a single-crystal X-ray analysis. Modes of formation and stereochemistry at C(20) of the oxazolidine and tetrahydro-1,3-oxazine derivatives are discussed.

The behavior of the oxazolidine ring of the atisine- and veatchine-type alkaloids has been one of the most intriguing aspects of the chemistry of C_{20}-diterpenoid alkaloids. Among these alkaloids, atisine (**1**, Scheme I) and veatchine (**2**) have been the subjects of extensive chemical and spectral investigations since the early 1950's.[2,3] In 1955, Wiesner and Edwards[4] ingeniously described the behavior of the oxazolidine ring of veatchine and garryine (**3**) in



2 Veatchine



3 Garryine

aqueous media and explained the reason for the higher basicity of veatchine (pK_a = 11.5) compared with garryine (pK_a = 8.7). After the publication of this significant work, many papers describing the detailed study of the isomerization and behavior of the oxazolidine ring of atisine and related compounds were published.[2] Pradhan and Girijavallabhan[5,6] correctly concluded that atisine exists as a mixture of epimers and not two conformers as proposed in an earlier study.[7] We subsequently confirmed the presence of these epimers in atisine and in other related alkaloids in a detailed study of their ^{13}C NMR spectra and also suggested that the interconversion of the epimers does not occur in nonpolar solvents.[8-10] Further, the X-ray crystallographic investigations of atisinium chloride, dihydroatisine, isoatisine, and veatchine firmly established their absolute configurations. The ^{13}C NMR data and X-ray crystal structure of veatchine showed it to be a mixture of C(20) epimers, indicating that the normal closure of the oxazolidine ring takes place on either side of the immonium double bond.[11] The conformational

(1) Parts of this paper were presented as a plenary lecture at the 20th Annual Meeting of the American Society of Pharmacognosy at Purdue University, Indiana, July 30–Aug 3, 1979.

(2) Pelletier, S. W.; Keith, L. H. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1970; Vol. 12, Chapter 2 and references cited therein.

(3) Pelletier, S. W.; Mody, N. V. In "The Alkaloids"; Manske, R. H. F., Eds.; Rodrigo, R., Academic Press: New York, 1981; Vol. 18, Chapter 2.

(4) Wiesner, K.; Edwards, J. A. *Experientia* **1955**, *11*, 255.

(5) Pradhan, S. K.; Girijavallabhan, V. M. *J. Chem. Soc. D* **1970**, 644.

(6) Pradhan, S. K. *Tetrahedron Lett.* **1978**, 263.

(7) Pelletier, S. W.; Oeltman, T. N. *Tetrahedron* **1968**, *24*, 2019.

(8) Pelletier, S. W.; Mody, N. V. *J. Am. Chem. Soc.* **1977**, *99*, 284.

(9) Mody, N. V.; Pelletier, S. W. *Tetrahedron* **1978**, *34*, 2421.

(10) Pelletier, S. W.; Mody, N. V. *Tetrahedron Lett.* **1977**, 1477.

(11) (a) DeCamp, W. H.; Pelletier, S. W. *Science (Washington, D.C.* **1977**, *198*, 726. (b) Pelletier, S. W. DeCamp, W. H.; Mody, N. V. *J. Am. Chem. Soc.* **1978**, *100*, 7976.

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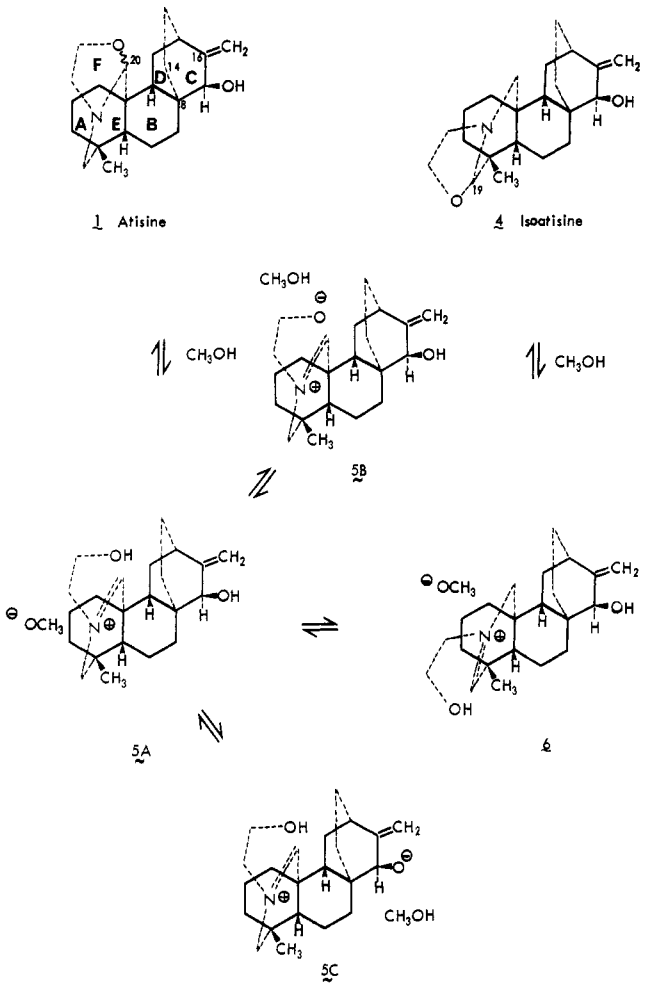
Scheme I



1 Atisine

4 Isoatisine

5B

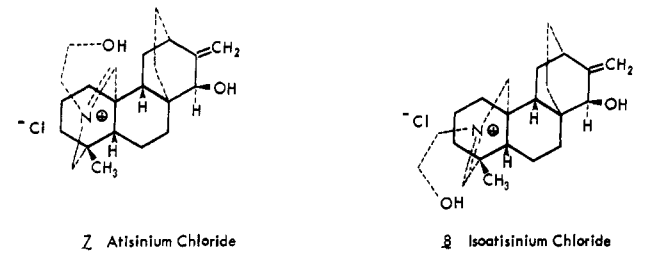
5A

6

5C

aspects of the oxazolidine ring in C_{20}-diterpenoid alkaloids have been discussed in many of our earlier publications.[3,12,13a]

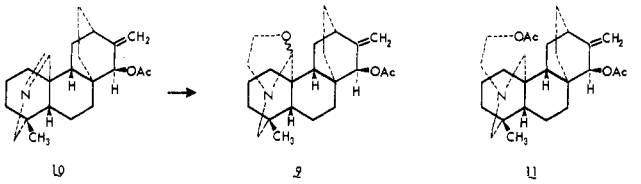
Atisine, an amorphous alkaloid, isolated from several *Aconitum* species,[3] is a very strong base (pK_a = 12.8) and is usually isolated in the form of its hydrochloride salt (atisinium chloride, 7). The strucure of 7 has been confirmed by an X-ray analysis.[11b] Atisine undergoes a facile isomerization of the oxazolidine ring from its "normal" position [closed on C(20)] to the "iso" position [closed on C(19)] of isoatisine (4) by refluxing in methanol or other hydroxylic solvents. This isomerization can be reversed by refluxing isoatisinium chloride (8) [hydrochloride salt of isoatisine] in DMF, Me_2SO, or high-boiling alcohols.[13b] Veatchine (2), a major alkaloid of *Garrya veatchii* Kellog,



7 Atisinium Chloride

8 Isoatisinium Chloride

Scheme II

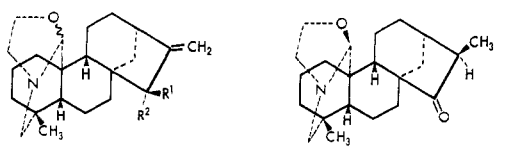


10 9 11

has chemical properties similar to those described for atisine. The crystal structure of veatchine shows[11] that both C(20) epimers exist in the unit cell in a disordered relationship. This X-ray analysis of veatchine also demonstrated that closure of the oxazolidine ring to C(20) in an exo configuration is favored. These results are in agreement with the reported carbon-13 NMR analysis of veatchine.[8,9] Atisine and veatchine have shown similar chemical and spectroscopic behavior patterns in various solvents, and, therefore, atisine also exists as a mixture of epimers in the solid state as shown for veatchine.

To demonstrate the presence of methoxide ions in the methanolic solution of atisine as shown in species **5A**, we prepared 15-acetylatisine (**9**) from atisine azomethine acetate (**10**) as described earlier from our laboratory[14] (Scheme II) and examined the behavior of **9** in methanol. A solution of 15-acetylatisine (**9**) in methanol at 25 °C afforded a mixture of atisine (**1**) and isoatisine (**4**) within 9 h. Atisine acetate is stable in nonhydroxylic solvents such as chloroform and toluene, while in hydroxylic solvents it hydrolyzes to atisine within 3 h. However, dihydroatisine diacetate (**11**), which contains no oxazolidine ring, was stable in methanol, and hydrolysis of the acetyl group was not observed even after 24 h. Hydrolysis of 15-acetylatisine to atisine in methanol can be explained as involving opening of the oxazolidine ring by methanol to give the major methoxide ion containing species **5A** (acetyl derivative). The methoxide ion then hydrolyzes the acetyl group to give atisine. Clearly a solution of atisine in methanol exists as an equilibrium between the ionic species **5A** and the zwitterions **5B** and **5C**. Because of the acidic nature of methanol and its high concentration in solution, the methoxide ion containing species **5A** is present in substantial concentration. The slow isomerisation of atisine in methanolic solution to give isoatisine (**4**) must involve an intermediate ionic species such as **6**. This result constitutes the first direct chemical evidence confirming the earlier proposed behavior of atisine in ionic solvents.

Similarly, veatchine acetate (**12**) and garryfoline acetate (**13**, ovatine) in methanol at 25 °C afforded veatchine (**2**) and garryfoline (**14**), respectively, in quantitative yield



12 R^1 = H, R^2 = OAc Veatchine Acetate
13 R^1 = OAc, R^2 = H Ovatine
14 R^1 = OH, R^2 = H Garryfoline

15 Cuauchichicine

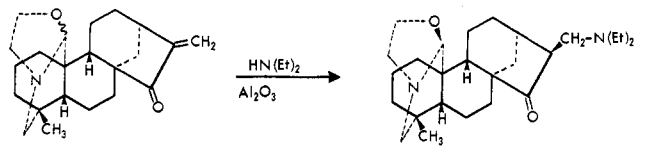
within 12 h. Hydrolysis of the C(15) acetyl group in veatchine acetate and garryfoline acetate is slower than hydrolysis of atisine acetate. The rate of hydrolysis of the C(15) acetyl group is directly related to the pK_a of the oxazolidine-ring-containing alkaloids, atisine, veatchine, and garryfoline. Treatment of γ-butyrolactone (500 mg)

(12) Pelletier, S. W.; Mody, N. V. *J. Nat. Prod.* **1980**, *43*, 41.
(13) (a) Pelletier, S. W.; Desai, H. K.; Finer-Moore, J.; Mody, N. V. *J. Am. Chem. Soc.* **1979**, *101*, 6741. (b) In ref 11b the formula drawing **2** for isoatisine shows a thick line for the C_{19}–oxygen bond. This should be corrected to a dotted line as represented in this paper, indicative of an *S* configuration at C_{19}.

(14) Pelletier, S. W.; Nowacki, J.; Mody, N. V. *Synthet. Commun.* **1979**, *9*, 201.

in methanol (15 mL) with a catalytic amount of veatchine (10 mg) at 25 °C afforded methyl γ-hydroxybutyrate and the starting material in the ratio of 6:4, respectively, after 12 h. The ratio of the product to the starting material was increased to 8:2 when the same reaction mixture was kept for another 12 h. γ-Butyrolactone failed to form methyl γ-hydroxybutyrate when it was treated with dihydrogarryfoline in methanol for 24 h. These results confirm the presence of methoxide ions in the methanolic solution of the oxazolidine-ring-containing derivatives. The immonium ion species of atisine exists in higher concentration in aqueous media than the oxazolidine form compared with veatchine and garryfoline. This phenomenon can be explained by the steric compression of one of the C(14) hydrogens on the C(20) position in atisine, whereas this steric compression is less in veatchine and garryfoline.

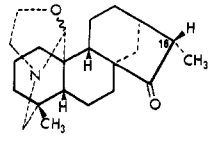
During our work on the structure of cuauchichicine (15), an alkaloid of *G. laurifolia*, we found by carbon-13 NMR analysis that it exists as a single compound and not a mixture of C(20) epimers, despite having the normal-type oxazolidine ring and the stereochemistry of the C(16) methyl group in a β configuration.[13] Subsequently, this proposed structure for cuauchichicine was confirmed by a single-crystal X-ray analysis.[13] In connection wtih other work, we observed[15] that addition of diethylamine to veatchinone (16) afforded compound 17, which showed the



16 Veatchinone 17

presence of a single C(20) epimer in solution by ^{13}C NMR analysis as well as in the solid state by X-ray analysis. In contrast, veatchinone was found to exist as a mixture of C(20) epimers. The stereochemistry of the C(16) $CH_2N(C_2H_5)_2$ group of 17 is in a β configuration as we observed in the case of cuauchichicine. From these results, we conclude that the behavior of the oxazolidine ring of diterpenoid alkaloids observed in solution by carbon-13 NMR spectroscopy is identical with that which was observed in the solid state by X-ray analysis. Since cuauchichicine (15) and compound 17, which both contain the C(16) group in a β configuration, showed the presence of a single C(20) epimer, we were prompted to investigate the influence of the C(16) methyl group on the conformation of the oxazolidine ring of atisine- and veatchine-related derivatives.

In view of the fact that cuauchichicine exists as a single epimer at C(20), we became interested in finding whether 16-epicuauchichicine (18) exists as one epimer or a pair



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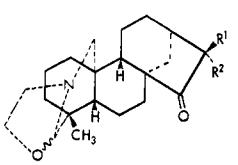


19 $R^1 = CH_3$; $R^2 = H$
20 $R^1 = H$; $R^2 = CH_3$

of epimers at C(20). We prepared 16-epicuauchichicine from cuauchichicine in four steps.[16] Cuauchichicine was

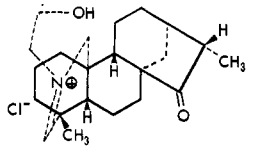
(15) Pelletier, S. W.; Venkov, A. P.; Finer-Moore, J.; Mody, N. V. *Tetrahedron Lett.* **1980**, *21*, 809.
(16) Pelletier, S. W.; Mody, N. V.; Desai, H. K. *J. Org. Chem.* **1981**, *46*, 1840.

Table I. ^{13}C NMR Chemical Shifts and Assignments for the N-CH_2CH_2OH Derivatives[a,b]

	29	30	31	32	33	34
C(1)	41.5	41.4	41.5	41.3	40.0	40.3
C(2)	18.6‡	18.8‡	18.6‡	18.0	23.3	23.3
C(3)	41.0	40.9	40.9	39.9	41.5	41.4
C(4)	33.8	33.9	33.7	33.7	33.6	33.7
C(5)	51.8	50.7	49.8	49.4	49.8	49.8
C(6)	19.0‡	19.2‡	19.6‡	18.0	17.6	17.3
C(7)	34.0	34.7	37.9	32.4	32.6	31.8
C(8)	47.3	48.6	46.3	52.3	35.6	36.3
C(9)	50.4	50.2	43.3	48.6	38.9	38.9
C(10)	40.4	40.5	39.8	40.6	38.1	38.1
C(11)	23.5	30.5	23.6	23.3	27.5	27.5
C(12)	25.1	23.5	26.1	24.8	35.3	42.5
C(13)	38.7	42.7	43.3	38.4	27.5	28.5
C(14)	38.7	40.1	38.7	34.5	27.5	28.5
C(15)	88.5	82.6	80.7	224.7	76.1	83.0
C(16)	47.8	40.9	38.4	47.8	32.4	31.8
C(17)	13.6	15.0	9.7	10.2	13.4	19.6
C(18)	26.6	26.6	26.6	26.4	26.4	26.6
C(19)	60.6	60.4	60.5	60.5	60.3	60.2
C(20)	56.1	56.0	56.2	55.7	54.0	54.1
C(21)	58.1	58.0	58.0	58.1	58.0	58.0
C(22)	60.9	60.8	60.8	60.9	60.8	60.7

[a] Chemical shifts in ppm downfield from Me_4Si. Spectra were taken in $CDCl_3$ at 15.03 MHz in the Fourier mode on using a JEOL FX-60 spectrometer. [b,‡] These assignments may be interchanged in any vertical column. These assignments are based on ref 9.

isomerized at reflux temperature in methanol to give isocuauchichicine (19), which was refluxed in a solution of 2% sodium hydroxide in methanol to afford a mixture of 16-epiisocuauchichicine (20) and isocuauchichicine (19). This mixture was separated by careful alumina column chromatography with hexane and benzene as the eluting system. Treatment of compound 20 with HCl afforded the immonium salt 21. The latter was converted to the



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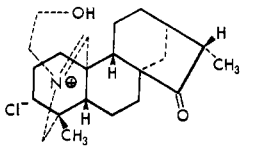

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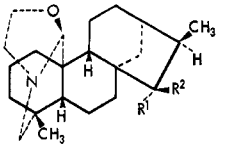
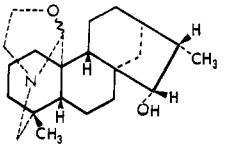


23 $R^1 = OH$; $R^2 = H$
24 $R^1 = H$; $R^2 = OH$



25

normal-type immonium salt 22 by refluxing in Me_2SO. Treatment of 22 with base effected ring closure to give 16-epicuauchichicine (18). The latter was prepared also by oxidation of compound 25 with pyridinium chlorochromate. The ^{13}C NMR spectrum of 18 in $CDCl_3$ reveals two sets of signals for the oxazolidine ring (Table II), indicating that 18 exists as a pair of epimers at C(20). This observation clearly demonstrates that orientation of the C(16) methyl group has a profound influence on direction of the normal-type oxazolidine ring closure in veatchine-type alkaloids. Interestingly, we observed that isocuauchichicine (19), but *not* its 16-epimer, which possess an iso-type oxazolidine ring, exist as a mixture of C(19) ep-

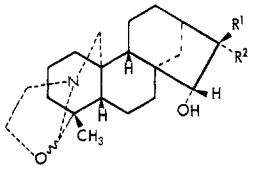
Table II. ^{13}C NMR Chemical Shifts and Assignments for the Normal-Type Oxazolidine-Ring-Containing Derivatives[a]

	15	18	23	25	24	35	36[b]
C(1)	41.6	41.8, 41.3	42.0	41.9, 41.4	42.0	42.2, 41.4	41.8, 41.6
C(2)	18.4	18.8, 20.9	19.2	19.4, 20.5	19.8	21.2	22.3
C(3)	38.4	37.4	38.3	40.5, 40.3	38.4	39.6, 39.0	39.9
C(4)	34.0	34.2	34.2	34.2	34.2	33.9	34.1
C(5)	52.4	52.1	53.0	53.0, 52.8	52.4	51.9	52.0
C(6)	17.9	18.3, 19.6	18.8	19.2, 17.9	19.4	17.9	18.1
C(7)	32.6	32.9, 31.1	35.2	35.3, 35.2	35.2	32.6	32.8
C(8)	52.0	52.8	52.7	48.7	46.5	35.8, 36.4	36.8, 37.4
C(9)	47.7	46.8, 47.5	47.6	51.8	44.6	45.5	43.7, 42.4
C(10)	40.5	41.0	40.7	40.9	40.5	40.5, 41.1	40.9, 39.9
C(11)	22.7	22.7	23.2	22.9, 22.0	22.9	22.5	23.1
C(12)	22.4	28.7, 29.7	22.9	29.2, 28.4	22.2	34.6	35.0
C(13)	33.7	34.2	34.7	34.7	39.3	33.0	32.6
C(14)	34.7	36.6	35.2	35.0	39.0	26.1	29.2
C(15)	224.7	226.0	88.6	83.1, 84.5	81.7	76.5, 76.3	83.2[c]
C(16)	49.5	49.2	47.2	43.2, 43.1	38.4	27.6, 28.5	29.0, 28.3
C(17)	10.0	15.9	13.6	15.0	9.7	13.2, 13.8	19.2, 19.0
C(18)	25.5	25.9, 25.2	26.0	26.0	26.0	26.4, 26.6	26.3, 27.0
C(19)	56.7	56.7, 55.9	56.7	56.5, 56.1	56.9	56.3, 53.3	56.6, 53.5
C(20)	92.7	92.9, 93.8	93.0	92.8, 94.2	93.4	94.1[b]	94.5, 94.8
C(21)	50.5	50.6	50.5	50.4	50.6	50.4[b]	50.6, 49.4
C(22)	64.5	64.7, 59.0	64.5	64.4, 59.0	64.5	64.1, 59.3	64.5, 59.4

[a] Same footnotes as in Table I. [b] Spectrum of compound 36 was taken in C_6D_6 because of its instability in chloroform solution. [c] Very intense.

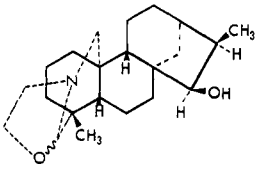
imers, as shown distinctly by their ^{13}C NMR spectra (Table III).

The above results prompted us to extend our study to other diterpenoid alkaloid derivatives having the methyl group at the C(16) position and a hydroxy group at the C(15) position. The normal-type oxazolidine-ring-containing veatchine-type compounds **23–25** and their iso-type oxazolidine-ring-containing compounds **26–28** were pre-



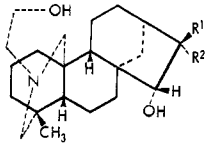
26 $R^1 = CH_3$; $R^2 = H$

27 $R^1 = H$; $R^2 = CH_3$



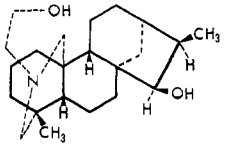
28

pared from veatchine and garryfoline. Catalytic hydrogenation of veatchine afforded a mixture of the C(16) epimers of tetrahydroveatchines **29** and **30**. These epimers



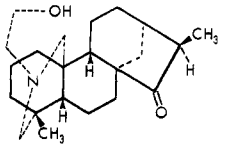
29 $R^1 = CH_3$; $R^2 = H$

30 $R^1 = H$; $R^2 = CH_3$



31

were separated by preparative TLC and crystallization to afford **29** as the major component (mp 165–166 °C, $[\alpha]^{30}_D$ −65°) and **30** as the minor component (mp 119–120 °C $[\alpha]^{30}_D$ −75.1°). The structures of compounds **29** and **30** were based on their ^{13}C NMR analysis (Table I). Previous workers reported[17] obtaining a single compound, mp 147–149 °C, by catalytic hydrogenation of veatchine. However, our work demonstrates that catalytic hydrogenation of veatchine affords both C(16) epimers. Catalytic hydrogenation of garryfoline (**14**) also yielded two compounds. Separation of these two compounds by preparative TLC afforded the known tetrahydrogarryfoline (**31**) as the major component and dihydrocuauchichicine (**32**) as a minor component.[18] Interestingly, the compound



32

containing the C(16) α-methyl group was not formed, but instead dihydrocuauchichicine (**32**) was formed via an acid-catalyzed rearrangement of garryfoline. The structures of compounds **31** and **32** were confirmed by carbon-13 NMR analysis (Table I). The tetrahydro derivatives **29–31** were cyclized to their corresponding normal- and iso-type oxazolidine-ring-containing analogues **23–28** by using our recently developed[19] method of oxidative cyclization with alkaline potassium ferricyanide. The chemical shift assignments of compounds **23–28** are presented in Tables II and III. The assignments of the stereochemistry at the C(19) and C(20) positions in these compounds were made with the help of direct analysis of nonprotonated carbon centers and completely and partially decoupled spectra, as well as with a direct comparison with related compounds.[9] On the basis of proton and carbon-13 NMR spectral analysis, compounds **23** and **24**, which contain the C(16) β-methyl group, are shown to exist as a single epimer at C(20), while compound **25** with the C(16) α-methyl group is shown to exist with the oxazolidine ring in both epimeric forms with the epimer containing the C(20) *syn* proton (with respect to the bicyclooctane system) as the major component. The iso-type oxazolidine-ring-containing compounds **26–28** exist as a mixture (8:2 ratio) of the C(19) epimers regardless of the conformation of the C(16) methyl group.

We directed our attention toward certain atisine-related compounds to investigate whether the oxazolidine ring of these compounds follows the same behavior pattern ob-

(17) Wiesner, K.; Figdor, S. K.; Bartlett, M. F.; Henderson, D. R. *Can. J. Chem.* **1952**, *30*, 608.

(18) Djerassi, C.; Smith, C. R.; Lippman, A. E.; Figdor, S. K.; Herran, J. *J. Am. Chem. Soc.* **1955**, *77*, 4805.

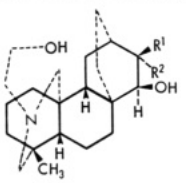
(19) Pelletier, S. W.; Ateya, A. M.; Mody, N. V.; Desai, H. K.; Schramm, L. C. *Tetrahedron Lett.* **1980**, *21*, 3647.

Table III. ^{13}C NMR Chemical Shifts and Assignments for the Iso-Type Oxazolidine-Ring-Containing Derivatives[a]

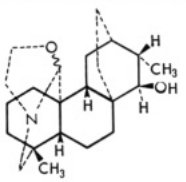
	19	20	26	27	28	37	38
C(1)	40.6	40.8	40.7	40.7	40.8	40.7	40.6
C(2)	20.1	20.2	21.1, 21.3	21.3	21.8	22.2	22.2
C(3)	39.7	39.9	40.7, 41.6	40.7, 41.6	40.8	39.9	42.3
C(4)	40.6	40.6	40.4	40.4	69.9	38.3	38.2
C(5)	50.6	50.7	51.8, 52.8	51.1, 52.8	48.8	48.8	48.8
C(6)	18.0	18.3	18.4, 19.5	18.7, 19.4	18.7, 19.9	19.6	19.2
C(7)	33.0	32.9	34.4	34.6	37.9	32.5	32.3
C(8)	52.4	52.8	47.4	48.6	46.5	36.1	36.4
C(9)	47.9	47.8	49.3	50.9, 50.4	43.5, 43.1	39.1	40.2
C(10)	35.9	36.0	36.1	35.9, 35.5	36.1, 34.4	35.7	36.0
C(11)	22.3	30.1	22.4, 22.6	30.5, 30.1	22.5	21.5	21.2
C(12)	24.9	22.3	24.4, 24.0	22.4	26.1, 25.8	35.3	39.1
C(13)	38.5	37.0	38.7, 38.3	42.7	39.2	27.7	28.5
C(14)	34.6, 34.2	36.5	37.9	40.1	38.7	27.6	27.7
C(15)	224.7	225.3	88.5, 88.3	82.6, 82.4	80.9	76.1	83.1, 84.0
C(16)	48.8	46.3	47.2	49.2	38.3	33.0	32.0
C(17)	10.1	15.9	13.6, 13.4	15.0	9.7	13.4	19.6
C(18)	24.3	24.3	25.1, 24.6	24.4, 23.9	24.5, 24.0	24.3	24.4
C(19)	98.4, 96.8	98.4, 96.8	98.4, 96.7	98.3, 96.5	98.6, 96.8	99.5, 96.5	98.9, 96.3
C(20)	48.4	48.4	51.0, 51.4	51.1, 51.6	51.3, 51.7	49.9	50.1
C(21)	54.9, 56.5	54.8	54.9, 59.0	54.9, 58.7	55.0	55.1	55.0
C(22)	58.8, 64.9	58.8, 64.9	58.4, 64.9	58.7, 64.7	58.8, 64.8	58.7	58.7

[a] Same footnotes as in Table I.

served in the case of the veatchine-related compounds. The α- and β-tetrahydroatisines **33** and **34**, respectively,



33 $R^1 = CH_3$; $R^2 = H$
34 $R^1 = H$; $R^2 = CH_3$



36

were prepared according to the reported procedure[20a] by catalytic hydrogenation of atisine. The structures of compounds **33** and **34** were assigned by carbon-13 NMR data, and the structure of **34** was confirmed by a single-crystal X-ray analysis.

Crystal data for "β"-tetrahydroatisine (**34**) are as follows: orthorhombic, $a = 8.1495$ (9) Å, $b = 12.993$ (1) Å, $c = 18.572$ (1) Å, space group = $P2_12_12_1$, $d_{calcd} = 1.16$ g cm^{-3} for four molecules of $C_{22}H_{32}NO_2$ in the unit cell. Unique reflections with $\theta \leq 60°$ were measured on an Enraf-Nonius CAD-4 diffractometer using Cu K_α radiation ($\lambda = 1.5418$ Å), ω–2θ scans of width $(1.0 + 0.14 \tan \theta)°$, and a variable scan speed. Intensities of three control reflections did not change significantly during data collection. After correcting for Lorentz and polarization effects, 1460 of the 1691 reflections measured were observed ($I \leq 2\sigma(I)$).

The structure was solved by direct methods.[21] After isotropic and anisotropic refinements of the non-hydrogen atoms, a difference map revealed all hydrogens except those on the nitrogen side chain.[22] The anisotropic thermal parameters for C(22) were unusually large. To check for disorder, C(22) and O(22) were removed and the remaining atoms refined for two cycles. Three peaks corresponding to C(22) then appeared on a calculated difference map, but one of these did not behave well during subsequent refinements and twofold disorder for C(22) was assumed. Two atoms representing C(22) were refined isotropically with occupancies fixed at 0.50; then the occupancies were allowed to vary while the isotropic temperature factors were fixed at their average refined value. The final model included C(22) in two positions with occupancies of 0.57 and 0.43 and hydrogens for all atoms except C(21), C(22), and O(22). Non-hydrogens were anisotropically refined and hydrogens isotropically refined by using the observed data weighted by $w = (4.4 + 0.01F^2 + 0.0006F^3)^{-1}$. At convergence, $R = 0.052$, $R_w = 0.069$, and the largest peak in a difference map was 0.24 e Å^{-3}. None of the atoms had unusually large or nonpositive definite temperature factors.

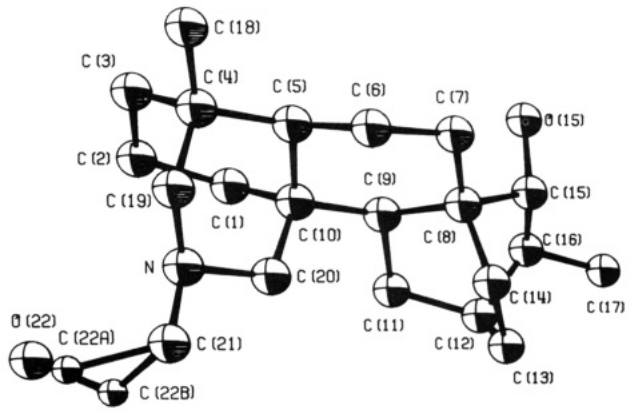


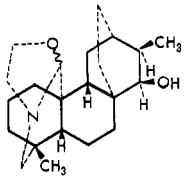
Figure 1. ORTEP drawing of β-tetrahydroatisine (**34**).

Figure 1 shows the molecule with the two positions for C(22) labeled C(22A) (major position) and C(22B). Tables 5–8 (supplementary material) present fractional coordinates, bond distances, bond angles, dihedral angles, and temperature factors[25] for the non-hydrogen atoms. The methyl group at C(16) has the α configuration. The geometry of the molecule is basically the same as that of other C_{20}-diterpenoid alkaloids.[10b] The bicyclo[2.2.2]octane system has a conformation very close to that which it

(20) (a) Pelletier, S. W.; Parthasarathy, P. C. *J. Am. Chem. Soc.* **1965**, *87*, 777. (b) Pelletier, S. W.; Kawazu, K.; Gopinath, K. W. **1965**, *87*, 5229.
(21) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27*, 368.
(22) Stewart, J. M., Ed. "The X-RAY System Version of June, 1976", Technical Report TR-446, Computer Science Center, University of Maryland, College Park, MD.
(23) Kato, T.; Katagiri, N.; Yamamoto, Y. *Heterocycl.* **1980**, *14*, 1333.
(24) Johnson, C. K., ORTEP-II, ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN, 1971.
(25) The U's reported in Tables 5 and 9 (supplementary material) are the isotropic temperature factors equivalent to the components of the anisotropic temperature factor matrices U (see: Hamilton, W. C. *Acta Crystallogr.*, **1959**, *12*, 609).

assumes in isoatisine and is considerably more skewed than it is in dihydroatisine. The only intramolecular bond distances and angles that deviate significantly from expected values are the rather inaccurate ones involving the disordered atom. Intermolecular distances show O(15) to be hydrogen bonded to O(22) of a symmetry-related molecule: O(15)···O(22)′ = 2.869 (5) Å, H(O(15))H···O(22)′ = 2.132 (4) Å, $(x, y, z)' = -0.5 - x, 1 - y, 0.5 + z$.

Oxidative cyclization of tetrahydroatisines **33** and **34** with alkaline ferricyanide afforded the normal- and iso-type oxazolidine-ring-containing compounds **35–38**. The



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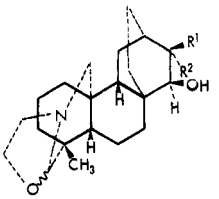


37 $R^1 = CH_3$, $R^2 = H$
38 $R^1 = H$, $R^2 = CH_3$

structures of these compounds were based on carbon-13 NMR analysis, and their chemical shift assignments are presented in Tables II and III. Compound **35** showed the presence of both epimers at C(20). Similarly, compound **36**, which contains the C(16) α-methyl group, existed as a mixture of C(20) epimers with the epimer containing the C(20) *syn* proton (with respect to the bicyclooctane system) as the major component. The iso-type oxazolidine-ring-containing compounds **37** and **38** were found to exist as a mixture of C(19) epimers. On the basis of these results, the following observations are presented for the atisine- and veatchine-related derivatives:

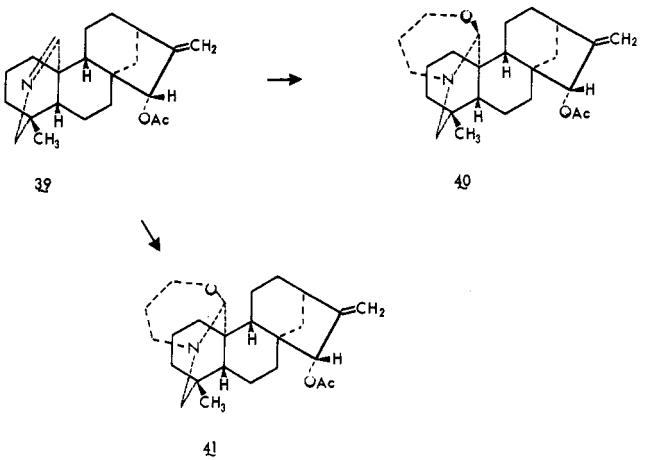
(1) When the C(16) methyl group is in the β configuration, the normal-type oxazolidine ring closes from the exo side of the C(20) trigonal carbon to give a single compound containing the C(20) syn proton in veatchine-related derivative.

(2) When the C(16) methyl group is in the α configuration, the normal-type oxazolidine ring closes from both sides of the C(20) trigonal carbon to give a mixture of C(20) epimers in both atisine- and veatchine-type of derivatives.

(3) The iso-type oxazolidine ring closes from both sides of the C(19) trigonal carbon to give a mixture of C(19) epimers irrespective of the configuration of the C(16) methyl group.

Comparison of the molecular models of cuauchichicine (**15**) and the C(16) β-methyl group containing derivatives (**23** and **24**) with those of the C(16) α-methyl group containing compounds (**18** and **25**) suggests that the major conformational differences between these structures are in rings D and F. The methyl group at C(16) in the β position is spatially crowded in contrast to the α position. Thus in compounds containing the β-methyl group, ring D can exist in the twist conformation, while in the compounds containing the α-methyl group, it can approximate an envelope conformation with C(14) as the flap. The oxazolidine ring F is disordered in compounds **18** and **25**, and can exist both in the twist conformation and in the envelope conformation with C(20) as the flap. In compounds **15**, **23**, and **24**, the oxazolidine ring F can assume an N-flap envelope conformation. One of the C(14) hydrogens appears to be much closer to the syn side of C(20) in compounds with a C(16) β-metyl group than in compounds with a C(16) α-methyl group. Thus, the close contact of the C(14) H to the syn side of C(20) may prevent formation of the second epimer at C(20) in compounds containing the C(16) β-methyl group during the treatment

Scheme III

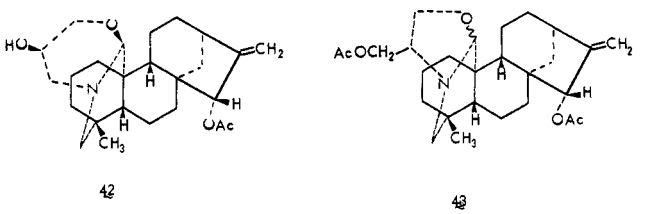


39 **40** **41**

of the ternary immonium salt with base.

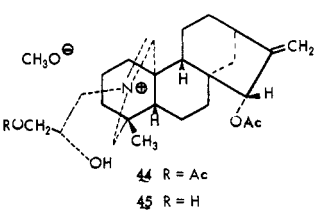
Recently, we reported[14] a method for forming the oxazolidine and thiazolidine rings in C_{20}-diterpenoid alkaloids by treatment of ethylene oxide and ethylene sulfide with various imine derivatives. We also demonstrated that formation of the oxazolidine ring in these compounds occurs via a disfavored 5-endo-trig process.[12] To provide tetrahydro-1,3-oxazine derivatives for biological testing[23] and for a study of the differences in the behavior pattern between the five-membered oxazolidine ring and the six-membered tetrahydro-1,3 oxazine ring, we examined the reaction of oxetane and glycidol with various imine derivatives of C_{20}-diterpenoid alkaloids.

Treatment of veatchine azomethine acetate (**39**) with oxetane in acetic acid at 50–60 °C afforded homoveatchine acetates **40** and **41** in 25% yield (Scheme III). The initial product was found to be a mixture of C(20) epimers by carbon-13 NMR analysis and TLC. Crystallization of the mixture from acetone afforded a compound whose structure (**40**) was established by spectral analysis (Table IV). Further crystallization of the mother liquor failed to give a pure crystalline sample of compound **40** or **41**. Treatment of veatchine azomethine acetate with glycidol afforded compound **42** as the major product, which was



42 **43**

separated by repeated crystallization; its structure was established by carbon-13 NMR spectroscopy and confirmed by X-ray crystallography as described below. As expected, treatment of **39** with glycidol acetate in methanol also afforded **42** as the major product. In this reaction, the oxazolidine-ring-containing compound **43** formed first, which in methanol afforded species **44**. The methoxide



44 R = Ac
45 R = H

ion of **44** hydrolyzed the primary acetate group to give species **45**, which closed in basic solution to form the more stable six-membered tetrahydro-1,3-oxazine ring (**42**) in-

Table IV. ^{13}C NMR Chemical Shifts and Assignments for the Tetrahydro-1,3-oxazine Derivatives[a]

	40	42	47	49	50[c]
C(1)	41.6	41.3	41.5	41.1	41.7
C(2)	19.3	19.2	22.5, 22.6	22.0	22.3, 21.9†
C(3)	36.3	35.9	41.5	36.4	41.4, 40.9
C(4)	33.2	32.2	33.0, 29.7	32.9	33.8, 28.0
C(5)	52.9	52.5	52.1, 52.3	49.6	49.4, 46.8
C(6)	18.7	18.7	17.6, 17.4	24.5	20.8, 21.6†
C(7)	33.7	33.5	35.2, 33.6	72.3	73.2, 72.5
C(8)	47.3	47.3	36.6	40.9	39.9
C(9)	51.8	51.6	41.1	36.4	42.6, 42.0
C(10)	42.3	42.3	41.9	42.2	40.7, 40.6
C(11)	22.3	23.2	27.3	35.0	34.4
C(12)	31.7	31.7	37.1	27.2	36.3
C(13)	43.0	42.8	27.3	23.4	25.5#
C(14)	38.3	38.3	25.6	22.8	24.3, 23.6#
C(15)	83.7	83.5	77.5	72.4	73.9, 73.6
C(16)	156.4	156.0	152.4	151.5	151.6
C(17)	109.2	109.6	110.8, 110.5	111.4	110.8, 109.7
C(18)	26.3	26.3	26.2	26.1	26.5, 26.0
C(19)	54.7	60.7	60.5	60.5	56.4, 56.1
C(20)	94.3	94.3	95.8, 94.5	95.5	93.9[b]
C(21)	61.0	60.7	60.7, 61.8	60.7	53.3, 50.4
C(22)	26.3	73.0	72.2	73.1	64.4, 59.5
C(23)	68.4	64.8	64.6, 63.0	64.6	
C=O	171.3	171.3	171.8	171.5, 171.0	171.5, 171.0
CH_3	21.3	21.3	21.5	21.3, 21.1	21.3, 21.1

[a] Same footnotes as in Table I. [b] Very intense. [c] The assignments with similar symbols may be interchanged.

stead of the possible five-membered oxazolidine ring.

22-Hydroxyhomoveatchine acetate (**42**), $C_{25}H_{37}NO_4$, crystallized as large, clear prisms that were well-suited to X-ray analysis. The crystal data are as follows: orthorhombic, $P2_12_12_1$, $Z = 4$, $a = 7.647$ (2) Å, $b = 12.000$ (1) Å, $c = 24.096$ (3) Å, $V = 2211.2$ (7) Å^3, $d_{calcd} = 1.27$ g cm^{-3}, $d_{meas} = 1.27$ g cm^{-3}, radiation = Cu K_α ($\lambda = 1.5418$ Å). 1849 Reflections with $2\theta \leq 120°$ were measured on an Enraf-Nonius CAD-4 diffractometer using ω–2θ scans of width $(1.15 + 0.142 \tan \theta)°$ and a variable scan speed. Three orientation control reflections were measured once every 200 reflections. In addition, three intensity control reflections were measured every 3 h to monitor crystal stability; their intensities had not declined significantly by the end of data collection. Data were corrected for Lorentz and polarization effects before conversion to structure factors and E's. Direct phasing of the 200 largest E's followed by an E synthesis served to locate all non-hydrogen atoms.[21] Hydrogens were located on a difference map after partial refinement of the heavy atoms.[22] Isotropic refinement of all but the methyl hydrogens and anisotropic refinement of the non-hydrogens converged at $R = 0.048$ and $R_w = 0.066$ for the 1393 observed reflections. The weighting scheme used during refinement, $w = 1.00(4.75 + |F| + 0.02F^2)$, was chosen to give negligible variation in the averge value of $w(\Delta F)^2$ over the range of $|F|$ and sin θ (F).

Figure 2 is a perspective drawing[24] of the molecule, drawn with the same absolute configuration as the parent compound, veatchine.[11b] Tables 9–12 (supplementary material) present fractional coordinates, temperature factors,[25] bond distances, bond angles, and dihedral angles for the non-hydrogen atoms. Rings A–E in the molecule have basically the same conformation as the corresponding rings in veatchine.[11b] C(14), the flap of envelope-shaped ring D, is 0.68 Å from the plane through the remaining atoms in the ring. Ring F is in the chair conformation with a β-hydroxyl group at C(22) [22(R)]. C(20) has the S configuration, resulting from β-closure of the oxazolidine ring.

There are no intermolecular contacts less than 3.4 Å in the crystal structure, but there is a weak intramolecular

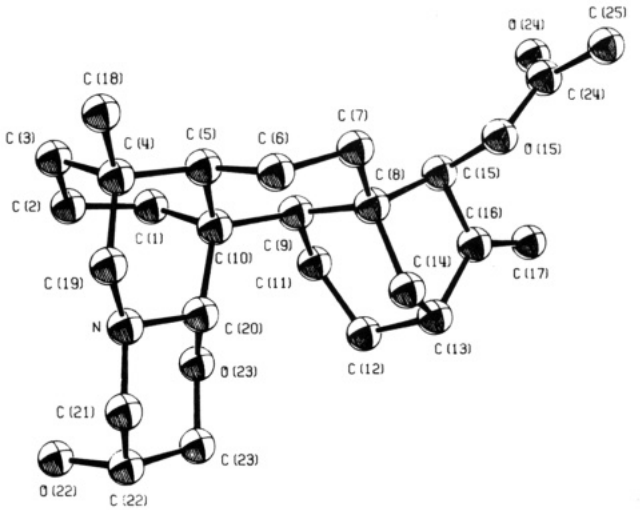
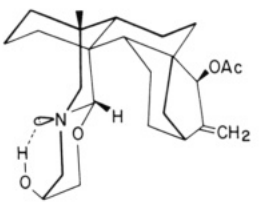


Figure 2. ORTEP drawing of 22-hydroxyhomoveatchine acetate (**42**).

hydrogen bond between the nitrogen and the hydroxyl group: N···O(22) = 2.903 (7) Å, N···H(O(22)H = 2.68 (5) Å, and N···H(O(22)H)–O(22) = 94 (4) Å. Evidence for the

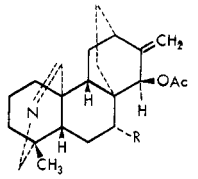


42

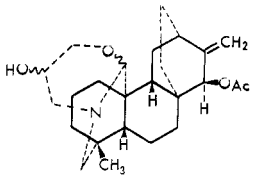
intramolecular hydrogen bond also appears in the IR spectrum of the compound. Inspection of molecular models shows that this intramolecular interaction is impossible in the 20(R) isomer of the compound unless the tetrahydro-1,3-oxazine ring assumes a boat conformation. Therefore, one would expect the 20(S) isomer to be more stable than the 20(R) isomer, and it is not surprising that the 20(R) isomer is only a minor product of the glycidol addition reaction and that the two C(20) epimers do not

cocrystallize as did the C(20) epimers of veatchine.[11b]

In a similar reaction, atisine azomethine acetate (**46**)

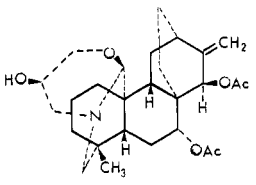


46 R = H
48 R = OAc

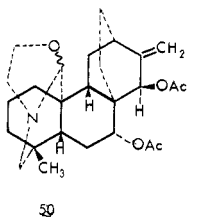


47

reacted with glycidol to give a mixture of the C(20) epimers of compound **47**, which showed a single spot on TLC. Surprisingly, treatment of ajaconine azomethine diacetate (**48**) with glycidol gave a single C(20) epimer (**49**). How-



49



50

ever, treatment of **48** with ethylene oxide afforded compound **50**, which was found to be a mixture of both C(20) epimers by proton and carbon-13 NMR spectral analysis. This behavior suggests that the 7-α-acetoxy group and the secondary hydroxy group at C(22) both exert a profound influence on the direction of closure of the heterocyclic ring. Interestingly, none of the imines formed an oxazolidine-ring derivative with glycidol.

Experimental Section

Melting points are corrected and were taken on a Thomas-Kofler hot stage equipped with a microscope and a polarizer. Rotations were taken in $CHCl_3$ unless otherwise noted on a Perkin-Elmer Model 141 polarimeter. Infrared spectra were recorded on a Perkin-Elmer Model 237B spectrophotometer. Proton NMR measurements were made in $CDCl_3$ solutions, unless otherwise mentioned, on a Varian T-60 spectrometer with Me_4Si as an internal standard, and all the signals are reported as δ values. The following abbreviations are used to express the multiplicity of the signals: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet. Carbon-13 NMR spectra were taken at 15.03 MHz on a JEOL FX-60 spectrometer. ^{13}C chemical shifts are reported in parts per million downfield from Me_4Si. Spectra were determined in $CDCl_3$ solution (which also provided the lock signal). Thin-layer chromatography (TLC) of the alkaloids was accomplished on Merck aluminium oxide GF-254 (type E or 60/E), and the compounds were visualized in UV light and by spraying with Dragendorff reagent. Column chromatography was conducted on Merck neutral aluminium oxide (activity state III, 70–230 mesh ASTM). Preparative thick-layer chromatography (PTLC) was carried out on 20 × 40 cm plates coated with a 2.5-mm layer of Merck aluminium oxide 150 PF-254-366 (Type T), and compounds were visualized in UV light. The solvent system used for TLC and PTLC was mainly hexane–toluene–ethyl acetate–diethylamine (4.25:4.25:1.0:0.5) unless otherwise mentioned.

Catalytic Hydrogenation of Veatchine (2): Preparation of Tetrahydroveatchines 29 and 30. Veatchine (0.7 g) in acetic acid (70 mL) was hydrogenated in the presecne of PtO_2 (0.3 g) at atmospheric pressure for 17 h. The reaction mixture was filtered carefully, and the filtrate was evaporated to dryness in vacuo below 40 °C to give a mixture of epimers. The latter was separated by PTLC using seven plates. Two major bands (between R_f 0.3 to 0.6) were isolated. The less polar band gave **30** (gum, 0.32 g) and the more polar band gave **29** (gum, 0.34 g).

Compound **30**, crystallized from light petroleum ether with difficulty and exhibited the following properties: mp 119–120 °C; $[\alpha]^{30}_D$ −75.1° (*c* 1.5); IR (Nujol) ν_{max} 3380 cm^{-1} (OH); ^1H NMR δ 0.83 (3 H, s, C(4) CH_3), 0.99 (3 H, d, J = 9 Hz, C(16) CH_3), 3.67 (2 H, t, C(22) H_2). For ^{13}C NMR analysis, see Table I. $C_{22}H_{37}NO_2$ requires C, 76.03; H, 10.73; N, 4.03; found C, 76.05; H, 10.88; N, 3.92.

Compound **29** crystallized from acetone: mp 165–166 °C; $[\alpha]^{30}_D$ −65.0° (*c* 1.0); IR (Nujol) ν_{max} 3315 (OH) cm^{-1}; ^1H NMR δ 0.80 (3 H, s, C(4) CH_3), 1.16 (3 H, d, J = 8.5 Hz, C(16) CH_3), 3.67 (2 H, t, C(22) H_2). For ^{13}C NMR analysis, see Table I. $C_{22}H_{37}NO_2$ requires C, 76.03; H, 10.73; N, 4.03; found C, 76.01; H, 10.74; N, 4.02.

Catalytic hydrogenation of veatchine using MeOH instead of AcOH resulted in a very poor yield of compound **30**.

Oxidative Cyclization of 30 Using $K_3Fe(CN)_6$: Preparation of Compounds 25 and 27. A solution of potassium ferricyanide (0.35 g) in water (10 mL) was added to a stirred solution of **30** (0.103 g) in alcohol (10 mL). To this mixture was added aqueous sodium hydroxide solution (4 mL, 8%) at ambient temperature. The progress of the reaction was monitered by TLC on alumina. After 2.8 h the reaction mixture was extracted with dichloromethane (3 × 50 mL). Evaporation of the washed (H_2O) and dried (anhydrous Na_2SO_4) dichloromethane extract afforded a gum (0.076 g) that gave mainly two spots on TLC different from that of the starting material. This mixture consisted of mainly the normal- and iso-type oxazolidine ring forms of the cyclized products. The well-dried gum (0.076 g) was dissolved in dry ether (25 mL), and a slight excess of methanolic hydrochloric acid (1:1) was added to the clear solution with cooling (ice–water bath) when white precipitates of the hydrochloride salts separated. These were collected by decantation after one more washing with dry ether. The white solid was dissolved in water (10 mL), and the cooled solution was basified to pH 8 with saturated potassium carbonate solution. The basic solution was then extracted with CH_2Cl_2 (3 × 30 mL) to give compound **27** as a gum (0.0294 g). The latter was obtained also by cyclization of **30** using our active MnO_2 method.[12]

The basic aqueous layer (pH 8) was further basified in the cold to pH 12 by using sodium hydroxide solution (20%) and then extracted with CH_2Cl_2 (3 × 40 mL) to give compound **25** as a gum (0.0272 g). Compounds **25** and **27** gave the following data on purification.

Compound **25** could not be induced to crystallize and hence it was converted into its HCl salt, which crystallized from methanol: mp 300–305 °C dec; $[\alpha]^{28}_D$ −32.0° (*c* 0.42, MeOH); IR (free base, Nujol) ν_{max} 3395 (OH) cm^{-1}; ^1H NMR (free base) δ 0.82 (3 H, s, C(4) CH_3), 0.95 (3 H, d, J = 7.0 Hz, C(16) CH_3), 4.30 (1 H, br s, C(20) H). For ^{13}C NMR analysis of the free base, see Table II. Mass spectrum: m/z 345 (M^+) and 346 (M + 1); $C_{22}H_{35}NO_2$ requires m/z 345.5 (M^+).

Compound **27** crystallized from acetone: mp 75–77 °C; $[\alpha]^{25}_D$ −45.4° (*c* 0.77); IR (Nujol) ν_{max} 3455 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 and 0.90 (3 −32.0° s, C(4) CH_3), 1.16 (3 H, d, C(16) CH_3), 3.96 (1 H, br s, C(19) H). For ^{13}C NMR analysis, see Table III. Mass spectrum: m/z 345 (M^+) and 346 (M + 1); $C_{22}H_{35}NO_2$ requires m/z 345.5 (M^+).

Oxidative Cyclization of Compound 29 Using $K_3Fe(CN)_6$: Preparation of Compounds 23 and 26. Compound **29** (0.110 g) was cyclized by using $K_3Fe(CN)_6$ exactly as described above in 1.0 h, and products **26** (gum, 0.0396 g) and **23** (gum, 0.0506 g) were isolated in the same manner. The physical data for both compounds are as follows.

Compound **26** crystallized from acetone: mp 86–88 °C; $[\alpha]^{22}_D$ −38.8° (*c* 1.0); IR (Nujol) ν_{max} 3455 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 and 0.90 (3 H, s, C(4) CH_3), 1.10 (3 H, d, C(16) CH_3), 4.1 (1 H, br s, C(19) H). For ^{13}C NMR analysis see, Table III. Mass spectrum: m/z 345 (M^+) and 346 (M + 1); $C_{22}H_{35}NO_2$ requires m/z 345.5 (M^+).

Compound **23** could not be induced to crystallize and hence it was converted into its HCl salt, which crystallized from methanol: mp 287–293 °C dec; $[\alpha]^{27}_D$ −26.8° (*c* 0.4, MeOH); IR (free base, Nujol) ν_{max} 3375 (OH) cm^{-1}; ^1H NMR δ 0.81 (3 H, s, C(4) CH_3), 1.12 (3 H, d, J = 7.0 Hz, C(16) CH_3), 4.30 (1 H, s, C(20) H). For ^{13}C NMR analysis of the free base, see Table II. Mass spectrum: m/z 345 (M^+) and 346 (M^+ 1); $C_{22}H_{35}NO_2$ requires m/z 345.5.

Compound **26** was obtained also by cyclization of **29** using active MnO_2,[12] but attempts to convert **26** into **23** by the known pro-

cedure[20b] resulted in a very poor yield of **23**.

Oxidation of Compound 25 Using PCC: Preparation of 16-Epicuauchichicine (18). To a stirred solution of compound **25** (0.08 g) in CH_2Cl_2 (13 mL) was added pyridinium chlorochromate (0.1 g), and the progress of the reaction was checked by TLC. After 13 min, the reaction was completed. The major product **18** (0.065 g) was isolated by chromatography on an Al_2O_3 (activity III) column. It crystallized from acetone in clusters of white needles: mp 136–138 °C; $[\alpha]^{28}_D$ –74° (*c* 0.72); IR (Nujol) ν_{max} 1735 (ketone) cm^{-1}; ^1H NMR δ 0.91 and 0.74 (3 H, s, C(4) CH_3), 1.16 (3 H, d, J = 8.5 Hz, C(16) CH_3), 4.38 (1 H, br s, C(20) H). For ^{13}C NMR analysis, see Table II. $C_{22}H_{33}NO_2 \cdot 0.5H_2O$ requires C, 74.95; H, 9.72; N, 3.97; found C, 74.58; H, 9.57; N, 3.81.

Catalytic Hydrogenation of Garryfoline (14): Preparation of Tetrahydrogarryfoline (31). A solution of garryfoline (0.283 g) in methanol (37 mL) was hydrogenated in the presence of Adam's catalyst (0.05 g) at 45 psi for 5 h. The gum (0.273 g), obtained after the usual workup, showed two spots on TLC which differed from that of the starting material. The mixture was separated by PTLC (93:7 hexane–ethanol) to afford two compounds. The less plar compound (0.08 g) was identified as dihydrocuauchichicine (**32**) by comparison with an authentic sample. The polar compound (0.19 g) was identified as tetrahydrogarryfoline (tetrahydroepiveatchine, **31**); mp 174–176 °C (lit.[18] mp 175–177 °C). For ^{13}C NMR analysis, see Table I.

Oxidative Cyclization of Compound 31 Using $K_3Fe(CN)_6$: Preparation of Compounds 24 and 28. The tetrahydro compound **31** (0.11 g) was cyclized to its iso (**28**) and normal (**24**) type oxazolidine ring forms in 1.5 h by using the procedure described for **30** with the same quantities of reactants.

Compound **24** (0.05 g) could not be induced to crystallize, and hence it was transformed into its hydrochloride salt, which crystallized from methanol: mp 313–316 °C dec; $[\alpha]^{27}_D$ –30.7° (*c* 0.4, MeOH); IR (free base, Nujol) ν_{max} 3465 (OH) cm^{-1}; ^1H NMR (free base) δ 0.80 (3 H, s, C(4) CH_3), 0.96 (3 H, d, J = 7.0 Hz, C(16) CH_3), 4.25 (1 H, s, C(20) H). For ^{13}C NMR analysis of the free base, see Table II. Mass spectrum: m/z 345 (M^+) and 346 (M + 1); $C_{22}H_{35}NO_2$ requires m/z 345.5 (M^+).

Compound **28** (0.041 g) obtained as a gum could not be induced to crystallize but resulted in an amorphous solid: mp 128–131 °C; $[\alpha]^{28}_D$ –49.7° (*c* 1.0). IR (Nujol) ν_{max} 3395 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 and 0.87 (3 H, s, C(4) CH_3), 0.99 (3 H, d, C(16) CH_3), 3.84 and 3.68 (1 H, s, C(19) H). For ^{13}C NMR analysis, see Table III. Mass spectrum: m/z 345 (M^+) and 346 (M + 1); $C_{22}H_{35}NO_2$ requires m/z 345.5 (M^+).

Catalytic Hydrogenation of Atisine (1): Preparation of α- and β-Tetrahydroatisines 33 and 34. These compounds were prepared according to the reported procedure.[20a] The separation of **33** and **34** from the resulting mixture of at least four compounds, was achieved through PTLC. The physical constants of these compounds were identical with those reported.[20a] For ^{13}C NMR analysis of compounds **33** and **34**, see Table I. The structure of **34** was confirmed by X-ray analysis.

Oxidative Cyclization of Compound 34 Using $K_3Fe(CN)_6$: Preparation of Compounds 36 and 38. Compound **34** (0.14 g) was cyclized in 2.0 h to give compounds **38** (0.065 g) and **36** (0.062 g) by using the procedure described for compound **30** above.

Compound **36** could not be induced to crystallize, and hence it was transformed into its HCl salt, which crystallized from methanol: mp 315–317 °C dec; $[\alpha]^{26}_D$ +22.2° (*c* 0.36, MeOH); IR (free base, Nujol) ν_{max} 3455 (OH) cm^{-1}; ^1H NMR (free base) δ 0.80 and 0.75 (3 H, s, C(4) CH_3), 1.0 (3 H, d, J = 7.0 Hz, C(16) CH_3), 4.31 and 4.08 (1 H, br s, C(20) H). For ^{13}C NMR analysis of the free base, see Table II. Mass spectrum: m/z 345 (M^+) and 346 (M + 1); $C_{22}H_{35}NO_2$ requires m/z 345.5 (M^+).

Compound **38** could not be induced to crystallize, and hence it was transformed into its HCl salt, which crystallized from methanol: mp 298–301 °C dec; $[\alpha]^{28}_D$ –29.8° (*c* 0.65, MeOH); IR (free base, Nujol) ν_{max} 3413 (OH) cm^{-1}; ^1H NMR δ 1.05 and 0.98 (3 H, s, C(4) CH_3), 1.13 (3 H, d, C(16) CH_3), 3.91 (1 H, br s, C(19) H). For ^{13}C NMR analysis of the free base, see Table III. Mass spectrum: m/z 345 (M^+) and 346 (M + 1); $C_{22}H_{35}NO_2$ requires m/z 345.5 (M^+).

Oxidative Cyclization of Compound 33 Using $K_3Fe(CN)_6$: Preparation of Compounds 35 and 37. Compound **33** (0.14 g) was cyclized in 1.5 h to give compounds **37** (0.052 g) and **35** (0.057 g) by using the procedure described for compound **30** above.

Compound **37** could not be crystallized, and hence it was transformed into its HCl salt, which crystallized from methanol: mp 303–308 °C dec; $[\alpha]^{28}_D$ +6.4° (*c* 0.5, MeOH); IR (free base, Nujol) ν_{max} 3426 (OH) cm^{-1}; ^1H NMR (free base) δ 1.05 and 1.11 (3 H, s, C(4) CH_3), 1.0 (3 H, d, C(16) CH_3), 3.95 (1 br s, H, s, C(19) H). For ^{13}C NMR analysis of the free base, see Table III. Mass spectrum: m/z 345 (M^+) and 346 (M + 1); $C_{22}H_{35}NO_2$ requires m/z 345.5 (M^+).

Compound **35** was obtained as a gum, and hence it was transformed into its HCl salt, which crytallized from methanol: mp 310–313 °C dec; $[\alpha]^{26}_D$ +8.1° (*c* 0.4, MeOH); IR (free base, Nujol) ν_{max} 3385 (OH) cm^{-1}; ^1H NMR (free base) δ 0.81 and 0.75 (3 H, s, C(4) CH_3), 1.14 (3 H, d, J = 11 Hz, C(16) CH_3), 4.30 and 4.10 (1 H, br s, C(20) H). For ^{13}C NMR analysis of the free base, see Table II. Mass spectrum: m/z 345 (M^+) and 346 (M + 1); $C_{22}H_{35}NO_2$ requires m/z 345.5 (M^+).

Oxidation of Veatchine (2) Using Sarett Reagent: Preparation of Veatchinone (16). A solution of veatchine (0.36 g) in dry pyridine (3.7 mL) was added dropwise to a stirred solution of CrO_3/Py complex prepared from CrO_3 (0.31 g) and dry pyridine (3.1 mL) at 10–15 °C. The reaction mixture was stirred gently at 10 °C for 8 h and then left in a refrigerator overnight. The next day it was stirred at abmient temperature for 2 h. The dark muddy reaction mixture was loaded on an Al_2O_3 (13.0 g, activity III) column and eluted with a mixture of benzene and diethylamine (1%) until the last of the fractions did not give any residue. The solvents were evaporated in vacuo to dryness. The residue (0.22 g) solidified on standing and crystallized from acetone in white clusters of needles: mp 152–154 °C (shrinking from 143 °C); $[\alpha]^{23}_D$ –137° (*c* 1.0); IR (Nujol) ν_{max} 1730 (>C=O), 1650 and 890 (>C=CH_2) cm^{-1}; ^1H NMR δ 0.80 and 0.76 (3 H, s, C(4) CH_3), 3.71–3.95 (2 H, m, C(22) H_2), 4.30 (1 H, br s, C(20) H), 5.20 and 5.90 (each 1 H, br s, >C=CH_2). The ^{13}C NMR spectrum of veatchinone gave the following signals: 211.8, 210.7, 150.9, 150.2, 113.7, 93.8, 92.8, 64.7, 59.1, 56.7, 55.7, 53.3, 52.2, 50.6, 49.9, 49.3, 41.8, 41.1, 40.7, 38.3, 37.8, 34.4, 34.2, 34.1, 32.7, 32.4, 31.0, 29.8, 26.5, 25.9, 22.7, 21.7, 19.2, 18.9, 18.0 ppm. $C_{22}H_{31}NO_2$ requires C, 77.39; H, 9.15; N, 4.10; found, C, 77.25; H, 9.15; N, 4.06.

Treatment of Veatchine Azomethine Acetate (39) with Oxetane. Veactchine azomethine acetate (100 mg) and oxetane (3 mL) in glacial acetic acid (10 mL) were heated at 50–60 °C for 72 h. The reaction mixture after cooling to –5 °C was basified with 20% NaOH to pH 8–9 and extracted with chloroform. The aqueous phase then was made strongly basic and extracted again with chloroform. The chloroform solution of the weakly basic fraction was shaken with 5% H_2SO_4 to remove unreacted veatchine azomethine acetate and then evaporated. The colorless liquid residue was distilled under atmospheric pressure. A total of 4.1 g of compound at 208–210 °C was collected. The ^1H NMR and IR spectra and boiling point of the compound were in agreement with trimethylene glycol diacetate ($H_3COOCH_2CH_2CH_2OCOCH_3$). The strongly basic fraction after evaporation of chloroform yielded 88 mg of colorless crystals (two spots on TLC plates). Crystallization of the mixture from acetone afforded 30 mg of the less polar compound **40**: mp 164–167 °C; IR (KBr) ν_{max} 1730, 1240 (acetate), 1660 and 900 (>C=CH_2), 1370 (CCH_3) cm^{-1}; ^1H NMR δ 0.83 (3 H, s, C(4) CH_3), 1.54 (3 H, s, $COCH_3$), 3.80 (2 H, m, C(23) H_2), 4.20 (1 H, s, C(20) H), 5.18 (1 H, br s, C(15) H), 5.22 (2 H, m, >C=CH_2). For ^{13}C NMR analysis, see Table IV. Further crystallization of the mothor liquor failed to yield a pure sample of **40** or **41**.

Treatment of Veatchine Azomethine Acetate (39) with Glycidol. Veatchine azomethine acetate (85 mg) in dry methanol (10 mL) was treated with glycidol (2 mL). This mixture was kept for 15 h at 25 °C without stirring. After that, the methanol was evaporated in vacuo and the oily residue was treated with cold 5% H_2SO_4 (20 mL). The acidic aqueous solution was extracted with chloroform (2 × 25 mL) to remove the excess glycidol. The aqueous phase was basified with cooling in an ice bath first with solid $NaHCO_3$ and then with cold 20% NaOH solution to pH 12. The cloudy aqueous solution was exracted with chloroform (5 × 25 mL) until it became clear. The chloroform extract was dried over anhydrous Na_2SO_4 and evaporated to give 102 mg of colorless residue. The latter showed two spots on an alumina TLC plate, neither of which was starting material. This mixture was chro-

matographed on a column of alumina (10 g of activity III) by using benzene, benzene/chloroform, and chloroform. The less polar compound **42** (46 mg) after crystallization from ethyl ether melted at 172-173 °C: IR (Nujol) ν_{max} 1730, 1240 (acetate) 1665, 925 (C=CH_2), 1375 (CCH_3), 3550 (OH) cm^{-1}; ^1H NMR δ 0.76 (3 H, s, C(4) CH_3), 2.05 (3 H, s, $COCH_3$), 4.37 (1 br s, H, C(20) H), 5.10 (1 H, br s, C(15) H), 5.20 (2 H, m, >C=CH_2). For ^{13}C NMR analysis, see Table IV. $C_{35}H_{37}NO_4$ requires C, 72.26; H, 8.97; N, 3.37; found, C, 72.29; H, 9.02; N, 3.33. The more polar fraction (51 mg) melted at 145-161 °C, and attempts to separate this mixture via column chromatography as well as by crystallization failed.

Treatment of Atisine Azomethine Acetate (46) with Glycidol. Atisine azomethine acetate (60 mg) in methanol (10 mL) was treated with glycidol (1 mL). The usual workup as described above afforded 61 mg of compound **47** as a colorless oil, which showed a single spot on TLC. The ^1H NMR spectrum of compound **47** showed the following signals: δ 0.65 and 0.88 (3 H, s, C(4) CH_3), 2.18 (3 H, s, $COCH_3$), 4.23 (1 H, br s, C(20) H), 4.95 (1 H, br s, C(15) H), 5.16 and 5.28 (each 1 H, br s, >C=CH_2). For ^{13}C NMR analysis, see Table IV.

Treatment of Ajaconine Azomethine Diacetate (48) with Glycidol. Ajaconine azomethine diacetate (50 mg) was subjected to the reaction procedure developed for the preparation of compound **42**. The crude reaction product after filtration through 5 g of silica gel gave 47 mg of compound **49** as a thick colorless oil. The ^1H NMR spectrum of compound **49** exhibited the following signals: δ 0.87 (3 H, s, C(4) CH_3), 2.03 (3 H, s, C(7) $OCOCH_3$), 2.15 (3 H, s, C(15) $OCOCH_3$), 4.13 (1 H, br s, C(20) H), 4.95 (1 H, br s, C(15) H), 5.13 and 5.33 (each 1 H, br s, >C=CH_2). For ^{13}C NMR analysis, see Table IV.

Treatment of Ajaconine Azomethine Diacetate (48) with Ethylene Oxide To Obtain 50. Ajaconine azomethine diacetate (70 mg) in absolute methanol (10 mL) was treated with ethylene oxide (2 mL) at 25 °C for 5 h. The solvent was removed in vacuo, and the residue was dissolved in chloroform and passed through a column of silica gel (10 g). The amorphous product (73 mg) was identified as 7-(α-acetoxy)atisine acetate (**50**). The ^1H NMR spectrum of compound **50** exhibited the following signals: δ 0.83 and 1.06 (3 H, s, C(4) CH_3), 2.01 (3 H, s, C(7) $OCOCH_3$), 2.12 (3 H, s, C(15) $OCOCH_3$), 4.2 (1 H, br s, C(20) H), 5.01 (2 H, br m, C=CH_2). The ^{13}C NMR spectrum (Table IV) indicated it to be a mixture of C(20) epimers.

Supplementary Material Available: Tables of atomic coordinates, bond distances, and bond angles for β-tetrahydroatisine and 22-hydroxyhomoveatchinchine acetate (11 pages). Ordering information is given on any current masthead page.

Benzenesulfonylcarbonitrile Oxide. 4. Substitution Reactions of 3-(Phenylsulfonyl)isoxazolines

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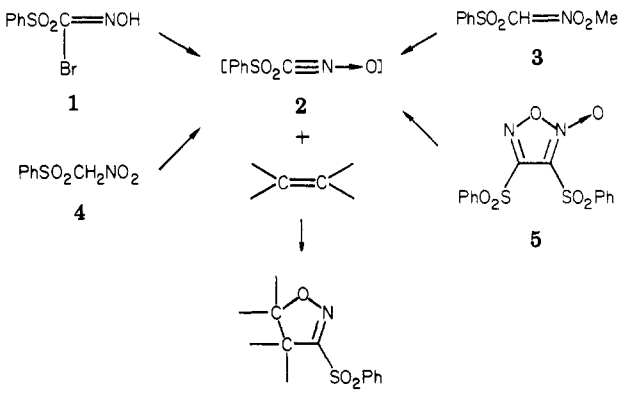
3-(Phenylsulfonyl)isoxazolines, readily obtained from alkenes by cycloaddition with benzenesulfonylcarbonitrile oxide, undergo a variety of substitution reactions. Alkyl, aryl, and acetylenic lithium reagents, cyanide, lithium or sodium alkoxides, and sodium borohydride are all useful nucleophiles. Tandem alkylations are possible with alkyllithium reagents when excess base and alkyl iodide are used. Excess base can also be used to cleave the isoxazoline ring of the initial substitution products. 3-(2-Propenyloxy)isoxazolines will undergo an aza-Claisen rearrangement on heating.

3-(Phenylsulfonyl)isoxazolines are readily prepared from alkenes by a number of routes in which the key intermediate is benzenesulfonylcarbonitrile oxide (**2**). This nitrile oxide can be generated by base[1] or silver(I)[2] treatment of bromo oxime **1**, base treatment of the methyl nitronic ester **3** of (phenylsulfonyl)nitromethane,[2] and thermolysis of furoxan **5**[3] (Scheme I). (Phenylsulfonyl)nitromethane (**4**) also gives nitrile oxide **2** under acidic conditions at elevated temperature.[4] The utility of sulfonyl isoxazolines as synthetic intermediates for the syn-cyano hydroxylation of alkenes and the preparation of certain other 3-substituted isoxazolines has previously been reported.[1,2] The present study is concerned with the use of sulfonyl isoxazolines for the general preparation of 3-substituted isoxazolines and compounds easily derived from them.

The phenylsulfonyl group attached at the 3-position of an isoxazoline is easily substituted by a variety of nucleophiles.[5] This is consistent with the general ability of

Scheme I



the sulfonyl function at unsaturated carbon to serve as a leaving group.[6] Alkyl-, aryl-, and alkynyllithium reagents all give clean substitution under relatively mild conditions (Scheme II). For methyl-, *n*-butyl-, *sec*-butyl-, and phe-

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(2) Wade, P. A.; Pillay, M. K. *J. Org. Chem.* **1981**, *46*, 5425.
(3) Whitney, R. A.; Nicholas, E. S. *Tetrahedron Lett.* **1981**, 3371.
(4) Using *p*-toluenesulfonic acid at 160 °C: Wade, P. A.; Amin, N. V., studies currently in progress.
(5) For a preliminary account, see ref 1.
(6) Some examples include: (a) Farrar, W. V. *J. Chem. Soc.* **1964**, 904. (b) Smorada, R. L.; Truce, W. E. *J. Org. Chem.* **1979**, *44*, 3444. (c) Schank, K. *Tetrahedron Lett.* **1977**, 2567.

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