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NMR STUDIES OF DITERPENE ALKALOIDS

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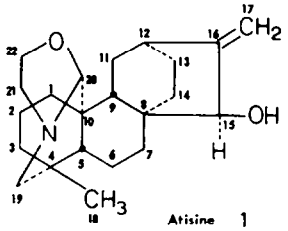
Abstract—A study of the NMR spectra of 44 diterpene alkaloids and derivatives is reported. A comparison of the NMR data for the C(4) Me group in a series of derivatives of atisine and veatchine provides support for the previous proposal regarding the conformation of ring E. Furthermore, the dependency of the chemical shift of the C(4) Me protons on the functionality of the N atom is also discussed.

INTRODUCTION

THE close structural similarities within the *Aconitum* and *Garrya* alkaloids suggested that a comparison of the NMR spectra of a series of atisine and veatchine derivatives could be valuable in confirming certain stereochemical points as well as offering potential aid in the structure determination of new derivatives. We have, therefore, carried out a study of the NMR spectra of 44 members of the *Aconitum* and *Garrya* groups. These derivatives of atisine and veatchine are listed in Table 1 and the general features of their spectra are listed in Table 2 using the modified steroid numbering system as in Fig. 1.



Atisine 1

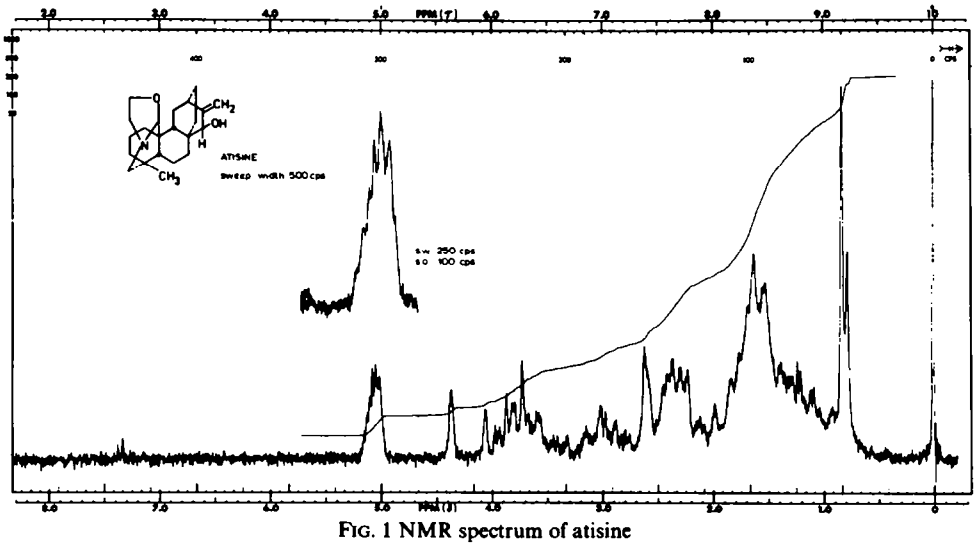


FIG. 1 NMR spectrum of atisine

TABLE 1

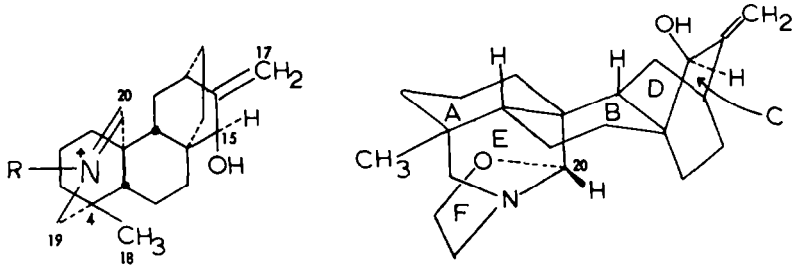
1	Atisine
2	Isoatisine
3	Veatchine
4	Atisinone
5	Isoatisinone
6	α-Oxoatisine
7	β-Oxoatisine
8	O-Acetyl-α-oxoatisine
9	O-Acetyl-β-oxoatisine
10	O-Acetylisoatisine
11	α-Oxoatisine dicarboxylic acid, dimethyl ester
12	F-Dihydroatisine
13	F-Dihydroatisine diacetate
14	α-Tetrahydroatisine
15	β-Tetrahydroatisine
16	F-Dihydro-β-oxoatisinone
17	Atidine
18	Atisinium chloride
19	Isoatisinium chloride
20	Veatchinium chloride
21	Garryinium chloride
22	Atisine azomethine
23	O-Acetylatisine azomethine
24	*Edwards* azomethine[1]
25	16, 17-Dihydro-15-desoxyatisine azomethine
26	Veatchine azomethine
27	O-Acetyleatchine azomethine
28	Des(N-β-hydroxyethyl)F-dihydroatisine
29	O-Acetyl-des(N-β-hydroxyethyl)F-dihydroatisine
30	Des(N-β-hydroxyethyl)F-dihydroveatchine
31	Des(N-β-hydroxyethyl)β-oxo-16, 17-dihydro-15-desoxy-F-dihydroatisine
32	Des(N-β-hydroxyethyl)α-oxo-F-dihydroatisinone
33	N-Acetyl-des(N-β-hydroxyethy)F-dihydroatisine
34	O,N-Diacetyl-des(N-β-hydroxyethyl)F-dihydroatisine
35	O.N-Diacetyl-des(N-β-hydroxyethyl)F-dihydroveatchinium chloride
36	N-Acetyl-des(N-β-hydroxyethy)F-dihydroveatchine dicarboxylic acid
37	N-Acetyl-des(N-β-hydroxyethy)F-dihydroveatchine dicarboxylic acid, dimethyl ester
38	N-Acetyl-des(N-β-hydroxyethyl)F-dihydro-veatchine dicarboxylic acid, monomethyl ester
39	O.N-Diacetyl-des(N-β-hydroxyethyl)F-dihydroatisine aziridine
40	N-Acetyl-des(N-β-hydroxyethyl)F-dihydroatisinone
41	*Edwards* azomethine dihydromethiodide
42	N-Ethyl-des(N-β-hydroxyethyl)F-dihydroatisine
43	O-Acetyl-N-Ethyl-des(N-β-hydroxyethyl)F-dihydroatisine
44	N-Ethyl-des(N-β-hydroxyethyl)F-dihydroatisinone

DISCUSSION

The NMR spectra of the atisine-type diterpene alkaloid derivatives listed in Table 1 were examined and the chemical shifts of pertinent resonance signals as well as their multiplicity and shapes have been studied allowing the following empirical correlations to be made.

C(4) *Methyl group*, (C(18) *protons*). From an examination of Table 2 the influence of the oxazolidine ring on the C(4) Me protons' resonance signal becomes obvious. Basic oxazolidine derivatives of atisine and veatchine at room temperature exhibited two sharp singlets of unequal intensity instead of the expected one singlet for the C(4) Me group. In several cases where there was a clean cut integration of these two singlets it became possible to demonstrate that neither of these two singlets accounted for all three of the C(18) protons. However, the sum of the two singlets represented all three of the C(18) protons in all cases. The appearance of two C(4) Me signals can arise where the possibility exists of more than one conformation in which the equilibrium between these conformations is slower than the response time required by the NMR spectrometer. That is, the equilibrium must be slow enough to observe the C(4) Me group of each conformer and not just an average conformation. In several cases it was even possible to estimate by integration the percentage of each conformer present.

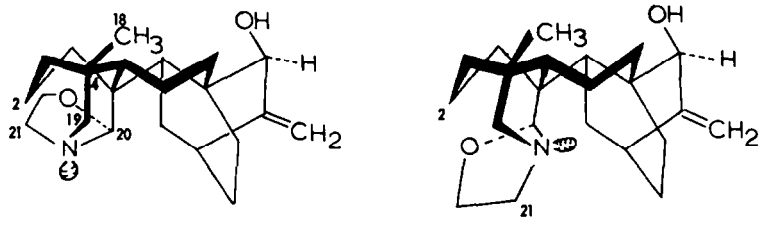
Since rings A and B in the atisine skeleton are held in a rigid conformation, the only conformationally mobile moieties that could effect the C(4) Me group are ring E, containing the N atom, and ring F, the oxazolidine ring. The fact that the oxazolidine ring of atisine may be regenerated easily from derivatives in which C(20) is trigonal,[2] as in structure **2**, suggests that the O atom should be substituted on the least hindered side of C(20), which would be the side away from ring C. Atisine would therefore be best represented by stereo isomer **3**.



2

The two possible conformations of ring E in structure **3** are responsible for the appearance of two Me signals in the NMR spectra of these derivatives, (cf. Fig. 1).

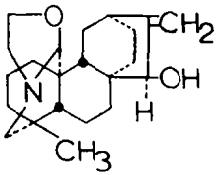
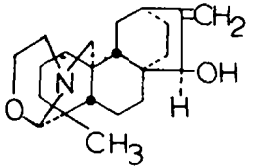
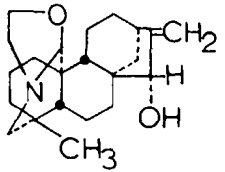
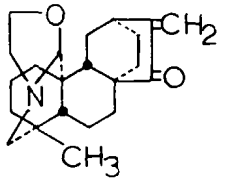
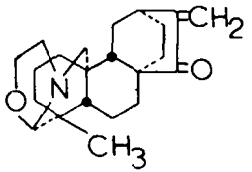
Inspection of Dreiding models clearly shows that in conformation **3a** (ring E in the chair form) the non-bonding electrons of the N are directed away from the C(4) Me group and that the N itself is removed in space from the C(4) Me group because of the C(19) methylene group. The C(18), C(4), C(19), and N atoms all lie in about the same plane and there is serious steric crowding between the C(2) and C(21) methylene protons. Conformation **3a** thus accounts for the smaller, upfield signal of the C(4) Me group.

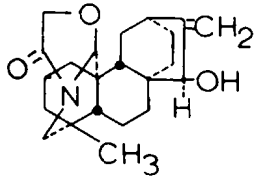
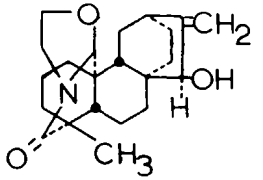
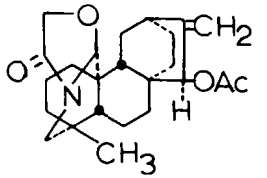
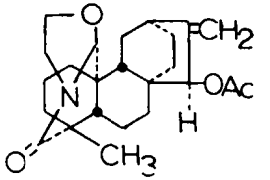


3a 3b

In conformation **3b**, in which ring E assumes that boat conformation, the non-bonding electrons of N are directed in such a manner that they are now in a position to deshield the C(4) Me group in much the same manner as the CO group causes deshielding through space as well as inductively. With ring E in the boat conformation there is also a great release of the steric strain which exists between the C(2) and C(21) methylene protons when ring E is in the chair form. This proximity of the non-bonding electrons of the N atom to the C(18) protons is indicated by the appearance of the second C(4) Me resonance signal at a slightly lower field. The fact that the signal at lower field is always larger than that of the upfield signal suggests that conformation **3b** is the favored conformation. The resonance signals of the C(4) Me groups in each conformation are usually separated by 5·0 c/s. This small separation between

TABLE 2*

Compound	18 CH_3	17 $=CH_2$	(19) 20 $>CH$	(19) 20, 21, 22, $—CH_2—$	15 $>CH$	Miscellaneous
 **1**	*s* 9·30 *s* 9·25 Note 1	*m* 5·05	C(20)H *s* 5·72			
 **2**	*s* 8·94 *s* 9·09 Note 2	*t* 4·95	C(19)H *s* 6·05	$C(20)H_2$ *bs* 7·22		
 **3**	*s* 9·18 *s* 9·23 Note 3	*bs* 4·92 *bs* 4·79 Note 4	C(20)H *s* 5·72	$C(22)H_2$ *m* 6·05–6·35		
 **4**	*s* 9·15 *s* 9·22 Note 1	*t* 4·75 *t* 4·03 Note 5	C(20)H *bs* 5·54			
 **5**	*s* 8·92 *s* 9·07 Note 2	*d* 4·05 *d* 4·77 Note 6	C(19)H *s* 6·05	C(20)H *s* 7·14 C(21, 22)H's *m* 6·20–7·10		

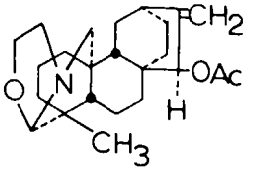
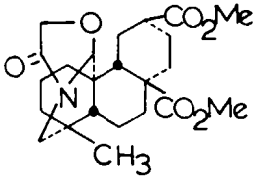
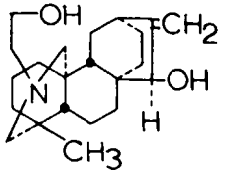
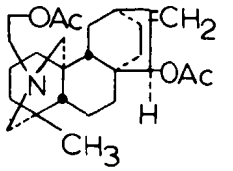
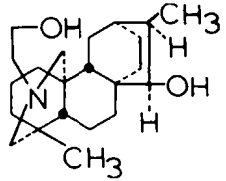
 **6**	*s* 9·09	*m* 4·92	C(20)H *bs* 4·15	C(19)H_2 *m* 5·75 C(22)H_2 *d* 6·21 *d* 7·11 Note 7	*s* 6·33	
 **7**	*s* 8·83	*m* 4·91	Note 8	Complex multiplets at 5·70 to 6·90	Note 8	
 **8**	*s* 9·09	*bs* 4·85 *bs* 4·97	C(20)H *bs* 4·20	C(19)H *d* 6·24 *d* 7·14 *J* = 13·0 c/s C(22)H_2 *bs* 5·75 Note 9	*bs* 5·05	—OAc, 7·88
 **9**	*s* 8·83	*m* 4·96	Note 8	Complex multiplets at 5·70 to 7·00	*bs* 5·05	—OAc, 7·85

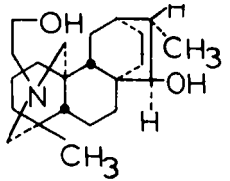
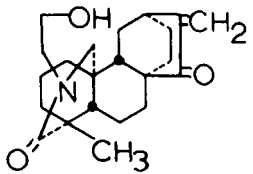
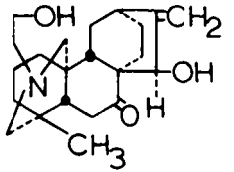
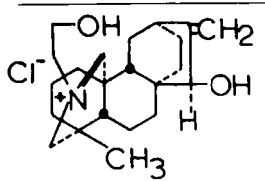
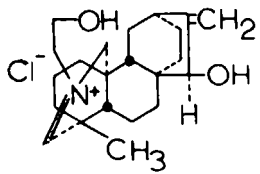
* All chemical shift data in Table 2 are given in ppm (τ) from TMS as the internal standard and the precision is estimated to be within 0·01 ppm. The multiplicity of each signal is given as follows:

s singlet *d* doublet *b* broad, centered at ...
t triplet *q* quartet *u* unresolved
m multiplet

Notes to Table are on p. 2031.

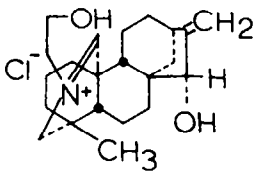
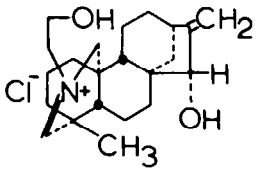
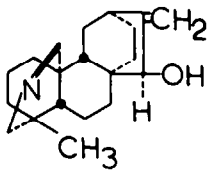
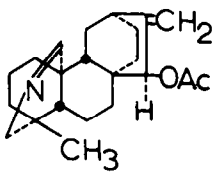
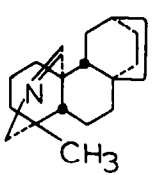
TABLE 2—*continued*

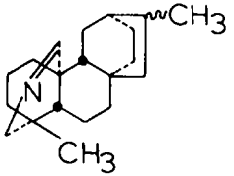
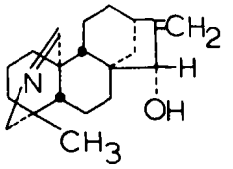
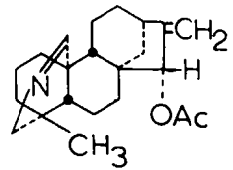
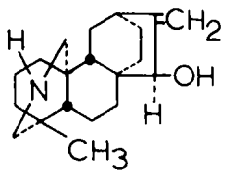
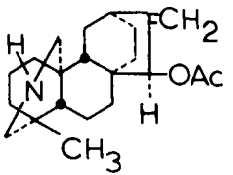
Compound		18—CH_3	17=CH_2	(19) 20 >CH	(19) 20, 21, 22, —CH_2—	15 >CH	Miscellaneous
	**10**	*s* 8·94 *s* 9·09 Note 2	*bs* 4·73 *bs* 4·92	Note 8	Complex multiplets at 5·05 to 6·40	*bs* 5·08	—OAc, 7·85 C(6)H, *bs* 7·50
	**11**	*s* 9·09		C(20)H *bs* 4·25	C(19)H_2 *d* 6·16 *d* 7·15 *J* = 13·0 C(22)H_2 *bd* 5·75 *J* = 2·0 Note 10		—CO_2Me *s* 6·32 CO_2Me *s* 6·28
	**12**	*s* 9·21	*m* 4·92	Note 11	C(22)H_2 *t* 6·34 C(21)H_2 *t* 7·54 *J* = 5·5	Note 8	
	**13**	*s* 9·23	*m* 4·94	Note 12	C(22)H_2 *t* 5·80 C(21)H_2 *t* 7·39 *J* = 5·5	*bs* 5·08	C(15) —OAc *s* 7·87 C(22) —OAc *s* 7·95
	**14**	*s* 9·21	—CH_3 *d* 8·98 *J* = 8·0	Note 13	C(22)H_2 *t* 6·33 C(21)H_2 *t* 7·54 *J* = 5·5	Note 12	

 **15**	*s* 9·21	$-CH_3$ *d* 8·94 *J* = 10·0	Note 13	C(22)H_2 *t* 6·34 C(21)H_2 *t* 7·54 *J* = 5·5	Note 8
 **16**	*s* 8·85	*d* 4·00 *d* 4·72 Note 14		C(22)H_2 *t* 6·35 C(21)H_2 *t* 7·54 *J* = 5·5	
 **17**	*s* 9·23	*m* 4·96 *m* 4·83 Note 15	Note 16	C(22)H_2 *t* 6·33 C(21)H_2 *t* 7·54 *J* = 5·5 Note 16	*bs* 5·47
 **18**	*s* 8·95	*d* 4·86 *J* = 2·0	C(20)H *bs* 1·35	C(22)H_2 *um* 6·25 C(21, 19)H_2 *um* 5·88	
 **19**	*s* 8·66	*d* 4·88 *J* = 2·0	C(19)H *bs* 1·48	C(20, 21, 22)H_2 *bm* 5·95	

Notes to Table are on p. 2031.

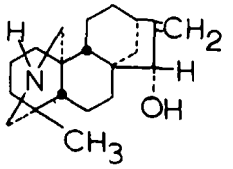
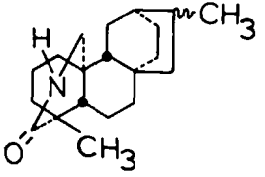
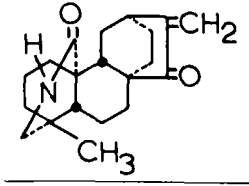
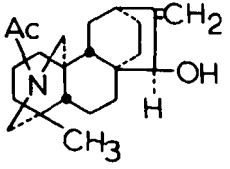
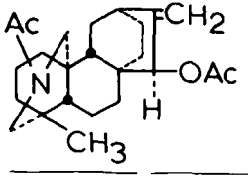
TABLE 2—*continued*

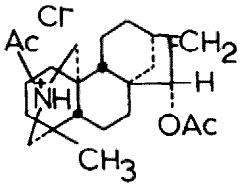
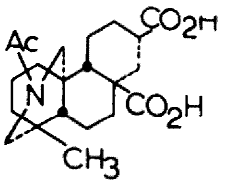
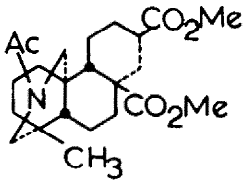
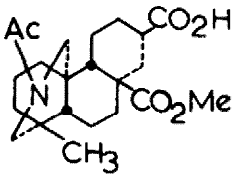
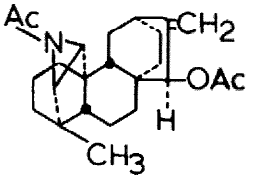
Compound	18 CH_3	17 $=CH_2$	(19) 20 >CH	(19) 20, 21, 22, $—CH_2—$	15 >CH	Miscellaneous
 **20**	*s* 8·95	*bs* 4·75	C(20)H *bs* 1·36	C(19, 21, 22)H_2 *bm* 5·90–6·25		
 **21**	*s* 8·66	*bs* 4·75	C(19)H *bs* 1·47	C(20, 21, 22)H_2 *bm* 5·95		
 **22**	*s* 9·15	4·89	C(20)H *bs* 2·10	C(19)H_2 *d* 5·57 *J* = 3·0	*bs* 6·31	C(15)OH *bs* 7·47 C(12)H *bs* 7·60 Note 17
 **23**	*s* 9·15	4·80 *m* 4·94 Note 18	C(20)H *bs* 2·10	C(19)H_2 *d* 6·57 *J* = 3·0	*bs* 5·10	C(15)OAc *s* 7·87 C(12)H *bs* 7·60
 **24**	*s* 9·17		C(20)H *bs* 2·11	C(19)H_2 *d* 6·56 *J* = 3·0		

	**25**	*s* 9·17	—CH_3 *d* 9·04 *J* = 6·0	C(20)H *bs* 2·11	C(19)H_2 *d* 6·56 *J* = 3·0		
	**26**	*s* 9·16	*bs* 4·88 *bs* 4·74	C(20)H *bs* 2·11	C(19)—H_2 *d* 6·62 *J* = 3·0	*bs* 6·10	C(15)OH *s* 7·11 C(12)H *bs* 7·25 Note 19
	**27**	*s* 9·17	*bs* 4·86 *bs* 4·62	C(20)H *bs* 2·11	C(19)H_2 *d* 6·61 *J* = 3·0	*bs* 4·86	C(15)OAc *s* 7·90 C(12)H *bs* 7·25
	**28**	*s* 9·28	*d* 4·94 *d* 4·98 *J* = 2·0	Note 21	Note 21	*t* 6·42 *J* = 2·0 Note 20	N—H Note 21
	**29**	*s* 9·28	*d* 4·95 *d* 4·98 *J* = 2·0	Note 21	Note 21	*bs* 5·05	C(15)OAc 7·86 N—H Note 21

Notes to Table are on p. 2031.

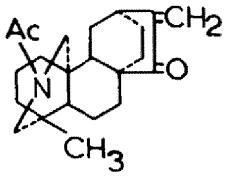
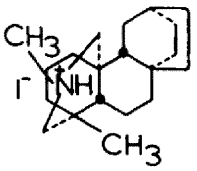
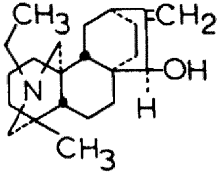
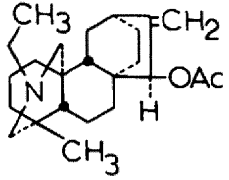
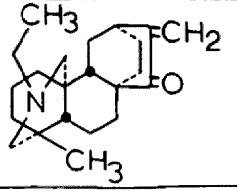
TABLE 2—*continued*

Compound	18 —CH_3	17 =CH_2	(19) 20 >CH	(19) 20, 21, 22, —CH_2—	15 >CH	Miscellaneous
 **30**	*s* 9·27	*bs* 4·91 *bs* 4·75 Note 22	Note 23	Note 23	*bs* 6·21	N—H Note 23
 **31**	*s* 8·88	—CH_3 *d* 9·04 *J* = 7·0	Note 24			N—H *bm* 3·70
 **32**	*s* 9·05	*d* 4·85 *d* 4·11 *J* = 2·0	Note 25			N—H *bm* 3·90
 **33**	*s* 9·12	*m* 4·88			*bs* 6·30	N—Ac *s* 7·88 *s* 7·92 Note 26
 **34**	*s* 9·12	*m* 4·90			*bs* 5·05	C(15)OAc *s* 7·82 N—Ac *s* 7·93 *s* 7·89 Note 26

	35	*s* 8·95	*bs* 4·84 *bs* 4·62	*bs* 4·84	C(15)OAc *s* 7·93 $\overset{+}{N}$—Ac *s* 7·93 $\overset{+}{N}$—H *bs* 1·65
	36	*s* 9·18			N—Ac *bs* 7·90 —CO_2H (2H area) *bs* 3·0 Note 27
	37	*s* 9·18			N—Ac *bs* 7·91 —CO_2Me (6H area) *s* 6·33
	38	*s* 9·18			N—Ac *bs* 7·91 CO_2H *bs* −0·15 CO_2Me *s* 6·32 Note 27
	39	*s* 9·14	*bs* 5·00 *bs* 4·75	*bs* 5·05	C(15)OAc *s* 7·85 N—Ac *s* 7·83 *s* 7·85

Notes to Table are on p. 2031.

TABLE 2—*continued*

Compound	18 —CH_3	17=CH_2	(19) 20 >CH	(19) 20, 21, 22, —CH_2—	15 >CH	Miscellaneous
 **40**	*s* 9·12	*d* 4·76 *d* 4·03 *J* = 2·0				N—Ac *s* 7·92 *s* 7·88
 **41**	*s* 9·05					$\overset{+}{N}$—CH_3 *d* 6·92 $\overset{+}{N}$—H *bs* 1·65
 **42**	*s* 9·21	*m* 4·93		C(21)H_2 *q* 7·75 C(22)H_2 *t* 9·98 *J* = 7·0 c/s C(19, 20)H_2 *m* 7·6		
 **43**	*s* 9·21	*m* 4·95		C(21)H_2 *q* 7·76 C(22)H_2 *t* 7·87 *J* = 7·0 c/s C(19, 20)H_2 *m* 7·6	*bs* 5·09	C(15)—OAc *s* 7·87
 **44**	*s* 9·22	*d* 4·07 *d* 4·79 Note 14		C(21)H_2 *q* 7·75 C(22)H_2 *t* 9·97 *J* = 7 c/s C(19, 20)H_2 *m* 7·6		

Notes to Table are on page 2031.

NOTES FOR TABLE 2

[1] The area of the low field signal is approximately twice the area of the high field signal.

[2] The area of the low field signal is approximately seven times the area of the high field signal.

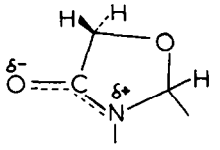
[3] The area of the signal at $\tau = 9{\cdot}18$ ppm is approximately seven times the area of the signal at $\tau = 9{\cdot}23$ ppm.

[4] Each signal is of one proton area and corresponds to an unresolved AB type pattern ($W_{\frac{1}{2}} = 4{\cdot}5$ c/s).

[5] These triplets ($J = 2{\cdot}0$ c/s, $\Delta\nu_{AB} = 44{\cdot}0$ c/s) can be explained by invoking allylic coupling to the C(12) proton. However, the exocyclic methylene protons appear as a simple AX pattern (i.e. two doublets) in all other derivatives with a CO at C(15).

[6] These two protons appear as a simple four line AX pattern ($J_{AX} = 2{\cdot}0$ c/s, $\Delta\nu_{AX} = 44{\cdot}0$ c/s).

[7] The signal of the C(19) proton is a two proton multiplet with $W_{\frac{1}{2}} = 4{\cdot}0$ c/s. The AB type pattern from the C(22) protons could be attributed to the resonance form:



This resonance could also account for the shift to lower field of the C(20) proton.

[8] The signals of the C(20) and the C(15) protons are often obscured by the complex patterns of the C(21) and C(22) methylenes.

[9] The AX pattern of the C(19) protons appears as broadened singlets ($W_{\frac{1}{2}} = 4{\cdot}0$ c/s) with $\Delta\nu_{AX} = 58$ c/s.

[10] The AX system of the C(19) protons appears as broadened singlets ($W_{\frac{1}{2}} = 4$ c/s) with $\Delta\nu_{AX} = 58$ c/s.

[11] The C(19) and C(20) protons are not assignable due to the complex pattern from overlap of signals which appear between $\tau = 7{\cdot}30$ and $\tau = 7{\cdot}95$.

[12] The C(19) and C(20) protons as well as the C(15) proton give a complex pattern between $\tau = 7{\cdot}10$ and $\tau = 7{\cdot}75$.

[13] The C(19) and C(20) protons give a complex pattern between $\tau = 7{\cdot}10$ and $\tau = 7{\cdot}90$.

[14] These protons appear as a 4-line AX pattern ($J_{AX} = 2{\cdot}0$ c/s, $\Delta\nu_{AX} = 44$ c/s).

[15] These lines could arise from a simple 4-line AB pattern which is coupled either to the proton at C(15) or C(12) ($J_{AB} = 2{\cdot}0$ c/s, $\Delta\nu_{AB} = 8$ c/s).

[16] The C(19) and C(20) protons give rise to a complex pattern between $\tau = 7{\cdot}05$ and $\tau = 8{\cdot}05$.

[17] The OH proton was assigned to the slightly broadened singlet at $\tau = 7{\cdot}47$ due to its disappearance on shaking with D_2O and its disappearance on O-acetylation.

[18] These two protons give an AB-type pattern due to the closeness of the acetate CO to one of the protons.

[19] The OH proton was assigned to $\tau = 7{\cdot}11$ due to its disappearance on shaking with D_2O and its disappearance on O-acetylation.

[20] The assignment of the α proton to the OH group was made due to its shift to $\tau = 5{\cdot}05$ on acetylation of the OH group.

[21] The C(19), C(20) and N—H protons give a complex pattern between $\tau = 6{\cdot}50$ and $\tau = 7{\cdot}50$.

[22] These broad singlets ($W_{\frac{1}{2}} = 3{\cdot}0$ c/s) are most probably unresolved doublets of an AB-type pattern.

[23] The C(19) and C(20) protons as well as the N—H proton give a complex pattern between $\tau = 6{\cdot}30$ and $\tau = 7{\cdot}50$.

[24] The C(20) protons occur as an AB part of an ABX pattern centered at $\tau = 6{\cdot}62$ ($J_{AB} = 13{\cdot}0$ c/s and J_{AX}, $J_{BX} = 3$ c/s).

[25] The C(19) protons give a complex pattern along with the C(6) proton between $\tau = 6{\cdot}50$ and $\tau = 7{\cdot}50$.

[26] The methyl of the N-Acetate always gives rise to two signals due to two different conformations. The signals are usually of the same intensity.

[27] The carboxylic hydrogen was confirmed with a D_2O exchange experiment; however, the large shift in the resonance frequency from the monoacid to the diacid can only be explained as a concentration dependency phenomenon.

the resonance signals shows that the N deshields the C(4) Me group only slightly owing to the distance through which the effect is manifested. The fact that there are two signals for the C(4) Me group, the larger being downfield, lends support to the ring E boat conformation which had been previously argued on conformational grounds.[3]

A temperature dependence study of the C(4) Me signals of atisine demonstrated that the two signals coalesce to a single resonance line of three proton area at approximately 85° (Fig. 2). Because of the high temperature required to coalesce the Me signals, the spectrum was taken in benzene solution. The change in solvent from $CDCl_3$ to benzene caused a slight upfield shift of the C(4) Me groups resonance signals of 5·0 c/s or about 0·08 ppm.

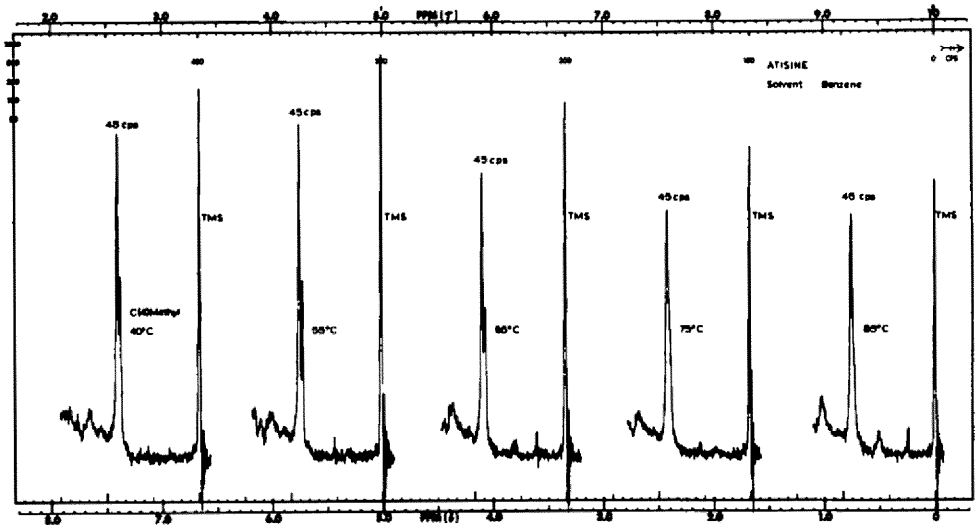


FIG. 2 NMR spectra of C(4)-methyl region of atisine at 40° to 85°

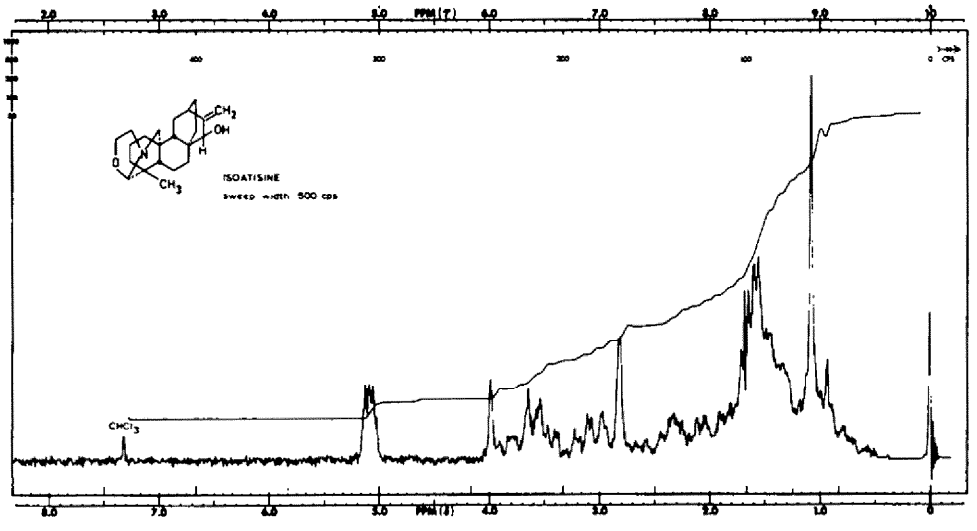
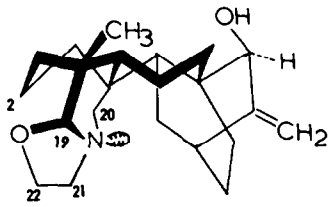
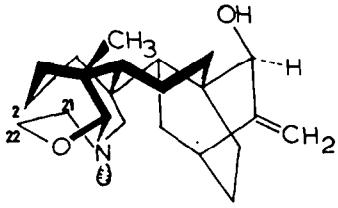


FIG. 3 NMR spectrum of isoatisine

In isoatisine and its derivatives there are again two C(4) Me signals (Fig. 3). However, both of these singlets appeared at a lower field than in either atisine or veatchine derivatives because of the effect of the nearness of the O atom of the oxazolidine ring. The larger C(4) Me singlet appeared at $\tau = 8{\cdot}93 \pm 0{\cdot}01$ and the smaller singlet appeared at $\tau = 9{\cdot}08 \pm 0{\cdot}01$. The presence of two C(4) Me signals supports the existence of the two conformations of ring E once again (**4a** and **4b**). The fact that the area of the lowfield signal is of the order of seven times as large as the area of the upfield signal suggests that in isoatisine the conformation in which ring E is in a boat form, isomer **4a**, is the most favored. This is probably due to the release of the steric interaction between the C(2) and C(21) methylene groups which exists when ring E is in the chair form, isomer **4b**.



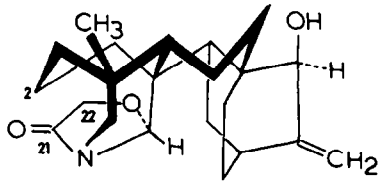
4a



4b

In all other derivatives studied which contained the oxazolidine ring the nitrogen was part of a lactam system, that is, either the C(19) or C(21) carbon atoms were CO groups.

Only one sharp singlet appeared from the C(4) Me protons at $\tau = 9{\cdot}09$ in all derivatives when the CO group was at C(21). Since there is no steric interaction between the C(2) and C(21) substituents, it is valid to assume that ring E would assume the more stable chair conformation **5**. In this conformation the non-bonding electrons of the N are directed away from the C(4) Me group, and the C(4) Me group and the CO oxygen have an unobstructed "view" of each other. The shift of the C(4) Me group to lower field is due to the deshielding effect of the C(21) CO group. It has been shown that the deshielding of a proton in a molecule is dependent both on its distance from the bond and its orientation with respect to that bond,[4] since anisotropic effects can act over long ranges.[5]

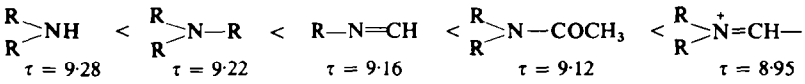


5

It is interesting to note that in structure **5** the C(4) Me signal appears at a lower field than when the non-bonding electrons of N are directed more favorably for a deshielding effect, namely, when ring E is in a boat conformation.

When the CO group is at C(19), the C(4) Me appears a sharp signal at $\tau = 8{\cdot}83$. Ring E must assume the boat conformation because of the C(2), C(21) methylene steric interaction. The paramagnetic shift of the C(4) Me signal is due to the inductive effect of the C(19) CO oxygen as well as its through-space deshielding effect.

In the absence of the oxazolidine ring, the chemical shift of the C(4) Me group depends on the functionality of the N atom. The deshielding effect of the nitrogen on the C(4) Me group follows the pattern:



In the three derivatives of veatchine in which ring C had been oxidized to the diacids (**36**, **37**, **38**, Table 2), the C(4) Me signal appeared at $\tau = 9{\cdot}18$. This τ value is higher than the τ values observed for the N-acetates in which ring C was intact ($\tau = 9{\cdot}12$).

When the N-acetyl nitrogen atom was contained in an aziridine ring the C(4) Me signal appeared at $\tau = 9{\cdot}14$. This chemical shifts is also at a slightly higher field than in other N-acetates.

In several derivatives the C(4) Me signals could not be placed into any one of the above categories. For example, the C(4) Me group of *Edwards* azomethine dihydromethiodide appeared at $\tau = 9{\cdot}05$.

C(16) *Exocyclic methylene group* (C(17) *protons*). The unambiguous assignment of the resonance signals of the exocyclic methylene protons presented a formidiable problem. Only in the case of AX systems, in which C(15) was a CO group, was the multiplicity of the resonance lines of this group unambiguous. In these cases the two protons appeared as a simple four line AX pattern with $\Delta\nu_{AX} = 44{\cdot}0$ c/s and $J_{AX} = 2{\cdot}0$ c/s.

In other derivatives the exocyclic methylene group gave resonance signals that varied from two broad singlets at $\tau = 4{\cdot}74$ and $\tau = 4{\cdot}88$ to a broad complex multiplet centered at $\tau = 5{\cdot}05$ (e.g. spectra number 1 and 5). In veatchine and its derivatives the exocyclic methylene group usually appeared as two broad singlets ($W_{\frac{1}{2}} = 4{\cdot}0$ c/s) separated by more than 0·13 ppm.

Only in the case of atisinone (Fig. 6) was allylic coupling ($J = 2{\cdot}5$ c/s) to the C(12) proton observed.

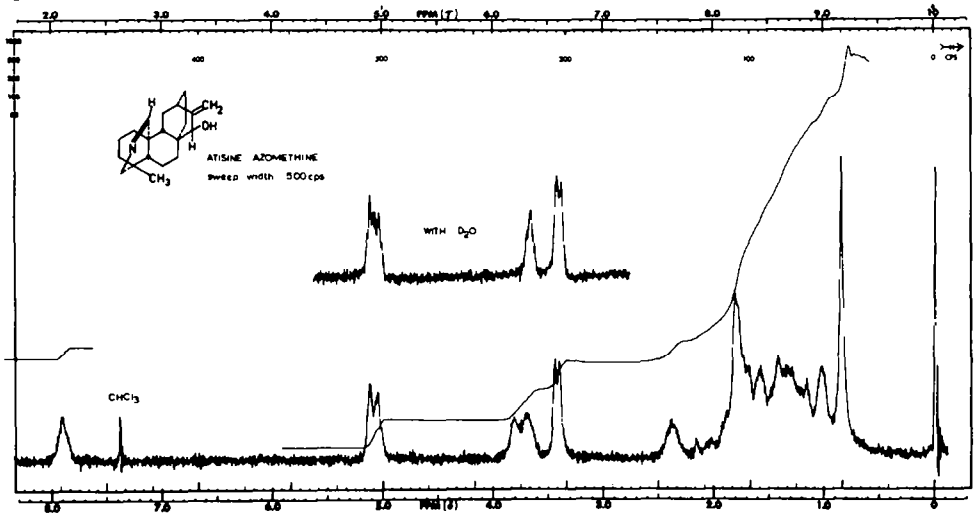


FIG. 4 NMR spectrum of atisine azomethine

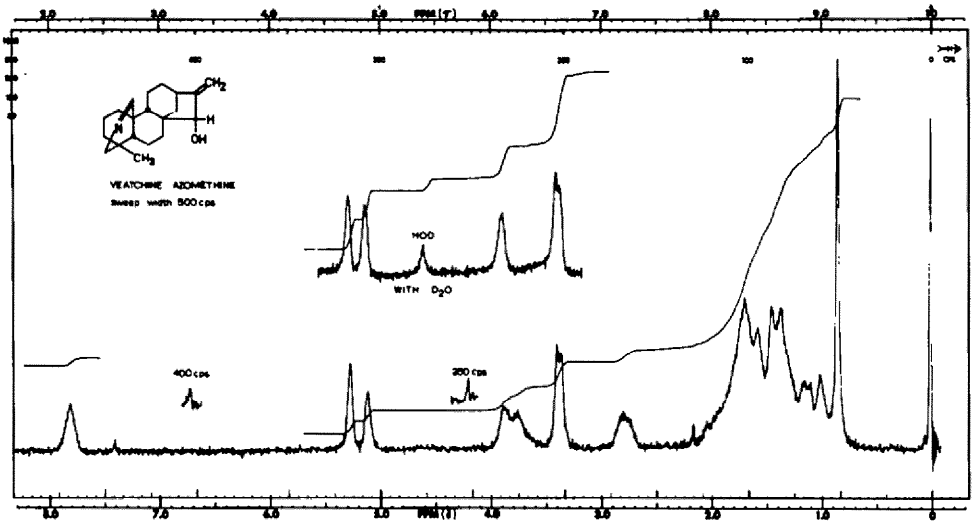


FIG. 5 NMR spectrum of veatchine azomethine

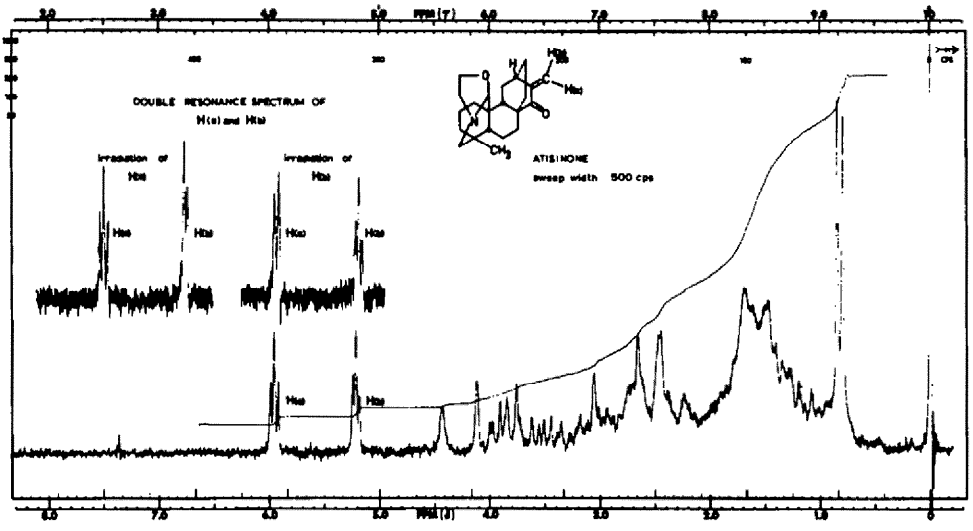
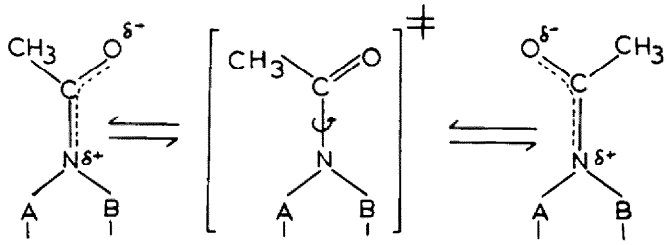


FIG. 6 NMR spectrum of atisinone

N-*Acetyl protons* (N—CO—CH_3). In the derivatives studied in which the N was not quaternarized or in which ring C had not been oxidized to the diacid (**36**, **37**, **38**, Table 2) the Me of the N-acetyl group appeared as two sharp singlets at $\tau = 7{\cdot}88 \pm 0{\cdot}1$ and $\tau = 7{\cdot}92 \pm 0{\cdot}01$ in all compounds studied. The separation of the two singlets was always 0·04 ppm and the two singlets were always of approximately equal intensity. Hindered rotation about the C—N bond in amides[6] easily explains the observed two signals for the N-acetyl Me group in the derivatives of atisine and veatchine.

In the N-acetyl derivatives of atisine and veatchine the amide N is contained in



8a 8 8b

Low temperatures; Both isomer **8a** and **8b** observed.
High temperatures; An average isomer observed.

a cyclohexane ring which is unsymmetrically substituted and thus, at low temperatures, both isomers **8a** and **8b** are observed in the NMR spectra by the appearance of two C-Me signals. At higher temperatures (benzene solution, 85°) the two C-Me signals coalesce to a single sharp resonance signal since the energy requirements to overcome the rotational barrier have been met. Since the equilibrium between isomer **8a** and **8b** is now faster than the response time of the NMR spectrometer, only a single average isomer is observed.

In aziridine **39** (Table 2) the C-Me of the N-acetyl group gave the expected two signals. However, they appeared at a slightly lower field, $\tau = 7{\cdot}83$ and 7·85. This shift to lower field is to be expected since the N is contained in a cyclopropane ring.

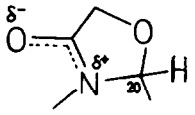
In the derivatives in which ring C had been oxidized (**36, 37, 38**, Table 2) the C-Me group appeared as a broad singlet at $\tau = 7{\cdot}91 \pm 0{\cdot}01$. This line broadening ($W_{\frac{1}{2}} = 3{\cdot}5$ c/s) is probably due to accidental degeneracy of the expected two C-Me singlets.

C(15) O-*Acetyl group*, (C(15)—O—CO—CH_3). In atisine and its derivatives the Me protons of the O-acetyl group appeared over a range of 0·06 ppm. The lowest field at which the Me group of the acetate appeared was at $\tau = 7{\cdot}82$ and the highest field was $\tau = 7{\cdot}88$. In veatchine and its derivatives these acetate protons appeared at a higher field ($\tau = 7{\cdot}90$ or higher). The shift to higher field is most probably due to the fact that the acetate is attached to a cyclopentane ring. The C(22) acetate group derived from F-dihydroatisine exhibited a sharp signal at $\tau = 7{\cdot}95$. All of the chemical shift values recorded were well within the expected region for the Me protons of an O-acetyl group.

C(20) *Hydrogen* (*atisine*) *or* C(19) *hydrogen* (*isoatisine*). In the derivatives of atisine and veatchine the C(20) proton is located on a trisubstituted bridgehead carbon contained in an oxazolidine ring. This proton appears as a broad singlet at $\tau = 5{\cdot}72$ ppm in both atisine and veatchine. When the oxazolidine ring is oxidized (e.g. α-oxoatisine) the C(20) proton appears between $\tau = 4{\cdot}15$ and 4·25. This downfield shift is to be expected since the N, as part of a lactam system, is now able to support a partial positive charge through resonance as shown in partial structure **9**.

In atisinium and veatchinium chloride the C(20) proton appears at $\tau = 1{\cdot}35$. In these compounds the N atom has a formal positive charge and the deshielding effect that it exerts on the C(20) proton is much greater than when the N has only a partial positive charge as in structure **9**.

In derivatives in which C(20) is an imine carbon (cf. spectra no. 4 and 5) the C(20)



9

proton exhibits a broad singlet at $\tau = 2{\cdot}11 \pm 0{\cdot}01$. This is to be expected since an imine is a stronger electron withdrawer than the corresponding C=C double bond.

In isoatisine the bridgehead proton is located at C(19) and appears as a singlet at $\tau = 6{\cdot}05$. In isoatisinium chloride this proton appears at $\tau = 1{\cdot}48$.

C(15) *Hydrogen.* In derivatives of atisine the C(15) proton, being part of a cyclohexanol system, appears as a broad singlet centered at $\tau = 6{\cdot}32 \pm 0{\cdot}01$ ppm. This broadening is a result of unresolved allylic coupling with the exocyclic methylene group at C(16). However, in des-(N-β-hydroxyethyl)F-dihydroatisine (**28**, Table 2) the C(15) proton appears at $\tau = 6{\cdot}42$ as a triplet.

The resonance signal of this α-proton shifted to $\tau = 5{\cdot}05$ upon acetylation of the C(15) OH group. In veatchine and its derivatives the α proton of the secondary alcohol was contained in a cyclopentanol system and appeared at a lower field; in atidine (7) this α proton appeared at $\tau = 5{\cdot}47$ due to the presence of the carbonyl group located at C(7).

When the C(15) OH was converted to an acetate the C(15) proton of the atisine derivatives was shifted downfield to $\tau = 5{\cdot}05 \pm 0{\cdot}01$. In a few cases the downfield shift was not so marked, but never did the resonance line for this α-proton appear at higher than $\tau = 5{\cdot}10$ after conversion of the OH to an acetate.

In veatchine and its derivatives, in which C(15) is in a cyclopentane ring, the C(15) proton shifted to $\tau = 4{\cdot}85 \pm 0{\cdot}01$ upon acetylation of the C(15) OH group.

C(21) *and* C(22) *Methylene protons* (—N—CH_2—CH_2—O—). In α-oxoatisine and α-oxoatisine dicarboxylic acid the C(22) protons appeared as an AB quartet with $\Delta\nu_{AB} = 54{\cdot}0$ c/s and $J_{AB} = 13{\cdot}0$ c/s.

In F-dihydroatisine and its derivatives the C(21) methylene exhibited the expected triplet at $\tau = 7{\cdot}54$ and $J = 6{\cdot}0$ c/s and the C(22) methylene also appeared as a triplet at $\tau = 6{\cdot}34 \pm 0{\cdot}01$. These signals are in agreement with the resonance positions of a methylene group attached to an amine nitrogen and the methylene group of a primary alcohol, respectively. Upon acetylation of the C(22) OA group the C(21) methylene triplet was shifted to $\tau = 7{\cdot}39$ and the C(22) methylene triplet was shifted to $\tau = 5{\cdot}80$.

Carbomethoxy groups (—CO_2—CH_3). In the derivatives of atisine and veatchine in which ring C had been oxidized and the resulting dibasic acid esterified to dimethyl esters, the protons of the Me group of the carbomethoxy group appeared at $\tau = 6{\cdot}32 \pm 0{\cdot}01$ as sharp singlets. However, in α-oxoatisine dicarboxylic acid dimethyl ester the secondary carbomethoxy singlet appeared at a slightly lower field, $\tau = 6{\cdot}28$. These chemical shifts are within the expected region for a carbomethoxy group.

C(15) *Hydroxyl proton* (C(15)—OH). Since the chemical shift of a OH proton is a function of concentration as well as solvent and temperature, a correlation of the assigned OH protons is uniformative. The OH groups were assigned only after the disappearance of the hydroxylic proton signal in a D_2O exchange experiment. The

D_2O exchange experiments were carried out only to allow the unambiguous assignments of other protons whose chemical shifts were near that of the OH protons (i.e. see veatchine azomethine, Fig. 5).

Summary. The most favorable conformation for ring E in atisine and other atisine-type diterpene alkaloids which contain the oxazolidine ring has been shown to be the boat conformation. The existance of pseudo *cis* and *trans* isomers about the C—N amide bond in N-acetyl derivatives has also been clearly demonstrated. Much of the data collected, while not explicitly correlated, will lend itself to empirical correlations with new derivatives of atisine-type diterpene alkaloids as they are prepared or isolated.

EXPERIMENTAL

All spectra were obtained with a Varian A-60 spectrometer with V-6058A spin-decoupler, V-6057 variable temp system, and C-1024 time average computer attachments. Approximately 20 mg of sample in 0·5 ml $CDCl_3$ solns using 1% TMS as an internal standard was usually employed. Several spectra were taken in both $CDCl_3$ and benzene since the b.p. of $CDCl_3$ was too low to use the variable temp probe above 60°. In several cases the variable temp probe was heated to as high as 85° while observing spectra in benzene. When there were only small amounts of sample available, these were studied in a precision, ground-glass, thick-walled (I.D. ca. 2 mm) NMR tube supplied by Nuclear Magnetic Resonance Specialties, Inc., or in Varian's NMR microcell kit.

Those samples that were not soluble in $CDCl_3$ were studied in D_2O solns using 3-(Trimethylsilyl)1-propanesulfonic acid sodium salt as the internal standard.

The chemical shift data are given in ppm (τ) from TMS and the precision is estimated to be within 0·01 ppm.

Several spectra were calibrated by the usual side band method employing a Hewlett–Packard 241A oscillator with a Hewlett–Packard 5233L electronic counter.

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