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NUCLEAR MAGNETIC RESONANCE SPECTRA OF VERATRUM ALKALOIDS*

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Abstract—An intercomparison of the NMR data for the methyl protons in a series of thirty-seven alkaloids of the Veratrum group provides additional support for previous proposals regarding the β-configuration of the C-27 methyl group in all of these compounds and the *cis* A/B ring fusion in the sabine derivatives. Furthermore, the variations of the chemical shift for the C-21 methyl protons strongly suggest that the conformation of the D-ring is changed upon formation of the D-*ortho*acetate grouping.

INTRODUCTION

IN RECENT years, investigations of the Veratrum alkaloids by a number of groups of workers have led to the elucidation of the structure and stereochemistry of many of these compounds.[1] The close similarities of structure within the Veratrum group, a common carbon skeleton with variations in the number, location and/or orientation of hydroxyl functions, suggested that an intercomparison of the nuclear magnetic resonance (NMR) spectra of a series of these derivatives could be valuable in confirming certain stereochemical points as well as offering potential aid in the structural elucidation of new derivatives. For these reasons, we have carried out a study of the NMR spectra of 37 members of the Veratrum group with representative examples derived from each of the following parent compounds: veracevine,[2] cevine,[2,3] germine,[4] zygadenine,[5] protoverine,[6] cevagenine,[7] and sabine.[8] (General formulas I, II and III.)

* This paper represents Part IV in the series *Nuclear Magnetic Resonance Studies* [J.B.S.; Part III: W. A. Ayer, C. E. McDonald and J. B. Stothers, *Canad. J. Chem.* **41**, 1113 (1963)] and Part LII in the series *Veratrum Alkaloids* [S.M.K.; Part LI: L. C. Weaver, W. R. Jones and S. M. Kupchan, *J. Pharm. Sci.* **51**, 1144 (1962)].

[1] O. Jeger and V. Prelog, *Steroid Alkaloids: Veratrum Group*, in *The Alkaloids* (Edited by R. H. F. Manske) Vol. VII; p. 363. Academic Press (1960).

[2] D. H. R. Barton, O. Jeger, V. Prelog and R. B. Woodward, *Experientia*, **10**, 81 (1954); S. M. Kupchan, W. S. Johnson and S. Rajagopalan, *J. Amer. Chem. Soc.* **80**, 1769 (1958).

[3] S. M. Kupchan, W. S. Johnson and S. Rajagopalan, *Tetrahedron* **7**, 47 (1959).

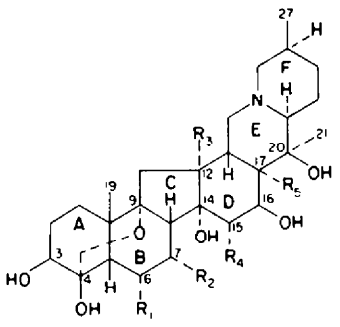
[4] S. M. Kupchan and C. R. Narayanan, *J. Amer. Chem. Soc.* **81**, 1913 (1959).

[5] S. M. Kupchan, *J. Amer. Chem. Soc.* **81**, 1925 (1959).

[6] S. M. Kupchan, C. I. Ayres, M. Neeman, R. H. Hensler, T. Masamune and S. Rajagoplan, *J. Amer. Chem. Soc.* **82**, 2242 (1960).

[7] S. M. Kupchan, *J. Amer. Chem. Soc.* **77**, 686 (1955).

[8] S. M. Kupchan, N. Gruenfeld and N. Katsui, *J. Med. Pharm. Chem.* **5**, 690 (1962).



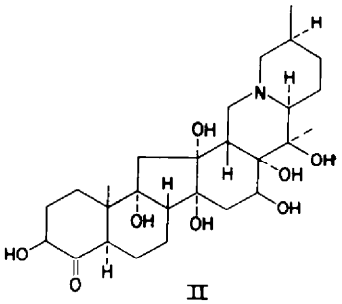
I

(a) $R_1=R_2=R_4=H$; $R_3=R_5=OH$, Veracevine

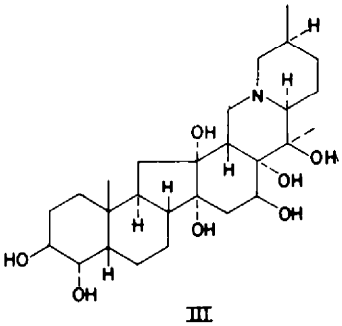
(b) $R_1=R_3=R_5=H$; $R_2=R_4=OH$, Germine

(c) $R_1=R_2=R_3=R_5=H$; $R_4=OH$, Zygadenine

(d) $R_3=R_5=H$; $R_1=R_2=R_4=OH$, Protoverine



II



III

EXPERIMENTAL

All spectra were obtained with a Varian DP-60 spectrometer and the peak positions were calibrated by the usual audio side-band technique. The audio oscillator was continuously monitored with a Hewlett-Packard 522B frequency counter. For most of the samples, approximately 5–8% (w/v) solutions in $CDCl_3$ containing ca. 1% tetramethylsilane (TMS) were employed. In a few cases, however, only 3–5 mg material was available and these smaller samples (2·2–3·5%) were studied in a precision, ground-glass, thick-walled cell (I.D. ca. 2 mm) supplied by Nuclear Magnetic Resonance Specialties, Inc. The chemical shift data are given in ppm from TMS and the precision is estimated to be within 0·01 ppm.

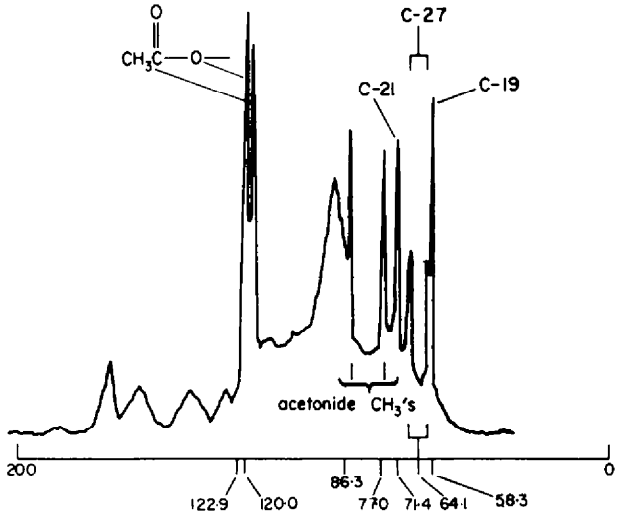


FIG. 1(a)

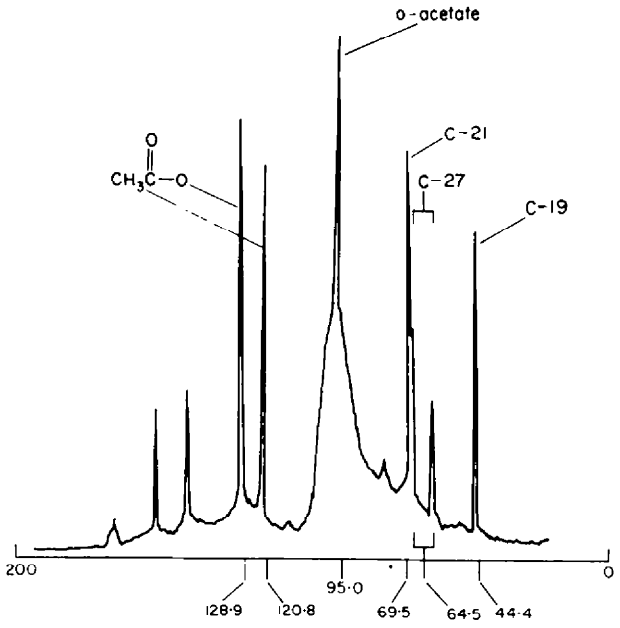


FIG. 1(b)

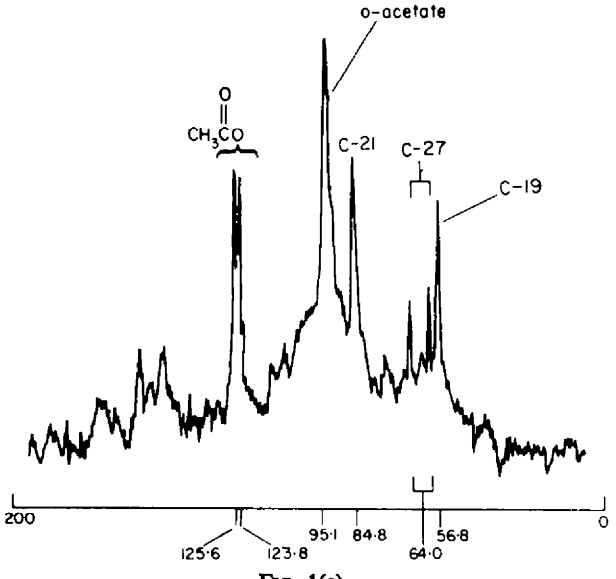


FIG. 1(c)

FIG. 1. Typical 60 Mc/s spectra (in $CDCl_3$) of compounds (a) zygadenine acetonide diacetate, (b) cevagenine C-*ortho*acetate diacetate, and (c) 16-dehydrosabine D-*ortho*-acetate diacetate (3 mg in narrow-bore tube). Line positions are given in c/s from TMS.

RESULTS

The chemical shift data for the various methyl protons are tabulated in Tables 1–5. The various types of methyl groups are easily recognized

$$\left(\text{i.e. } CH_3C{-}{=}O,\ CH_3{-}C(O)_3,\ CH_3{-}C(O)_2,\ \text{and } CH_3{-}\overset{|}{\underset{|}{C}}{-}\right)$$

and there is no ambiguity for most of the assignments as presented in the Tables. The effects of structure on the peak positions for the C—CH_3 groups at C-19, C-21, and C-27 are discussed in detail in the following section. Some comments on other distinctive features within this group of spectra are included in the final section. The structures of the parent compounds for each group are shown in the general formulas: veracevine (Ia), germine (Ib), zygadenine (Ic), protoverine (Id), cevagenine (II) and sabine (III). A number of cevine derivatives have been included in this survey and it should be noted that these differ from the corresponding veracevine derivatives in that the C-3 oxygen function is in the α-orientation.

To illustrate the general features of the NMR spectra of these alkaloids, some typical curves are reproduced in the Figure. The line positions are given in c/s from TMS and the various types of methyl groups are indicated. One typical example of a spectrum obtained from 3 mg material (16-dehydrosabine*ortho*acetate diacetate, Mol. wt. 601) has been included for comparison with those obtained under more usual operating conditions.

An intercomparison of the chemical shift data for the various methyl protons in these derivatives provides corroborative evidence for the assignment of the β-(axial) configuration to the C-27 methyl group in zygadenine, germine, protoverine, and sabine, as previously proposed. In addition, the NMR data for the C-21 protons strongly indicate a change in the conformation of the D-ring upon formation of the D-*ortho*acetate structure. Also, these data offer further support for the *cis* A/B ring fusion in the sabine derivatives. The long range shielding effects of various substituents, particularly at the angular methyl protons (C-19), appear to be additive as may be expected from the well-known results of similar studies of steroids[9–11] and the effects are comparable in both systems. This observation suggests the possible role of NMR spectroscopy as an aid in future structural elucidations of new Veratrum alkaloid derivatives.

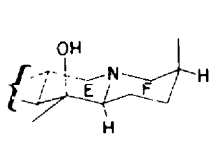
DISCUSSION

C-27 *Methyl protons.* With the exception of the two dehydrocevine derivatives (Cpd. 10 and 11) and the two formamido ketones (Cpd. 12 and 30), the compounds included in this survey have a common structural feature, the *trans*-quinolizidine ring system (Rings E and F in IV) and the C-27 methyl group. Throughout the series, the only structural variation close to this methyl group occurs at C-17 and the presence of an additional α-oriented hydroxyl group at this position in the veracevine and cevine derivatives would not be expected to influence the chemical shift of the C-27 methyl protons significantly. It is reasonable to expect that structural variations in Rings A, B, C and D would not affect these protons and the results provide confirmation. In all cases, the doublet exhibited by these protons is centred at 1·07 ±

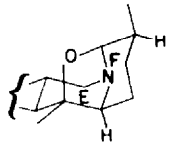
[9] J. N. Shoolery and M. T. Rogers, *J. Amer. Chem. Soc.* **80,** 5121 (1958).
[10] R. F. Zurcher, *Helv. Chim. Acta* **44,** 1380 (1961).
[11] Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto and K. Tsuda, *Chem. Pharm. Bull.* **10,** 338 (1962).

0·03 ppm and the observed spacing of doublet peaks falls within the normal range, 7·1 ± 0·8 c/s. Although both components of the doublet were not separately resolved in all of these spectra, the separation of the two signals is more than 6·0 c/s in all cases. Since these signals are found within such a narrow range, i.e. 3 c/s, it is reasonable to conclude that the configuration of this methyl group is the same in all cases and, therefore, is in the β-(axial) orientation (partial formula IV) on the basis of the known configuration in cevine.[12,13] This assignment had been previously proposed for zygadenine,[5] germine,[4] protoverine,[6] and sabine[8] in view of the exceedingly close similarity to cevine in structure as well as configuration at many other common asymmetric centres. Thus, the present NMR data offer strong corroborative evidence to support the assignment.

The two dehydrocevine derivatives (Cpd. 10 and 11) posses a *cis*-quinolizidine ring system in which the C-27 methyl group is equatorial[3] as shown in partial formula V. For these cases the doublet due to this methyl group appears at higher field than



IV



V

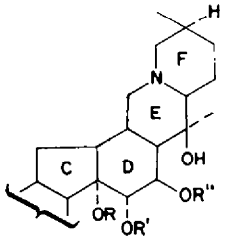
in the other examples, at 0·86 ppm. The observed difference in chemical shift for the conformational change, axial → equatorial, is in agreement with the results recently reported by other workers from studies of various methyl quinolizidines for which it was found that the equatorial 3-methyl protons absorb at higher field than those of a corresponding axial grouping.[14–16] In addition, the observed spacing of the doublet in Cpd. 10 and 11, 6 c/s, is slightly smaller than that observed for the other compounds, in accord with previous results for equatorial and axial methyl groups in the quinolizidine system.[14,16]

C-21 *Methyl protons.* Throughout this series the C-21 methyl group is in an equatorial orientation and on carbon bearing oxygen. Apart from the two dehydrocevine derivatives (Cpd. 10 and 11), having the carbinolamine ether structure shown in formula V, the C-20 substituent is hydroxyl. The C-21 methyl protons, therefore, give rise to a sharp singlet in the NMR spectra which can be identified by the fact that the peak position is independent of structural changes in the A and B rings. Thus, for most cases, this signal is readily distinguished from that due to the C-19 protons. Structural modifications in the C and D rings, however, affect the chemical shift of the C-21 methyl group and it appears over the range, 1·01–1·43 ppm. For discussion of the C-21 methyl shifts, the alkaloids examined in this study fall into main classes depending on the presence or absence of an oxygen function at C-17.

Those compounds having no substituent at C-17 include the zygadenine, protoverine and germine derivatives (Tables 2 and 3) for which the C-21 methyl protons absorb within the range, 1·15–1·25 ppm. *A priori*, one would expect only the substituents

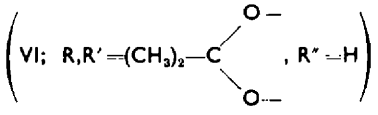
[13] O. Jeger, V. Prelog, E. Sundt and R. B. Woodward, *Helv. Chim. Acta.* **37**, 2302 (1954).
[14] W. T. Eeles, *Tetrahedron Letters* No. 7, 24 (1960).
[14] T. M. Moyneham, K. Schofield, R. A. Y. Jones and A. R. Katritsky, *J. Chem. Soc.* 2637 (1962).
[15] M. Kotake, I. Kawasaki, T. Okamoto, S. Matsutani, S. Kusumoto and T. Kaneko, *Bull. Chem. Soc. Japan*, **35**, 1335 (1962).
[16] S. Ito and J. B. Stothers, unpublished observations.

shown in part structure VI to exert effects on the C-21 methyl protons. An examination



VI

of the data for zygadenine, angeloylzygadenine and veratroylzygadenine and zygacine (Table 2, Cpd. 13, 14, 18, 19) shows that acylation at C-3 is without effect, and since zygadenilic acid δ-lactone (Table 4, Cpd. 31) absorbs at the same position, it is clear that Ring A substituents are unimportant in determining the shielding at C-21. These shifts, 1·24 $\pm$ 0·01 ppm (for VI; R=R'=R''=H) appear to be unaffected by formation of an acetonide at C-14, C-15

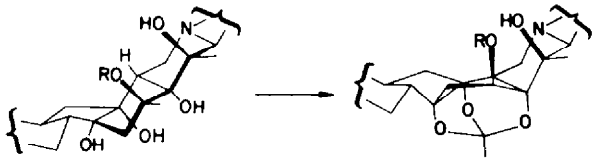


as shown by Cpd. 15, 16, 20 and 32, although acylation at C-15 tends to shield the C-21 protons slightly (3 c/s) as illustrated by Cpd. 24 and 25. Acetylation at C-16 causes a similar up-field shift of the C-21 methyl group (cf. Cpd. 17, 23, 26 and 27).

The remaining examples belong to the cevine and sabine series in which there is an α-hydroxylic function at C-17. Wider variations in the substitution of these derivatives cause somewhat larger changes in the shifts of the C-21 protons and the signals are found over the range, 1·05–1·43 ppm. The additional hydroxyl group at C-17 tends to shield the C-21 protons by ca. 5·5 c/s as shown by Cpd. 1 and 32, near 1·14 ppm while Cpd. 13, 15, 18, 19, 31 appear near 1·23 ppm. Again, acetylation at C-16 produces an up-field shift of ca. 4·4 c/s (Cpd. 2, 3, 28, 34 at 1·08 ppm) if the C-14, C-15 substituents are hydroxyls. It is interesting that the replacement of the C-16 β-hydroxyl by a C-16 keto grouping does not change the shift of the C-21 methyl group (cf. 7 with Cpd. 1 and 33) provided the C-14, C-15 substituents are hydroxyl groups.

The most striking chemical shift differences for the C-21 protons are observed for those compounds having an *ortho*acetate group in the D-ring involving the C-12, C-14, and C-17 oxygen functions. Since the effects of the C-16 substituents are different for these cases from those discussed above, it follows that the relative orientation of the C-16 substituent and the C-21 methyl group must also be different and a detailed examination of the C-21 methyl shifts for these compounds leads to the conclusion that the conformation of Ring D is changed upon formation of the D-*ortho*acetate. A number of observations support this conclusion. First, the C-21 protons shift to lower field by 5 c/s upon formation of the D-*ortho*acetate for those compounds having a 16 β-OH. For example, the C-21 methyl group in Cpd. 5 and 36 absorbs near 1·22 ppm while in Cpd. 1 and 33 this group appears near 1·14 ppm. Second, in the event the conformation of Ring D were the same for the D-*ortho*-acetate examples as for those having hydroxyls at C-12, C-14 and C-17, one would

expect a significant difference in the shift of the C-21 protons for the configurational change, C-16 β-OH to 16 α-OH. In fact, however, Cpd. 6 shows that the effect of the 16 α-OH (with D-*ortho*acetate) is the same as the 16 β-OH group with free hydroxyls at C-12, C-14 and C-17. Third, in contrast to the results discussed previously, there is a marked downfield shift of ca. 15 c/s for the C-21 methyl protons upon introduction of a C-16 keto group, in those compounds having the D-*ortho*acetate structure (Cpd. 8, 9 and 37 exhibit this signal at 1·40 ppm). Clearly the C-21 methyl group must be close to the plane of the carbonyl group in these compounds since the geometry of the long range shielding effect of the carbonyl bond due to its diamagnetic anisotropy is well established.[17–20] Fourth, some evidence that the inclusion of the C-17 hydroxyl group in the *ortho*acetate group is not responsible for these large changes in the C-21 methyl shift is provided by the two formamido-ketone derivatives, Cpd. 12 and 30, in both of which the C-21 methyl signal appears at 1·29 ppm although Cpd. 12 has a D-*ortho*acetate grouping and Cpd. 30 has a free C-17 OH. (It should be noted that while there may be a small shielding difference for the change in oxygen function at C-17, it cannot exceed 3–4 c/s). In sum, these observations accord best with the view that a chair → twist-boat conformation of the D-ring takes place upon formation of the D-*ortho*acetate. This is illustrated in structures VII and VIII. With standard



VII VIII

molecular models, the D-*ortho*acetate cannot form if ring D possesses a chair conformation, while it is readily formed from a boat D-ring. Solvolysis studies, however, appear to preclude the pure boat conformation for ring D, since the C-20 hydroxyl grouping has been shown to assist solvolysis of C-16 acetates in a number of Veratrum derivatives.[2,4,21,22] In order to satisfy the evidence to date, the best interpretation of both the NMR and the solvolysis data, therefore, is that the D-ring exists in a twist-boat conformation. In this form the C-20 hydroxyl group could facilitate methanolysis of the C-16 acetate and the C-16 grouping would be closer in space to the C-21 methyl group than if ring D was in the chair conformation.

One further point to note is the effect of rupture of Ring F, in the formamido-ketones 12 and 30 for which the C-21 protons appear at 1·29 ppm which is at somewhat lower field than those compounds having an intact ring F. An intercomparison of the entire series indicates that oxygen functions, either —OH or —OCOR, at the 3α and β, 4α and β, 6α, 7α, and 9α positions and a keto group at C-7 exert virtually no effect on the shielding of the C-21 protons.

[17] L. M. Jackman, *Applications of NMR in Organic Chemistry* Chap. 7. Pergamon Press, New York (1959).

[18] L. M. Jackman and R. H. Wiley, *J. Chem. Soc.* 2881, 2886 (1960).

[19] L. Crombie and J. W. Lown, *Proc. Chem. Soc.* 299 (1961).

[20] W. A. Ayer, R. Hayatsu, P. de Mayo, S. T. Reid, and J. B. Stothers, *Tetrahedron Letters* No. 18, 648 (1961).

[21] S. M. Kupchan, *J. Amer. Chem. Soc.* **81**, 1921 (1959).

[22] S. M. Kupchan, S. P. Eriksen and Y. T. Shen, *J. Amer. Chem. Soc.* **85**, 350 (1963).

C-19 *Methyl protons.* In this series of alkaloids, there are examples having both *cis* and *trans* A/B ring fusions. Most of the compounds possess the former stereochemistry owing to the presence of the C-4, C-9 hemiketal grouping. Recent studies[8] have shown that the sabine derivatives retain the *cis* A/B system, although there is no C-9 oxygen function. The present NMR results offer further support for this conclusion. For comparative purposes, a few cevagenine derivatives have been examined since these compounds provide model systems with a *trans* A/B ring fusion. For all of these alkaloids, the environment of the C-19 methyl protons would be expected to be closely similar to that in steroid systems. This is found to be the case and the shielding effects (at the C-19 protons) of substituents on the A and B rings are comparable in magnitude for the two systems. A detailed discussion of these effects follows.

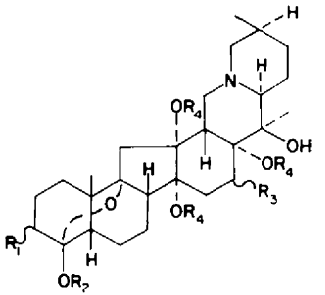
The data for those compounds having the C-4, C-9 hemiketal system (general formula I) are listed in Tables 1–3 from which it can be seen that the total range of chemical shift observed for the angular methyl protons is 0·89–1·36 ppm. An intercomparison of these data indicates that the effects of the various substituents are additive in a manner similar to that previously reported for a number of steroids.[9–11] Zygadenine was selected as the parent system and the effects of the substituents on the C-19 proton chemical shift value of 0·97 ppm were noted. Although the effect of every substituent could not be examined in the absence of other substitutions, it appears that the effects are additive. A summary of the observed shielding effects of the various substituents is presented in Table 6. Using these data and assuming an additive relation, one can calculate the C-19 shifts for these compounds to within 0·015 ppm. Most of the effects observed are small, ca. 1–2 c/s, but the fact that there is a consistent change in the C-19 chemical shift for these substituents in a number of derivatives indicates that the effects are real. A few can be compared to the values observed in steroids. For example, the C-7 keto grouping exhibits a deshielding effect of 0·24 ppm, while in steroids the observed effect has been reported as 0·28[10] and 0·27 ppm.[23] (The latter value is specifically for *cis* A/B steroid systems.) Small differences in the substituent effects for these two systems is not unexpected since there will be differences in the distortion of the ring systems. The number of comparisons made for each substituent are indicated in the Table and in view of the limited number possible in the present series of 27 compounds, the additivity relation must be used with caution. The use of these data as aids in the structural elucidation of new Veratrum alkaloid derivatives, however, is clearly suggested.

An examination of the C-19 shift data for the cevagenine derivatives (Table 4) indicates that these shifts are very close to those expected for the C-19 protons in a similarly substituted steroid on the basis of the published substituent correlations.[10,11] It is interesting that the formation of the C-*ortho*acetate grouping leads to an increased shielding at the C-19 protons by ca. 9 c/s. Presumably this shift is due to a change in the relative orientation of the D, E, F ring system and the angular methyl protons caused by the formation of the rigid C-*ortho*acetate group.

The observed shifts for the sabine derivatives (Table 5) appear to support the proposed *cis* A/B ring fusion. The chemical shifts of the angular methyl protons in the derivatives discussed previously are very close to those calculated for similarly

[23] E. R. Malinowski, M. S. Manhas, G. H. Muller and A. K. Bose, *Tetrahedron Letters* No. 18, 1161 (1963).

TABLE 1(a). NMR DATA FOR METHYL PROTONS IN VERACEVINE AND CEVINE DERIVATIVES (in p.p.m. from TMS)

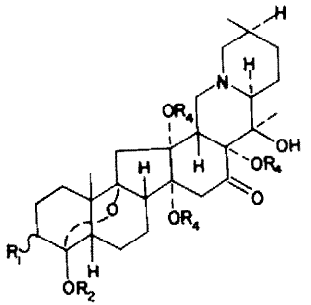


Compound	Substitution				Chemical shifts (δ)					Apparent J(c/s)
	R_1	R_2	R_3	R_4	27-Me	21-Me	19-Me	Me—C=O	Other Me's	27-Me
1. Veracevine	β-OH	H	β-OH	H	1·08	1·14	0·97	2·01		6·8
2. Veracevine triacetate	β-OAc	Ac	β-OAc	H	1·08	1·08†	1·05†	2·03 2·06		7·0
3. Cevine triacetate	α-OAc	Ac	β-OAc	H	1·09	1·08	1·03	1·99 2·07(2)		6·5
4. Veracevine D-*ortho*acetate triacetate	β-OAc	Ac	β-OAc	*o*-acetate	1·07	1·01†	0·98†	2·00 2·03 2·07	1·52	6·9
5. Cevine D-*ortho*acetate 3,4-diacetate	α-OAc	Ac	β-OH	*o*-acetate	1·04	1·22	0·95	2·04(2)	1·60	7·0
6. 16-Epicevadine D-*ortho*acetate-4-acetate	β-OAng*	Ac	α-OH	*o*-acetate	1·04	1·17	0·98	2·01	1·63 1·91	7·0

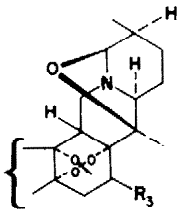
* OAng = angeloyl

† The assignments of the C-19 and C-21 peaks are not unequivocal but the reverse assignment would not affect any of the conclusions.

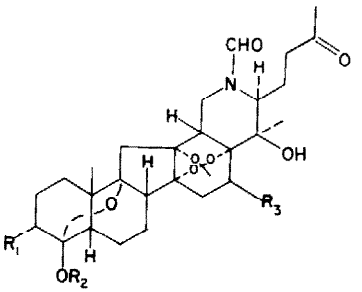
TABLE 1(b). NMR DATA FOR METHYL PROTONS IN VERACEVINE AND CEVINE DERIVATIVES (in p.p.m. from TMS)



A



B

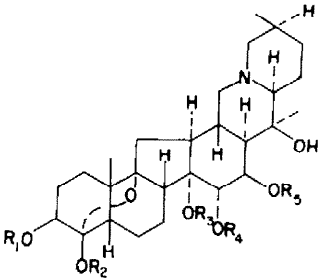


C

Compound	Substitution					Chemical shifts (δ)					Apparent J(c/s)
	Type	R_1	R_2	R_3	R_4	27-Me	21-Me	19-Me	Me—C=O	Other-Me's	27-Me
7. 16-Dehydrocevine 3,4 diacetate	A	α-OAc	Ac	=O	H	1·09	1·15	1·00	2·06(2)		7·2
8. 16-Dehydrocevadine D-*ortho*acetate 4-acetate	A	β-OAng†	Ac	=O	*o*-acetate	1·06	1·40	1·00	2·01	1·57 1·90	6·6
9. 16-Dehydrocevine D-*ortho*acetate-3,4 diacetate	A	α-OAc	Ac	=O	*o*-acetate	1·06	1·40	1·00	2·00(2)	1·57 1·90	6·5
10. Dehydrovecine D-*ortho*acetate	B	α-OH	H	β-OH	*o*-acetate	0·85	1·43	0·89		1·51	6·0
11. Dehydrocevine D-*ortho*acetate triacetate	B	α-OAc	Ac	β-OAc	*o*-acetate	0·84	1·18	0·93	2·05(3)	1·61	6·0
12. Formamido ketone from cevine D-*ortho*acetate triacetate	C	α-OAc	Ac	β-OAc	*o*-acetate	—	1·30	0·94	2·06 2·08 2·09 2·15	1·50	—

* Ang = angeloyl

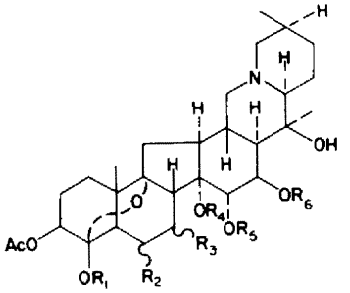
TABLE 2. NMR DATA FOR METHYL PROTONS OF ZYGADENINE DERIVATIVES



Compound	Substitution					Chemical shifts (δ)					Apparent J(c/s)
	R_1	R_2	R_3	R_4	R_5	27-Me	21-Me	19-Me	Me—C=O	Other Me's	27-Me
13. Zygadenine	H	H	H	H	H	1·07	1·23	0·97			7·7
14. Zygacine	Ac	H	H	H	H	1·07	1·24	1·00	2·09		7·8
15. Zygacine acetonide	Ac	H	C(Me)(Me)		H	1·07	1·23	0·96	2·09	1·29 1·37	7·2
16. Zygadenine acetonide	H	H	C(Me)(Me)		H	1·08	1·24	0·94		1·45 1·48	6·6
17. Zygadenine acetonide acetate	Ac	H	C(Me)(Me)		Ac	1·07	1·19	0·97	2·00 2·05	1·28 1·44	7·2
18. Angeloyl zygadenine	Ang*	H	H	H	H	1·07	1·24	1·02		1·92	7·2
19. Veratroyl zygadenine	Verat*	H	H	H	H	1·09	1·24	1·04		3·94(2)	6·3
20. Angeloyl zygadenine acetonide	Ang*	H	C(Me)(Me)		H	1·07	1·24	0·97		1·29 1·37 1·90	7·6
21. Zygadenine tetracetate	Ac	Ac	H	Ac	Ac	1·08	1.15	1·06	2·01(2) 2·05 2·08		7·8

* Ang = angeloyl; † Verat = veratroyl

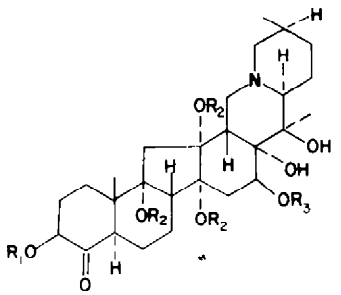
TABLE 3. NMR DATA FOR METHYL PROTONS IN GERMINE AND PROTOVERINE DERIVATIVES (in p.p.m. from TMS)



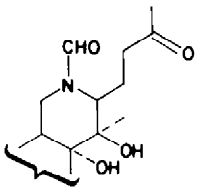
Compound	Substitution						Chemical shifts (δ)					Apparent J(c/s)
	R_1	R_2	R_3	R_4	R_5	R_6	27-Me	21-Me	19-Me	Me—C=O	Other Me's	27-Me
22. Germine tetraacetate	H	H	β-OAc	H	Ac	Ac	1·06	1·18	1·03			7·7
										1·93	1·44	6·8
23. 7-Dehydrogermine acetonide diacetate	H	H	=O	C(Me)(Me)		Ac	1·07	1·16	1·21	2·07		
24. Neogermitrine	H	H	α-OAc	H	secBu*	H	1·07	1·18	0·99	2·08 2·09		7·8
25. Protoverine pentacetate	Ac	α-OAc	α-OAc	H	Ac	H	1·07	1·18	1·13	1·98(2) 2·02(2) 2·11		7·1
26. Protoverine acetonide triacetate	H	α-OAc	α-OH	C(Me)(Me)		Ac	1·05	1·21	1·10	2·01 2·07 2·15	1·45 1·53	6·3
27. 7-Dehydroprotoverine acetonide triacetate	H	α-OAc	=O	C(Me)(Me)		Ac	1·07	1·21	1·34	1·97 2·07 2·21	1·47 1·45	7·2

* secBu = sec-butyryl

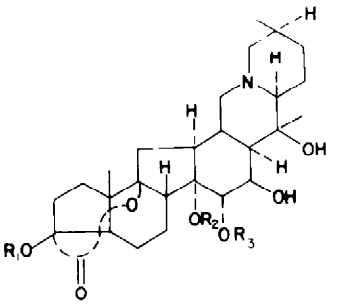
TABLE 4. NMR DATA FOR METHYL PROTONS IN CEVAGENINE AND ZYGADENILIC ACID DERIVATIVES



A



B



C

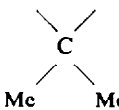
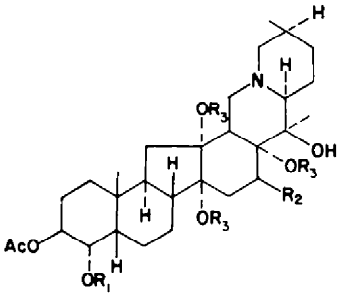
Compound	Substitution				Chemical shifts (δ)					Apparent J(c/s)
	Type	R_1	R_2	R_3	27-Me	21-Me	19-Me	Me—C=O	Other Me's	27-Me
28. Cevagenine diacetate	A	Ac	H	Ac	1·07	1·08	0·88	2·00 2·16		6·5
29. Cevagenine C-orthoacetate diacetate	A	Ac	o-acetate	Ac	1·08	1·16	0·74	2·01 2·15	1·58	7·3
30. Formamido ketone (derived from cevagenine C-ortho-acetate diacetate)	B	Ac	o-acetate	Ac	—	1·29	0·73	2·05 2·15	1·59	—
31. Zygadenilic acid δ-lactone	C	H	H	H	1·06	1·25	1·25			6·5
32. Zygadenilic acid δ-lactone acetonide	C	H			1·06	1·24	1·24		1·43	6·3

TABLE 5. NMR DATA FOR METHYL PROTONS IN SABINE DERIVATIVES (in p.p.m. from TMS)



Compound	Substitution			Chemical shifts (δ)					Apparent J(c/s)
	R_1	R_2	R_3	27-Me	21-Me	19-Me	Me—C=O	Other Me's	
33. Sabadine	H	OH	H	1·09	1·15	0·97	2·10		7·2
34. Sabine triacetate	Ac	OAc	H	1·08	1·08	1·01	2·00 2·07 2·09		7·7
35. Sabine D-*ortho*acetate triacetate	Ac	OAc	*o*-acetate	1·07	1·13	0·91	2·04 2·06 2·08	1·54	7·0
36. Sabine D-*ortho*acetate diacetate	Ac	OH	*o*-acetate	1·06	1·22	0·92	2·06 2·09	1·54	7·4
37. 16-Dehydrosabine D-*ortho*acetate diacetate	Ac	=O	*o*-acetate	1·07	1·41	0·95	2·06 2·09	1·59	7·0

TABLE 6. SHIELDING EFFECTS* OF SUBSTITUENTS ON ANGULAR METHYL PROTONS (C-19) OF VERATRUM ALKALOIDS (GENERAL FORMULA I)

Position of substituent	Substituent	Shielding effect c/s (at 60 Mc/sec)	Shielding effect ppm	No. of examples
C-3	β-$OCOCH_3$	+1·5	+0·025	12
	β-O-Angeloyl	+2·0	+0·03	4
	β-O-Veratroyl	+4·0	+0·07	1
	α-$OCOCH_3$	−1·0	−0·016	6
C-4	β-$OCOCH_3$	+3·0	+0·05	12
C-6	α-$OCOCH_3$	+6.5	+0·11	3
C-7	α-OH	+0·5	+0·008	1
	α-$OCOCH_3$	−1·0	−0·016	2
	β-$OCOCH_3$	+1·0	−0·016	1
	C=O	+14·5	+0·242	2
C-14, C-15	Acetonide	−2·0	−0·03	6
C-15	β-$OCOCH_3$	0·0	0·0	4
C-16	β-$OCOCH_3$†	+1·0†	+0·016†	8
	C—O	0·0	0·0	3
C-12, C-17	α-OH	0·0	0·0	4

* A *positive* substituent effect is *deshielding* because of the δ scale employed.

† Excluding compounds with the D-*ortho*acetate system. Formation of the D-*ortho*acetate ring modifies the effect of a 16 β-OAc by −5·5 c/s (−0·09 ppm) and the effect of a 16 β-OH group by −4·0 c/s (−0·065 ppm).

substituted steroids and although steroidal systems having the C-4, C-9 hemiketal bonding are not available, it appears that the effect of this bonding on the C-19 shifts is small. In the sabine series, a more direct comparison with steroids is possible. Using the known substituent effects for C-3, C-12, C-14, C-16, and C-17 substituents (from Table 6 and references 10 and 11) one can calculate a chemical shift for the C-19 protons for both the *cis* and *trans* A/B ring systems. No data appear to be available for the C-4 α-OH group, but its effect would be expected to be small for either system. In fact, the effect in the *trans* case would be close to that for a 6α-OH group, which has been found to be ca. 1 c/s.[11,24] Thus the calulated C-19 shifts would be approximately 0·83 ppm for the *trans* structure and 0·97 ppm for the *cis* A/B ring system. Clearly the latter case is in better agreement with the observed shifts and, therefore, the NMR results lend further support to the proposal that the sabine derivatives possess the *cis* A/B stereochemistry. The effects of the substituent changes in the D-ring are the same as those discussed previously and thus present evidence for the conformational interconversion of the D-ring upon formation of the D-*ortho*-acetate.

Other methyl groups. Most of the compounds examined have, in addition to the methyl protons already discussed, methyl groups on carbon bearing oxygen whose singlet signals are clearly separated from the others and are easily recognized. The methyl protons of the *ortho*acetate groupings appear from 1·50 to 1·63 ppm and no distinction between the C- and D-*ortho*acetates is possible. The two methyl groups of

[24] D. J. Collins, J. J. Hobbs, and S. Sternhall, *Tetrahedron Letters* No. 4, 197 (1963).

the acetonides usually appear separately in the region, 1·29–1·44 ppm. although substitution at C-6 and C-7 tends to shift these signals to slightly lower field, 1·44–1·54 ppm. The most commonly occurring group in this series, the acetoxyl, exhibits the characteristic sharp singlet in the range, 1·99–2·11 ppm for the majority of these compounds. Slight shifts outside this range are found for the C-7 keto derivatives, which have an acetyl methyl group near 1·95 ppm, and the formamido-ketones having a three proton signal at 2·15 ppm. While it appears likely that this latter signal is due to the methyl ketone group formed by cleavage of the F-ring, a definite assignment is not possible in the presence of the other methyl signals. It can be noted, however, that the appearance of this additional acetyl signal was helpful in the structural elucidation of the formamido-ketone 12.[3]

Another type of methyl group is found in the spectra of four of these derivatives, namely the α-methyl protons of the angeloyl group (Cpd. 6, 8, 18, 20). The band due to these protons appears in the range, 1·90–1·92 ppm. The signals arising from the β-methyl protons of the angeloyl grouping cannot be definitely assigned. The lone veratroyl ester (Cpd. 19) displays a strong six-proton signal at 3·94 ppm due to the methoxyl protons.

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