NMR INVESTIGATION OF ALKALOIDS.

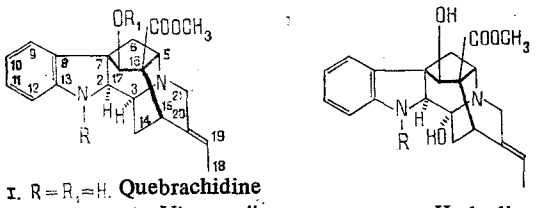
III. ^{13}C NMR SPECTRA AND RECONSIDERATION OF THE STEREOCHEMISTRY OF HERBAMINE AND HERBADINE*

M. R. Yagudaev

UDC 547.944.1.92

The stereochemistry previously proposed for herbamine (V) and herbadine (II) as C_2-βH has been reconsidered on the basis of a comparative study of the ^{13}C NMR of these compounds and of vincamajine, quebrachidine, ajmaline, vincamajoreine, and majoridine, and it has been established unambiguously that herbamine and herbadine belong to the dihydroindole alkaloids with C_2-αH, herbamine being C_3-hydroxyvincamajine, and herbadine C_6-hydroxyquebrachidine.

The alkaloids herbamine (V) and herbadine (II) were first isolated from *Vinca herbaceae*, and structures were given for them [2], and then the same alkaloids were isolated from *Vinca libanotica* and, on the basis of spectral characteristics and, mainly, from a comparison of the PMR spectra of (V) and (II) with those of vincamajine (III) and quebrachidine (I), respectively, structures and stereochemistries with the β orientation of H_2 were proposed [3, 4].



I. R = R_1 = H. **Quebrachidine**
III. R = CH_3, R_1 = H. **Vincamajine**
IV. R = CH_3, R_1 = $COCH_3$. **Vincamedine**

II. R = H. **Herbadine**
V. R = CH_3. **Herbamine**

The β orientation of the C_2-H atom in (V) and (II) was selected on the basis of the chemical shifts (CSs) of the protons of the C_{21} methylene group with the corresponding shifts in the spectra of the alkaloids (III) and (IV). We have shown previously [1] that the nonequivalence of the protons of the methylene group at C_{21} in herbamine (V) and herbadine (II) is due mainly to the influence of the magnetic anisotropy and of the electric field of the C–O bond and of the $2p_z$ UEP of the oxygen atom of the OH group at C_3 on the value of the CS of the C_{21}-H_α proton and does not depend on the orientation of the C_2–H hydrogen atom. Consequently, it appeared of interest to study the stereochemistry of these alkaloids with the aid of ^{13}C NMR spectroscopy.

In the present paper we give the results of a comparative analysis of the ^{13}C NMR spectra of the alkaloids (I–V), permitting us to reconsider and unambiguously to show the configurations of the C_2 centers in (II) and (V). The assignment of the ^{13}C signals of compounds (I–V) was made on the basis of the results of an experiment with incomplete decoupling of the C–H interactions, i.e., from the multiplicity of the ^{13}C signals in the off-resonance spectrum and by comparing the ^{13}C CS of (I–V) with literature figures for the ^{13}C NMR spectra of alkaloids of the ajmaline series, which have the same skeleton as compounds (I–V), vincamajine, vincamajoreine, and majoridine [5], and also taking into

*For Communication II, see [1].

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 731–735, November-December, 1982. Original article submitted February 15, 1982.

0009-3130/82/1806-0693$07.50

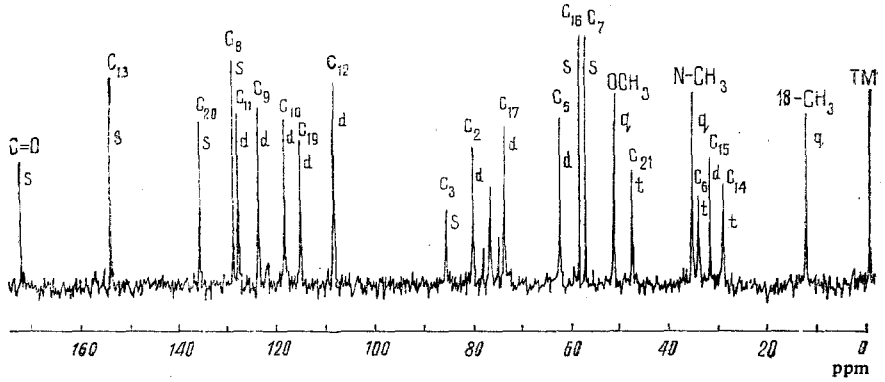


Fig. 1. ^{13}C NMR spectrum of herbamine in $CDCl_3$.

account the α, β, and γ contributions of the CH_3 and OH groups and the steric influence on the CSs of a series of carbon atoms [6–9]. In the spectra of all the alkaloids considered (I–V), the ^{13}C signals of the sp^2 carbon atoms C_8, C_{13}, C_{20}, and C=O are singlets, and those of C_9, C_{10}, C_{11}, C_{12}, and C_{19} doublets, and in the off-resonance spectrum they appear clearly in the 108–174 ppm region, with the exception of C_8, C_{13}, C_{20} and C=O in (II), and their CS values agree well with those for alkaloids of the ajmaline type [5] (Table 1). The CSs of the ^{13}C signals of the majority of the sp^3 carbons in (I–V) are also close to the analogous values of similar compounds. It has been reported previously [5] that a distinguishing feature of the ^{13}C NMR spectra of alkaloids of the ajmaline type with C_2-βH (ajmaline, vincamajoreine, majoridine) is a downfield shift of the signals of the C_2 and C_4 atoms by approximately 4–5 and 8–10 ppm, respectively, as compared with those for alkaloids having C_2-αH (vincamajine). Analysis of the features of the ^{13}C NMR spectra that we have obtained for quebrachidine (I) and vincamajine (IV) with C_2-αH completely confirms what has been stated above (see Table 1). The downfield shift of the signals of the C_2 carbon in vincamajine and vincamedine by 5–6 ppm as compared with the analogous signal of quebrachidine is obviously due to the descreening contribution of the methyl of the NCH_3 group on the CS of C_2 in (III) and (IV) with the replacement of N–H in (I) by NCH_3. This contribution of a N-CH_3 group to the carbon atom in the α position with respect to the nitrogen (C_2) for indoline alkaloids of the ajmaline type is close in magnitude to the increment ($\Delta \sim 6$ ppm) found for substituted pyrroles as model five-membered ring compounds [9] and depends on the degree of substitution of the β carbon atoms.

It can be seen from Table 1 that the CS of C_2 of herbamine (V) in $CDCl_3$ (80.8 ppm) practically coincides with the CSs of the C_2 atoms of the alkaloids majoridine (79.6 ppm, $CDCl_3$) and ajmaline (79.4 ppm, DMSO-d_6), belonging to the C_2-β series [5]. However, a substantial contribution to the CS of the C_2 carbon atom of herbamine (V) must undoubtedly be made by the α-oriented OH group at C_3, which is equatorial with respect to the C_2 of ring C in (V). The contribution of an equatorial OH group to a β-carbon atom in the case of cyclohexanol is +7.95 ppm [10] and obviously depends on the degree of substitution of the β-carbon atom [8]. The difference in the CSs of the C_2 atoms of herbamine (V) and vincamajine (III) is +6.4 ppm, which agrees well with the β contribution of the C_3-αOH. Consequently, in view of the fact that vincamajine (III) belongs to the dihydroindole alkaloids of the C_2-α series, herbamine also has the same C_2-αH configuration as vincamajine and not the C_2-βH configuration, as was considered previously [3]. Furthermore, analysis of the figures given in Table 1 shows that the CS of the C_{14} atom in herbamine (V) is shifted downfield by 8.1 ppm as compared with that of vincamajine (III), which is likewise due to the

TABLE 1. ^{13}C Chemical Shifts and Assignment of the Signals of the Carbon Atoms of the Dihydroindole Alkaloids (I–V)

Carbon atom and multiplicity	Quebrachidine (I)		Herbadine (II)	Vincamajine (III)		Vincamedine (IV)	Herbamine (V)
	$CDCl_3$	Py-d_5	Py-d_5	$CDCl_3$+ +CD_3OD [5]	Py-d_5	$CDCl_3$	$CDCl_3$
C_2s	68.3	69.3	76.3	74.4	75.6	74.7	80.8
C_3d	54.4	55.2	85.4 s	52.7	53.3	53.1	86.0s
C_5d	61.4	62.3	64.0	61.1	65.2	61.4	62.9
C_6t	35.5	36.8	36.6	35.0	36.7	36.3	34.6
C_7s	57.6	58.6	61.2	56.5	60.9	55.0	57.6
C_8s	129.8	131.5	*	129.7	132.2	128.6	129.4
C_9d	124.9	126.1	125.9	124.2	125.8	123.1	124.1
C_{10}d	119.3	118.8	118.3	118.2	119.1	118.7	118.9
C_{11}d	128.0	127.7	127.5	127.6	128.0	128.2	128.4
C_{12}d	110.7	110.5	110.2	108.4	109.1	109.1	108.9
C_{13}s	151.6	153.3	*	153.8	155.3	154.1	154.1
C_{14}t	22.3	22.9	30.1	21.4	22.4	21.5	29.5
C_{15}d	30.2	31.1	33.3	29.6	31.8	30.2	32.4
C_{16}s	59.6	58.6	58.6	59.6	58.3	58.8	59.0
C_{17}d	74.0	74.4	73.8	73.9	74.9	75.2	74.1
18–CH_3q	12.6	12.9	12.5	12.3	13.0	12.6	12.7
C_{19}d	115.9	115.2	114.0	116.1	115.0	116.5	115.7
C_{20}s	137.0	139.2	*	135.6	139.3	136.6	136.5
C_{21}t	55.2	55.9	49.1	54.7	56.0	55.4	48.4
NCH_3q	—	—		33.8	34.4	33.9	35.8
OCH_3q	51.3	51.0	50.7	51.1	51.2	51.4	51.4
–C(=O)–	173.0	173.3	*	172.8	173.6	172.1	172.6
O–C=O	—	—	—	—	—	168.2	—
CH_3q	—	—	—	—	—	20.5	—

*The signals of the quaternary sp^2 carbons are of low intensity and under the given experimental conditions are lost in the noise.

β contribution of the C_3-αOH group in (V) and is one more confirmation of the C_2-αH configuration of herbamine, since the CS of the C_{14} atom in the C_2-βH dihydroindoline alkaloids of the ajmaline type [5] containing no OH group at C_3 has a value (29.5 ppm), close to the CS of the C_{14} atom of herbamine. If herbamine had the C_2-βH configuration, then, taking into account the contribution of the C_3-βOH (∼8 ppm) the C_{14} CS should be approximately 38 ppm.

Thus, a comparison of the CSs of the C_2 and C_{14} atoms of herbamine and of vincamajine (III) permits us to reconsider the stereochemistry with C_2-βH suggested previously for herbamine and to establish unambiguously that herbamine belongs to the dihydroindole alkaloids with the α configuration of the H at C_2 and is C_3-hydroxyvincamajine (V).

Similar considerations are valid for herbadine, the CSs of the C_2 and C_{14} carbon atoms of which, taking into account the β contribution of the C_3-αOH as compared with those of quebrachidine (I) (see Table 1), give grounds for considering that herbadine has the same C_2-αH configuration as quebrachidine and is C_3-hydroxyquebrachidine (II).

The conclusion concerning the α configuration of C_2H in herbamine (V) and herbamine (II) that we have made on the basis of ^{13}C NMR spectra is completely confirmed by a comparative analysis of the circular dichroism spectra of herbamine and vincamajine with those of majoridine [11] and ajmaline. In contrast to the last two alkaloids, which have the C_2-βB configuration and give a positive Cotton effect at about 250 nm, herbamine (V), just like vincamajine (III), shows a negative Cotton effect at 247 nm ($\Delta\varepsilon = -6.67$) and 248 nm ($\Delta\varepsilon = -11.55$). As can be seen from Table 1, as a result of the α contribution of the 3-αOH group the CSs of the C_3 carbon atoms of herbadine and herbamine naturally undergo a paramagnetic shift of $\Delta\varepsilon$ = 30.4 and 33.3 ppm, respectively. However, the value of this contribution is considerably less than that observed for cyclohexanol ($\Delta\varepsilon$ = 39–43 ppm) [10]. As mentioned above, the α and β contributions of substituents are considerably affected by the degree of substitution of the α and β carbon atoms [8], and where an OH group is attached to a tertiary carbon atom its α contribution is considerably less than when it is attached to a secondary carbon atom. This fact can explain the difference in the values of the α contributions of

the OH groups in the ^{13}C NMR spectra of herbamine, herbadine, and cyclohexanol [6, 7].

The C_3, C_{14}, C_{15}, C_{20}, C_{21}, $N_\delta(4)$, C_5, and C_{16} atoms in herbadine (II), herbamine (V), and other alkaloids of the ajmaline type form a quinuclidine skeleton which, to some approximation, can be considered as a bicyclo[2.2.2]octane system. It is known that in the quinuclidine and bicyclo[2.2.2]octane molecules the piperidine and cyclohexane rings are present in the fixed "boat" conformation. In such a system the OH group exhibits different γ effects according to its syn or anti position with respect to the carbon atom under consideration [8, 12, 13]. In herbadine (II) and herbamine (V), the 3-αOH group, which is in the syn position to the C_{21} carbon atom, exerts a considerable γ effect on it, as the result of which the CS of the C_{21} carbon is shifted downfield by −6.8 and −6.3 ppm in comparison with the C_{21} CS of quebrachidine (I) and vincamajine (III), respectively (see Table 1). The γ effect of the 3-αOH group on the C_{21} carbon atom is of steric origin and is close in magnitude to the analogous γ effect of an OH group having the syn orientation with respect to C_5 in the molecules of quinuclidine [12, 13] and of bicyclo[2.2.2]octane [8]. The γ effect of the 3-αOH group on the C_5 carbon atom, in the anti position with respect to the OH, in (II), and (V) is considerably smaller, at −1.7 and −1.8 ppm, respectively, which likewise agrees with the analogous effect of an OH group on the C_7 carbon atom, in the anti arrangement with respect to it, in the molecules of quinuclidine [12, 13] and bicyclo[2.2.2]octane [8].

Thus, a comparative analysis of the ^{13}C NMR spectra of the dihydroindole alkaloids of the ajmaline type — herbadine and herbamine with quebrachidine, vincamajine, vincamajoreine, majoridine, and ajmaline — has permitted the C_2-βH configuration previously proposed for herbadine and herbamine to be reconsidered and has unambiguously shown that herbadine is C_3-hydroxyquebrachidine and herbamine is C_3-hydroxyvincamajine.

EXPERIMENTAL

The ^{13}C NMR spectra of the alkaloids (I–V) were obtained on Varian CFT-20 and XL-100-15 and Bruker WM-250 spectrometers in $CDCl_3$ (0 — TMS, $\delta_{TMS} = \delta_{CDCl_3} + 76.91$ ppm) and in the Py-d_5 (0 — TMS). All the spectra were obtained in the pulsed regime under conditions of complete and incomplete decoupling of C–H interactions, with subsequent Fourier transformation. The circular dichroism curves of ajmaline, vincamajine, and herbamine were obtained on a JASCO J-20 recording spectropolarimeter in CH_3OH.

SUMMARY

On the basis of a comparative study of the ^{13}C NMR spectra of herbamine (V) and vincamajine, quebrachidine, ajmaline, vincamajoreine, and majoridine, the stereochemistry for (V) and (II) as C_2-βH proposed previously has been reconsidered, and it has been shown unambiguously that herbamine and herbadine belong to the C_2-αH dihydroindole alkaloids and, accordingly, herbamine is C_3-hydroxyvincamajine and herbadine is C_3-hydroxyquebrachidine.

LITERATURE CITED

1. M. R. Yagudaev, Khim. Prir. Soedin., 608 (1981).
2. V. Yu. Vachnadze, V. M. Malikov, K. S. Mudzhiri, and S. Yu. Yunusov, Khim. Prir. Soedin., 341 (1972).
3. G. H. Aynillian, C. L. Bell, N. R. Farnsworth, and D. J. Abraham, Lloydia, 37(4), 589 (1974).
4. G. H. Aynillian, C. L. Bell, and N. R. Farnsworth, J. Pharm. Sci., 64, No. 2, 341 (1975).
5. A. Chatterjee, M. Chakrabarty, A. K. Gnosh, E. W. Hagaman, and W. Wenkert, Tetrahedron Lett., 3879 (1978).
6. E. Breitmayer and W. Voelter, ^{13}C NMR-Spectroscopy, Verlag Chemie, Weinheim (1974).
7. F. W. Wehrli and T. Wirtlin, Interpretation of Carbon-13 NMR Spectra, Heyden, London (1976).
8. P. J. Garrat and R. Riguera, J. Org. Chem., 41, No. 3, 465 (1976).
9. E. Wenkert, J. S. Bindra, C.-J. Chang. D. W. Coehran, and F. M. Shell, Acc. Chem. Res., 7, 46 (1974).
10. H.-J. Schneider and V. Hoppen, Tetrahedron Lett., 579 (1974).
11. J. L. Kaul, J. Trojanek, and A. K. Bose, Collect. Czech. Chem. Commun., 35, 116 (1970).
12. F. I. Carroll, S. Smith, M. E. Wall, and C. G. Moreland, J. Med. Chem., 17, 985 (1974).
13. F. I. Carroll, A. Philip, and M. C. Coleman, Tetrahedron Lett., 1858 (1976).