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NMR INVESTIGATION OF ALKALOIDS.

II.* DETERMINATION OF THE CONFIGURATIONS OF THE C_{17} and C_2 ASYMMETRIC CENTERS IN INDOLINE ALKALOIDS OF THE AJMALINE TYPE BY THE DOUBLE PROTON RESONANCE METHOD†

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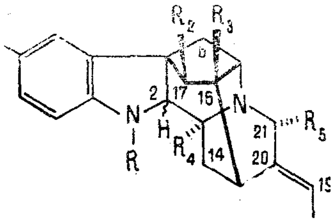
By the method of double proton resonance, in the alkaloids of the ajmaline type, ajmaline, majoridine, herbamine, quebrachidine (vincarine), vincamajine, and vincamedine a long-range stereospecific interaction through four σ-bonds between the $H_{6\alpha}$ and $H_{17\alpha}$ protons of about 1 Hz has been found and in compounds with C_2-βH and C_{17}-αH (ajmaline, majoridine), the $H_{2\beta}$ and $H_{17\alpha}$ protons exhibit a NOE of the order of 10%. These facts can be used successfully in determining the orientation of the hydrogen atoms and the corresponding configurations of C_{17} and C_2 asymmetric centers in such systems.

To determine the orientation of the H_{17} hydrogen atom and the corresponding configuration of the C_{17} asymmetric center in indoline alkaloids of the ajmaline type (I-VI) use is made of chemical methods [3, 4] and also of PMR spectroscopic characteristics (CSs and SSCCs) [3, 5-7]. In the present communication we give the results of the use of double-proton resonance methods — collapse and the intramolecular nuclear Overhauser effect (NOE) — to determine the configurations of the C_{17} and C_2 asymmetric centers in alkaloids of the ajmaline type (I-VI) (Table 1).



I. Ajmaline $R=R_3=R_4=H$, $R_1=CH_3$, $R_2=R_5=OH$, 19,20 dihydro $C_2-\beta H$.
II. Majoridine $R=OCH_3$, $R_1=CH_3$, $R_2=OAc$, $R_3=R_4=R_5=H$, $C_2-\beta H$.
III. Herbamine $R=R_5=H$, $R_1=CH_3$, $R_2=R_4=OH$, $R_3=COOCH_3$, $C_2-\alpha H$.
IV. Quebrachidine (vincarine [8]): $R=R_1=R_5=H$, $R_2=OH$, $R_3=COOCH_3$, $C_2-\alpha H$.
V. Vincamajine $R=R_4=R_5=H$, $R_1=CH_3$, $R_2=OH$, $R_3=COOCH_3$, $C_2-\alpha H$.
VI. Vincamedine. $R=R_4=R_5=H$, $R_1=CH_3$, $R_2=OAc$ $R_3=COOCH_3$, $C_2-\beta H$.

When the hydrogen atom at C_{16} in the alkaloids of the type under consideration is substituted and the hydrogen at C_{17} is β-oriented, the configuration of the C_{17} center can be established unambiguously from the value of the vicinal spin coupling constant of the $H_{17\beta}$ and $H_{16\beta}$ protons, since under these conditions, as can be seen from models, the dihedral angle between the $H_\beta-C_{17}-C_{16}-H_\beta$ protons is approximately 0 and, consequently, in accord-

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[*] For Communication I, see [1].
[†] Delivered at an All-Union Conference on Modern Advances in High-Resolution NMR spectroscopy, Tashkent, September, 1975 [2].

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TABLE 1. Results of Double Proton Resonance in Alkaloids of the Ajmaline Type

Compound	Solvent	CSs of the protons, ppm (O-TMS)		Experimental results	
		irradiated	observed for H_{17}	^4J, Hz	NOE, %
Ajmaline (I)	$CDCl_3$	$H_{2\beta}$ 2,95 $H_{6\alpha}$ 1,42	4,36	— ~1	10 —
Majoridine (II)	C_5D_5N*	$H_{2\beta}$ 2,68 $H_{6\alpha}$ 2,42	5,50	— 1,2	10 —
Herbamine (III)	$CDCl_3$	$H_3(NCH_3)$ 2,83 $H_{6\alpha}$ 1,65	4,00	— ~1	12 —
Quebrachidine (vincarine) (IV)	C_5D_5N	$H_{2\alpha}$ 4,17 $H_{6\alpha}$ 2,03	4,80	— ~1	— —
Vincamajine (V)	$CDCl_3$	$H_{2\alpha}$ 3,15 $H_{6\alpha}$ 1,65	4,18	— ~1	— —
Vincamedine (VI)	$CDCl_3$	$H_{2\alpha}$ 3,23 $H_{6\alpha}$ 1,80	5,68	— ~1	—

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*The spectrum of (II) was studied in C_5D_5N, since in $CDCl_3$ the $H_{17\alpha}$ signal is superposed on the H_{19} signal while in C_5D_5N the H_{17} signal is shifted downfield by 0.35 ppm.

ance with Karplus's rule their vicinal SSCCs may be 9-10 Hz. Thus, for example, the SSCC between these protons in 17-epideoxyajmaline O-acetate is 8.9 Hz [3]. When the hydrogen atom at C_{17} is α-oriented, as in the case of ajlamine (I) and majoridine (II), the $H_\alpha-C_{17}-C_{16}-H_\beta$ dihedral angle is close to 100° and the corresponding SSCC between them is extremely small and does not appear clearly. However, when the hydrogen at C_{16} is replaced by $COOCH_3$ or another substituent, the problem of determining the H_{17} orientation and, correspondingly, the C_{17} configuration becomes more complicated, since the H_{17} signal usually appears in the form of a broadened singlet because of the absence of vicinal coupling.

The orientation of the C^2—H proton and, accordingly, the configuration of the C_2 center can be determined unambiguously only in the case of its α orientation, or when the $H_\alpha-C_2-C_3-H_\alpha$ dihedral angle is approximately 30° and the vicinal SSCC is ∿ 5 Hz. It is precisely this value of the SSCC of the $H_{2\alpha}$ and $H_{3\alpha}$ proton that has been found previously in vincamajine [9] and that we have found in vincamedine. However, if the H_2 proton is β-oriented ($H_2\beta-C_2-C_3-H_{3\alpha}$ dihedral angle ∿ 85°), the vicinal SSCC is practically equal to 0. Of course, a vicinal SSCC of this proton is absent regardless of its orientation also when the hydrogen atom at C_3 is replaced, usually by OH, and therefore a difficulty arises in the unambiguous determination of the H_2 orientation. In determining the orientation of H_2 in herbamine (II) [9], and herbadine [10] by the PMR method, Aynilian et al. started from a comparison of the CSs of the protons of the methylene group at C_{21} with those in the spectra of the alkaloids vincamajine (V) and quebrachidine (IV). In the spectrum of herbamine in $CDCl_3$, the $C_{21}-H_2$ methylene protons prove to be nonequivalent and give two doublets at 3.88 and 3.00 ppm, respectively, ^2J = 15.5 Hz, while in the spectrum of vincamajine (V) in $CDCl_3$ the same protons are almost equivalent and appear in the form of a multiplet at 3.51 ppm [9]. The nonequivalence of the C_{21}—H_2 protons in herbamine is explained by Aynilian et al. [9] by the β-orientation of the proton at C_2, whereupon the $C_{21}-H_2$ protons are affected by the anisotropy of the ethylenic side chain and of the nonbound $N_{(\delta)}$ electrons, and in the case of the α orientation of C_2-H the same authors considered that the $C_{21}-H_2$ protons are present in a symmetrical environment relative to the two groups under consideration and therefore they are close to equivalence. On this basis for herbamine and herbadine they chose the β orientation of C_2-H [9, 10]. At the same time, a detailed analysis of models of the herbamine and vincamajine shows that a change in the C_2 configuration scarcely affects the surroundings (symmetry) of the $C_{21}-H_2$ protons, since the nonindoline part of the skeleton of these molecules forms a rigid carcass with an extremely stable conformation of the rings regardless of the configuration at C_2.

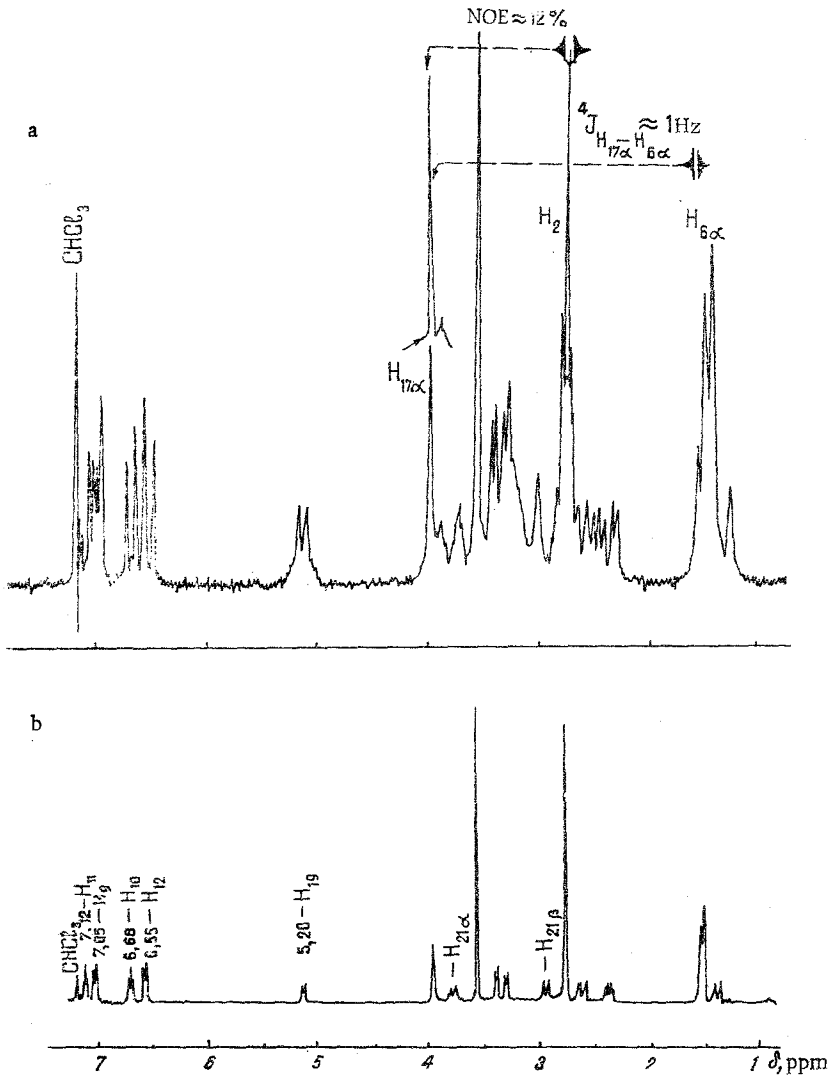


Fig. 1. PMR spectra of herbamine on instruments with working frequencies with respect to protons ν_0 = 100 MHz (a) and 360 MHz (b) in $CDCl_3$.

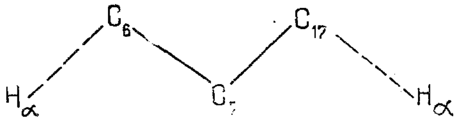
It is quite obvious that a substantial influence on the nonequivalence of the protons of the methylene group at C_{21} in herbamine and herbadine is exerted by the α-oriented OH group at C_3 in them, which is present almost in the same plane as the $C_{21}-H_\alpha$ bond. The distance from the center of the C_3-O bond of the OH group in herbamine to the H_{21} proton, measured in models, is approximately 2.6 Å. A rough calculation of the contribution of the magnetic anisotropy and of the electrical field of the C—O bond and of the $2p_z$ unshared pair of electrons of the oxygen atom to the SC of the $H_{21\alpha}$ proton gives a value of 0.8-0.9 ppm in the downfield direction [11]. Consequently, a doublet in the weak field at 3.88 ppm with ^2J = 15.5 Hz in the spectrum of herbamine in $CDCl_3$ must be assigned to the $H_{21\alpha}$ proton, and a doublet in the strong field at 3.00 ppm to the $H_{21\beta}$ proton (Fig. 1b).

Thus, the nonequivalence of the protons of the methylene group at C_{21} in herbamine and herbadine is due mainly to the presence in their molecule of an OH group at C_3, not present in the other alkaloids considered, and does not depend on the C_2-H orientation. Another confirmation of this is the fact that in majoridine (II) with $C_2-\beta H$ the $C_{21}-H_2$ protons are almost equivalent and give a signal (2H) in the form of an unresolved multiplet with a half-width $W_{1/2} \approx 7$ Hz at 3.36 ppm in $CDCl_3$ and 3.40 ppm in C_5D_5N. The assignment of the signal of the protons in majoridine was made with the aid of double resonance.

It must also be observed that in the paper of Aynilian et al. [9] the tabular values of the SCs of the signals of the olefinic $-H_{19}$ and of the aromatic protons in the δ range of 5-8 ppm for vincamajine and herbamine obtained from a spectrometer with a working frequency of 220 MHz in $CDCl_3$ and C_5D_5N are incorrect and are approximately 0.4-0.5 ppm high (the CSs of the other protons in the 0-5 ppm region coincide), as is reliably shown by the spectra of herbamine [12] in $CDCl_3$ that we have taken repeatedly on spectrometers with working frequencies for protons of 100 and 360 MHz (Fig. 1a and b).

A comparison of the H_{19} and Ar—H CSs of vincamajine (V) in $CDCl_3$ and C_5D_5N, which we measured on an instrument with ν_0 = 100 MHz also confirms what has been stated above, since these CSs in (V), both in $CDCl_3$ and in C_5D_5N are 0.45-0.60 ppm on the upfield side of those given by Aynilian et al. [9].

Methods of double proton resonance have proved extremely effect in the solution of problems connected with the determination of the orientations of $C_{17}-H$ and C_2-H hydrogen atoms in alkaloids of the ajmaline type. An analysis of models shows that the $H_{6\alpha}$ and $H_{17\alpha}$ hydrogen atoms together with the $C_6-C_7-C_{17}$ bonds form a zig-zag-shaped fragment of the W type, i.e.,



It is known that it is precisely in this fragment that the stereospecific long-range spin—spin coupling takes place through four σ-bonds with a value ^4J = 1-5 Hz [13]. It can also be shown from models that with the β orientation of the C_2-H hydrogen the difference between the $H_{2\beta}$ and $H_{17\alpha}$ protons amounts to approximately 2.5 Å. Consequently, a NOE must exist between them [14]. Furthermore, in the case of the α orientation of C_2-H (vincamajine, vincamedine, quebrachidine), the $H_{17\alpha}$ and $H_{14\beta}$ atoms approach one another to a distance of 2 Å and therefore likewise, a NOE must exist between them. In actual fact, in the PMR spectra of all the alkaloids of the ajmaline type studied (I-VI), a stereospecific long-range spin—spin coupling through four σ-bonds between the $H_{6\alpha}$ and $H_{17\alpha}$ protons has been found with a value ^4J = 1-1.2 Hz (Table 1). A similar ^4J coupling between the $H_{6\alpha}$ and $H_{17\alpha}$ protons has been detected by us previously in the indoleine alkaloid majorinine [15]. It must be mentioned that in majoridine (II), in addition to ^4J, we also found vicinal coupling between $H_{17\alpha}$ and $H_{16\beta}$ with a value ^3J < 1 Hz.

In compounds with the established $H_{2\beta}$ and $H_{17\alpha}$ orientations (ajmaline and majoridine), a NOE between these protons of the order of 10% is observed, which unambiguously confirms the β orientation of C_2-H in them. As the figures in Table 1 show, a NOE (12%) is likewise observed between the C_2-H (2.83 ppm) and $H_{17\alpha}$ protons in herbamine. However, in the spectrum of herbamine at 2.82 ppm the signal of the $N-CH_3$ protons appears, i.e., the C_2-H and $N-CH_3$ signals in it are superposed, and the distance from the center of the $N-CH_3$ protons to the $H_{17\alpha}$ proton, where the C_2-H has the α orientation and $N-CH_3$ the β orientation as in (III), is approximately 2.4 Å. Consequently, with such an arrangement of H_2 and $N-CH_3$ protons it is also possible to observe a NOE of the order of 10% between them in herbamine. It is therefore difficult from the figures given in Table 1 unambiguously to determine the orientation of the C_2-H proton in herbamine, and the solution to the problem requires further investigations.

When C_2-H and the $N-CH_3$ group have the β orientations, the distance from the center of the $N-CH_3$ protons to $H_{17\alpha}$ is about 6 Å, so that a NOE between them is excluded. We have also observed a NOE (15%) between the $H_{14\beta}$ (2.90 ppm) and $H_{17\alpha}$ (4.17 ppm) protons in quebrachidine (IV). These experimental facts can be used successfully to determine the orientations of the $C_{17}-H$ and C_2-H hydrogen atoms in similar systems.

EXPERIMENTAL

The spectra of the alkaloids (I-VI) were obtained on JNM-4H-100/100 MHz and Varian XL-100-15 spectrometers in $CDCl_3$ [substances (I, III, V, and VI)] and C_5D_5N [substances (II and IV)]; 0 — TMS. In order to exclude spin—spin coupling of OH with $C_{17}-H$, the spectra of (I, III, IV, and V) were obtained with the addition of a few drops of D_2O. The spectrum of herbamine was also recorded on a Burker WH-360 instrument with a working frequency for protons of 360 MHz in $CDCl_3$; 0 — TMS.

SUMMARY

Using the method of double proton resonance, a long-range stereospecific interaction through four σ-bonds of about 1 Hz has been found between the $H_{6\alpha}$ and $H_{17\alpha}$ protons in alkaloids of the ajmaline type and in compounds with $C_2-\beta H$ and $C_{17}-\alpha H$ (ajmaline, majoridine), the $H_{2\beta}$ and $H_{17\alpha}$ protons exhibit a NOE of the order of 10%. These facts can be used successfully to determine the orientations of the hydrogen atoms and, correspondingly, the configurations of the C_{17} and C_2 asymmetric centers in such systems.

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