A STUDY OF THE STRUCTURE AND STEREOCHEMISTRY OF UNGERNIA ALKALOIDS BY NMR SPECTROSCOPY

M. R. Yagudaev, Kh. A. Abduazimov, and S. Yu. Yunusov

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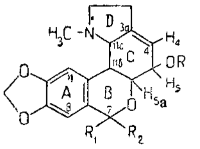
We have previously reported NMR-spectroscopic investigations of the structure of the alkaloid ungminorine [1]. In the present paper we give the results of an analysis of the NMR spectra of ungerine (I), dihydroungerine (II), hippeastrine (III), acetylhippeastrine (IV), dihydrohippeastrine (V), acetyldihydrohippeastrine (VI), and unsevine (VIII) in order to elucidate the stereochemical features and the structures of their molecules.

In the NMR spectrum of ungering (I), two one-proton singlets clearly appear in the weak-field region at τ 2.60 and 3.09 ppm, relating to aromatic protons. The signal in the weaker field relates to the H_8 proton, since it is affected by the considerable descreening influence of the lactone carbonyl. In actual fact, in unsevine (VIII), which does not contain a lactone carbonyl, the signal of the aromatic proton at C_8 is shifted in the strong-field direction to τ 3.08 ppm.

The positions of the H_8 and H_{11} protons in compounds II–VI change only slightly (table). As can be seen from the table, the two protons of the methylenedioxy group in the spectra of I–VI are equivalent and give a sharp singlet at τ 3.94–4.02 ppm. In unsevine (VIII), because of their nonequivalence, the two protons of this group form a system of the AB type with a geminal coupling constant J_{AB} = 1.5 Hz. All the spectra (I–VIII) have well-defined signals of the $N—CH_3$ group, those of I, II, and VII of the OCH_3 group, and those of IV and VI of the $OCOCH_3$ group. In the spectra of compounds I, III, IV, and VIII, the olefinic H_4 protons appear in the form of broad and poorly-resolved signals the position of which varies within narrow limits, from τ 4.35 to 4.48 ppm. The width of this signal is due to its interaction with the H_5 proton and to further spin-spin bonds with H_3 and H_{11c}. As was to be expected, when the 3a-4 double bond in I and III is hydrogenated—in dihydroungerine (II) and dihydrohippeastrine (V), and in dihydrohippeastrine acetate (VI)—the signal of the olefinic H_4 proton disappears completely. The absence of an OCH_3 signal in hippeastrine (III) and its derivatives IV–VI is also evident. The OH signal in III is found at τ 5.42 ppm, that in V at 6.18 ppm, and in VIII at 4.0 ppm. In the spectrum of the latter substance, the OH signal is superposed on the signal from the protons of the methylenedioxy group. In order to assign the signal of the OH protons in compounds III, V, and VIII, we obtained their spectra at a temperature of +50° C, at which this signal shifts in the strong-field direction.



In all the spectra the signals of the H_5 and the H_{5a} protons appear clearly, and those of the H_{11b} and H_{11c} protons appear less clearly. An analysis of the positions of the chemical shifts (CS) and of the nature of the splittings of the signals is extremely important for a study of the stereochemical features of the linkage of rings B and C, since this determines the orientation of the H_{5a} and H_{11c} protons. To find the CSs and the spin-spin coupling constants for the H_5, H_{5a}, H_{11b}, and H_{11c} protons we used the double resonance method. So far as concerns the assignment of the 6.14 ppm signal in the spectrum of I to H_5, this was done on the basis of a comparison of the spectra of ungerine (I) and hippeastrine (III). The latter has an analogous signal at τ 5.62 ppm, relating to H_5. It is known that the signal of a H—C—OH proton usually appears in a weaker field than the signal of $H—C—OCH_3$ [2]. The correctness of the assignment made is also confirmed by the paramagnetic shift to τ 4.62 ppm of the signal of the H_5 proton in hippeastrine (III) on acetylation.

In dihydroungerine (II) and dihydrohippeastrine (V), the H_5 signal undergoes a diamagnetic displacement by 0.26–0.46 ppm. This is obviously due to the difference in the geometry of ring C; on passing from a cyclohexene to a cyclohexane ring, some change in the angles takes place. The H_{5a} proton gives a signal in the weaker field (τ 5.40–5.76 ppm) than the H_5 proton. This circumstance is explained by the fact that the oxygen atom of lactone ring B

Chemical Shifts (τ ppm) and Spin-Spin Coupling Constants (J, Hz) of the Protons in Ungernia Alkaloids

Compound	H_4	H_{5a}	H_5	H_8	H_{11}	H_{11b}	H_{11c}	OCH_2O	OCH_3	NCH_3	OAc	OH
$R=CH_3$; $R_1+R_2=O$ Ungerine (I)	4.40	5.42 $J_{5a\cdot 5}=1.6$ $J_{5a\cdot 11b}=4.0$	6.14	2.60	3.09	6.80 $J_{11b\cdot 11c}=10.0$	7.50	3.98	6.62	8.04	—	—
3a,4-Dihydroungerine (II)	—	5.46 $J_{5\cdot 5a}=J_{5a\cdot 11b}=4.0$	6.40	2.59	3.10	7.02	7.50	4.02	6.68	8.05	—	—
$R=H$, $R_1+R_2=O$ Hippeastrine (III)	4.35	5.42	5.62	2.57	3.06	7.06	7.50	3.94	—	7.96	—	5.42
Hippeastrine acetate (IV)	4.48	5.48	4.62	2.60	3.10	—	—	4.00	—	7.95	8.00	—
3a,4-Dihydrohippeastrine (V)	—	5.46 $J_{5\cdot 5a}=4.3$ $J_{5a\cdot 11b}=6.0$	6.08	2.60	3.15	6.80	—	4.02	—	7.88	—	6.18
Dihydrohippeastrine acetate (VI)	—	5.40 $J_{5\cdot 5a}=4.3$ $J_{5a\cdot 11b}=6.0$	5.00	2.60	3.11	6.80	—	4.02	—	7.86	8.02	—
Clivonine acetate* (VII)	—	5.84 $J_{5\cdot 5a}=3.0$ $J_{5a\cdot 11b}=12.5$	4.65	2.28	2.60	6.82	7.68	4.03	—	7.49	8.00	—
$R=CH_3$; $R_1=OH$; $R_2=H$ Unsevine (VIII)	4.46	5.76	6.32	3.08	3.20	—	—	4.00	6.65	7.96	—	4.00

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*Figures taken from the literature [4].

adjacent to H_{5a} possesses a greater electron-accepting effect than that in the OCH_3 and OH groups. In the case of unsevine (VIII), where there is no lactone carbonyl in ring B, the oxygen atom has a weaker influence on the H_{5a} proton and its signal is found at τ 5.76 ppm.

On considering the spin-spin coupling constants of the H_5, H_{5a}, and H_{11b} protons ($J_{5,5a}$ = 1.6 Hz, $J_{5a,11b}$ = 4.0 Hz), it can be seen that the B/C ring-linkage is cis. In addition to this, the spin-spin coupling constant of the H_{11c} and H_{11b} protons is 10.0 Hz, which corresponds to their trans-diaxial interaction. Consequently, in ungerine (I), hippeastrine (II), and unsevine (VIII), ring C has the half-chair form, and the B/C ring-linkage is cis, as has been shown for neronine and other alkaloids of this series [3].

In dihydroungerine (II) there is an equalization of the angles between H_5—C—C—H_{5a} and H_{5a}—C—C—H_{11b}, in consequence of which the H_{5a} proton in the spectrum of this compound gives a triplet at τ 5.46 ppm with equal spin-spin coupling constants, $J_{5,5a} = J_{5a,11b}$ = 4.0 Hz.

These facts permit the orientation of the H_{11b}, H_{5a}, and H_5 to be established unambiguously. Since the H_{11b} proton is axial and the constant of 4.0 Hz corresponds to an equatorial-axial and a diequatorial vicinal coupling of the H_{11b}, H_{5a}, and H_5 protons, it follows that the H_{5a} proton is equatorial and H_5 is axial and, accordingly, the OCH_3 substituent at C_5 has the equatorial orientation.

However, Döpke et al. [4] showed by NMR spectroscopy that in the natural alkaloid clivonine, which is apparently a stereoisomer of dihydrohippeastrine, the B/C ring-linkage is trans. Consequently, it appeared of interest to study the NMR spectrum of dihydrohippeastrine and to compare it with the spectrum of clivonine. It can be seen from the table that in the spectra of dihydrohippeastrine (V) and of its acetate (VI) the position of the H_{5a} proton and the constants of its vicinal coupling with the H_5 and H_{11b} protons change very little in comparison with hippeastrine (III), i.e., the cis nature of the B/C ring linkage is retained on hydrogenation. The slight increase in the $J_{5,5a}$ and $J_{5a,11b}$ constants shows a slight change in the CH_5—CH_{5a} and CH_{5a}—CH_{11b} dihedral angles and the assumption by ring C of the conformation of a slightly deformed chair.

In a comparison of the NMR spectra of dihydrohippeastrine acetate (VI) and clivonine acetate (VII), a difference in the chemical shifts of all the protons and also in the $J_{5a,5}$ and $J_{5a,11b}$ constants is clearly seen (see table).

The high value of the $J_{5a,11b}$ constant (12.5 Hz) in clivonine acetate (VII) in fact shows that the H_{5a} and H_{11b} protons have the trans-diaxial positions.

The difference in the CSs of H_5, H_{5a}, H_{11b}, and H_{11c} in VI and VII can easily be explained by the different conformations of ring C and the different natures of the B/C ring-linkage in them. The position of the signal of the N—CH_3 group in VI and VII obviously depends upon its orientation with respect to the benzene ring—the signal of the N—CH_3 group is shifted in the weak-field direction by 0.37 ppm in VII as compared with VI.

On the basis of these facts it may be assumed that in VII this group comes into the range of the descreening effect of the benzene ring while in VI it comes into the range of the screening effect, i.e., it is located above the ring. Furthermore, the difference in the positions of the N—CH_3 groups in VI and VII has a fundamental influence on the CSs of the aromatic protons H_8 and H_{11}, the weak-field shift of which in VII as compared with VI confirms what has been said above. The results of a consideration of Dreiding-type models of the dihydrohippeastrine and clivonine molecules confirms the conformational changes in their molecules.

The spectra of all the compounds were obtained on a JNM-4H-100 instrument with a working frequency of 100 MHz in $CDCl_3$ solution. HMDS was used as the internal standard, its signal being taken as 10 (τ scale).

CONCLUSIONS

1. In a study of the NMR spectra of ungerine, dihydroungerine, hippeastrine, hippeastrine acetate, dihydrohippeastrine, dihydrohippeastrine acetate, and unsevine it has been shown that the B and C rings in these compounds have a cis linkage.

2. It has been found that, in contrast to the alkaloid clivonine, in dihydrohippeastrine the B/C ring-linkage is cis, and the N—CH_3 group is located above the plane of the benzene ring.

3. The orientations of the H_5, H_{5a}, and H_{11b} protons and the substituent OR at C_5 of ring C have been established.

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