NMR SPECTRA OF DIHYDROGALANTHAMINE AND DIHYDROEPIGALANTHAMINE AND OF THEIR ACETYL DERIVATIVES

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In a preceding communication [1] on the basis of the results of an analysis of the NMR spectra of galanthamine and epigalanthamine and their acetyl derivatives it was shown that these alkaloids exhibit an anomalous reversal of the chemical shift (CS) of the proton geminal to the hydroxy group, C_1-H, i.e. the signal of the quasiequatorial C_1-H proton in galanthamine resonates 0.52 ppm further upfield than the corresponding signal of the quasiaxial proton in epigalanthamine.

To determine the influence of the C_2-C_3 double bond in ring B on the parameters of the NMR spectra we have now studied the NMR spectra of dihydrogalanthamine (I) and dihydroepigalanthamine (III) and their acetyl derivatives (II) and (IV), respectively (Fig. 1).

The two protons of the aromatic ring in (I) (see Fig. 1a) give a typical pattern corresponding to a AB system with close CSs, $\tau_1 = 3.43$ and $\tau_2 = 3.53$ ppm, $J_{AB}^{ortho} = 8.5$ Hz. In the spectra of (II-IV), these parameters change only slightly. The results of a comparison of the CSs and J values of the aromatic protons in the dihydro derivatives (I-IV) studied with the corresponding values of the initial bases [1] shows that they change little, although in the dihydro series there is a tendency to an increase in the nonequivalence of these protons.

After the hydrogenation of the C_2-C_3 double bond, of course, the signal of the olefinic proton is absent and there is a considerable diamagnetic shift of the i and the C_1-H protons. The signal of the i proton in the dihydro series (I-IV), just as in the initial bases, consists of a poorly resolved triplet with a half width $W_{1/2} = 8.0$ Hz, which is found in the range of τ values from 5.85 to 5.65 ppm, i.e. the diamagnetic shift amounts to $\Delta\tau = 0.34$-0.37 ppm.

This upfield shift of the signal of the i proton can be explained by an increase in its screening as a consequence of the hydrogenation of the C_2-C_3 double bond in ring B and, accordingly, by a change in the conformation of the latter. It can be seen from the spectra of compounds (I) and (III) given (see Fig. 1a, c) that the CS of the C_1-H signal is not shown distinctly, as in the initial bases. Integration of the signals in the τ 5.9-6.5 ppm region in the spectra of (I) and (III) shows that their combined intensity is equal to six proton units; in this region are located the signals of $Ar-CH_2-N$ (2H), $Ar-OCH_3$ (3H) and C_1-H. The results of a comparison of the CSs of the C_1-H signals in the acetyl derivatives of dihydrogalanthamine and dihydroepigalanthamine (see Fig. 1b, c) – $\tau_1 = 5.00$ ppm and $\tau_2 = 4.95$ ppm – with the CS of the C_1-H signal in galanthamine and epigalanthamine acetates shows that the diamagnetic shift in the former amounts to $\Delta\tau_1 = 0.25$ and $\Delta\tau_2 = 0.60$ ppm, respectively. Such a shift is, of course, due in the first place to the change in the electron density on the C_1 atom as a result of the hydrogenation of the bond and the absence of the anisotropic influences of the C_2-C_3 double bond. It can be seen from the NMR spectra of (II) and (IV) (see Fig. 1b, d) that the CSs of the C_1-H signal appear in the form of unresolved multiplets through the vicinal spin–spin linkage of this proton with the protons of the methylene groups at C_2 and C_6.

It follows from the half-width ($W_{1/2}$) of the signals of the C_1-H proton in (II) and (IV), characterizing the sum of the vicinal constants of its spin–spin coupling with the four neighboring protons, that in dihydro-

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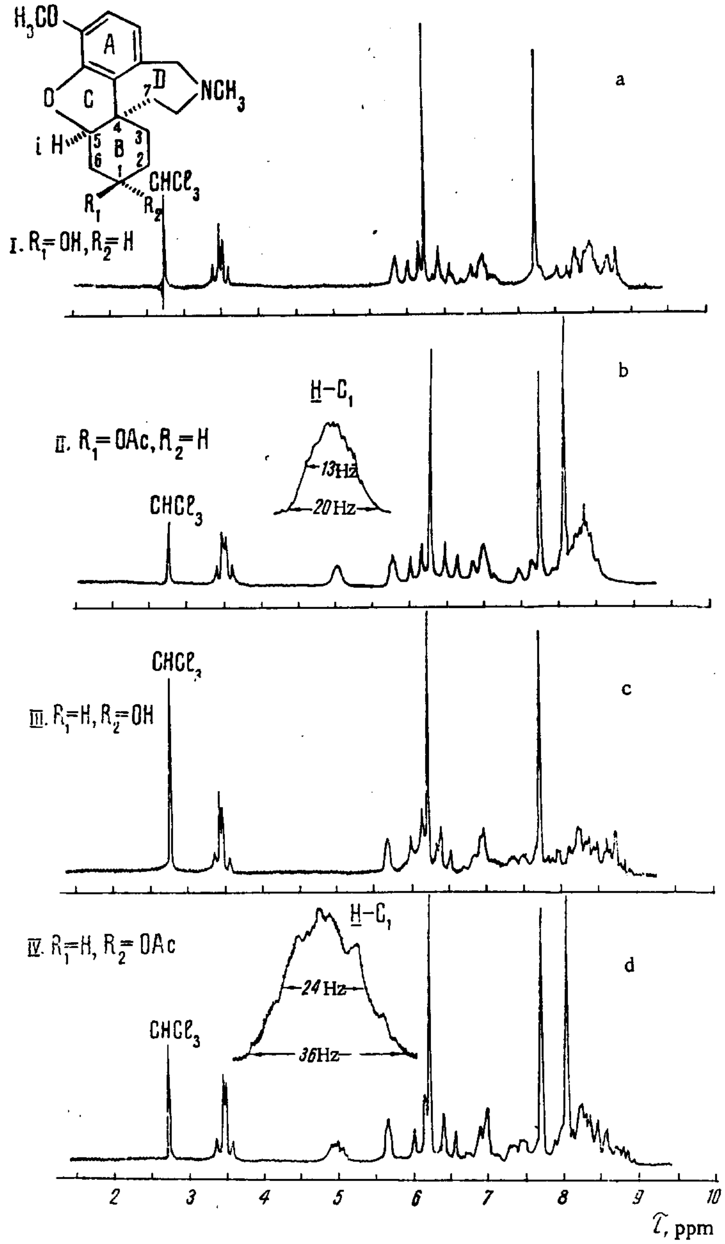

Fig. 1. NMR spectra of dihydrogalanthamine (a), dihydroepigalanthamine (c), and their acetyl derivatives (b and d).

galanthamine (I) and its acetate (II) this proton has the equatorial orientation, since $W_{1/2} = 13.0$ Hz. In dihydroepigalanthamine (III) and its acetate (IV), the half width of the signal of the C_1-H proton in (IV), 24 Hz, corresponds to its interaction with two large *aa* (10 Hz) and two small *ae* (~ 2-3 Hz) constants, which unambiguously shows the axial orientation of the C_1-H proton in (IV). At the same time, the CSs of the protons at C_1-H in (II) and (IV), although they are close ($\Delta\tau = 0.05$ ppm), nevertheless preserve the anomaly: in the cyclohexane derivatives the CS of the axial proton is located in a stronger field (by approximately 0.40 ppm) than the CS of the corresponding equatorial proton [2, 3]. Consequently, a substantial contribution to the value of CS of the C_1-H proton in the dihydro compounds (I)-(IV) is apparently made by the magnetic anisotropy and electric field of the C−O bond, and also by the unshared pair of electrons of the oxygen atom of ring C. In actual fact, in the calculation of the contribution of the magnetic anisotropy and of the electric field of the lone pair of electrons of the oxygen atom $(2P_z^2)$* and of the C−O bond of the dihydrofuran ring to the value of CS of the C_1-H axial proton in epigalanthamine and dihydrogalanthamine according to McConnell and Buckingham and Musher [5, 6], using the parameters for C−O and for $\ddot{O}\cdot$ taken

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*We took the value of μ for $2P_z^2\ddot{O}$ as 1D.

from a paper by Bogat-skii et al. [7], values of $\Delta\tau = 0.850$ and 0.350 ppm, respectively, downfield are obtained. If this contribution to the CS of the C_1-H axial proton is taken into account, the experimentally observed difference in the CSs of the e*a* protons in the NMR spectra of galanthamine, epigalanthamine [1], and their dihydro derivatives agrees well with the difference between the e*a* protons of cyclohexene [8] and cyclohexane [2, 3], respectively.

In the spectra of compounds (I-IV) (Fig. 1, a-d), the protons of the $Ar-CH_2-N$ methylene group, because of their nonequivalence, give two doublets at $\tau_1 = 6.05-6.09$ and $\tau_2 = 6.47-6.50$ ppm, $J_{gem} = 15.0$ Hz. The protons of the OCH_3 methyl group are represented by sharp three-proton singlets at $\tau = 6.21-6.23$ ppm, those of $N-CH_3$ at $\tau = 7.70-7.71$ ppm, and those of OAc at $\tau = 8.02$ ppm (II) and 8.03 ppm (IV). The signals of the methylene protons at C_2 and C_3 in the spectrum of (I) (see Fig. 1a) appear in the strongest field ($\tau = 8.35-8.80$ ppm) in the form of poorly resolved broad signals and are superposed on the signals of the methylene protons at C_7. The results of a comparison of the signals in this region in the spectra of (I) and (II) (see Fig. 1a, b) show that when the OH group is acetylated a considerable paramagnetic shift of the signals of the protons at C_2 and C_3 to τ 8.28 ppm takes place, obviously because of the influence of the $C=O$ group. The chemical shifts of these signals must naturally depend on the orientation of the $C=O$ group of the acetate residue. In actual fact, in the spectrum of dihydroepigalanthamine acetate (IV) (see Fig. 1d) in contrast to the spectrum of (II) (see Fig. 1b), the CSs of the signals under consideration change little in comparison with the spectrum of the unacetylated compound (III) (see Fig. 1c).

EXPERIMENTAL

The NMR spectra were taken on a JNM-4H-100/100 MHz instrument in deuterochloroform with HMDS as internal standard. Compounds (I-IV) were obtained by known methods [9].

CONCLUSIONS

1. On the basis of the results of a comparative study of the NMR spectra of dihydrogalanthamine and dihydroepigalanthamine and their acetyl derivatives it has been shown that in the hydrogenation of the C_2-C_3 double bond of galanthamine and its analog a diamagnetic shift of the i and C_1-H protons by 0.35 and 0.25-0.60 ppm, respectively, take place.

2. The anomalous nature of the CSs of the *a*e C_1-H protons in these compounds is due to the substantial influence on their magnetic anisotropy and electric field of the unshared pair of electrons of the O atom and the $C-O$ bond of ring C.

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