CHEMICAL SHIFT OF THE SIGNAL OF THE PROTONS OF THE N−CH_3 GROUP AND THE STEREOCHEMISTRY OF TETRAHYDROUNGERINE AND OF GALANTHUSINE

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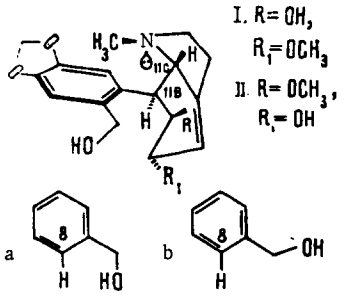
The chemical shift (CS) of the signal of an R−NCH_3 group in an NMR spectrum in deuterochloroform solution changes over a wide range (δ 1.88-4.20 ppm) according to the nature of R [1-5]. When the nitrogen atom is present in a saturated five-membered ring, i.e., in N-methylpyrrolidine, δ NCH_3 is 2.33 ppm, and in the alkaloid nicotine it is 2.15 ppm [1].

In the Amaryllis alkaloids, the NCH_3 signal of the pyrrolidine ring is found in the δ range from 2.0 to 2.5 ppm [6-9]. Only in a seco derivative of the alkaloid clivonine (III) does the CS of the NCH_3 have an anomalously low value of δ 1.84 ppm, which is due to the arrangement of this group above the center of the aromatic ring [10].

However, the CS of the NCH_3 group of the alkaloid galanthusine (II) appears at δ 1.58 ppm (0−HMDS) [11, 12] (the reason for such a large diamagnetic shift is not discussed by the authors of these papers). To determine the factor causing the anomalous upfield displacement of the NCH_3 signal in galanthusine, we have studied the NMR spectrum of tetrahydroungerine (I) [13], which has the same skeleton as galanthusine and differs from the latter by the mutual positions of the OCH_3 and OH groups in ring C. The spectrum of (I) was obtained on a JNM-4H-100/100 MHz instrument ($CDCl_3$, 0−TMS).

In the NMR spectrum of (I) the NCH_3 signal is found at 1.73 ppm, i.e., 0.60 ppm upfield as compared with the CS of the NCH_3 group of N-methylpyrrolidine [1].

The results of a consideration of models of (I) and (II) showed that the protons of the NCH_3 group in them are screened to the maximum extent by the aromatic ring when the N−CH_3 group is β-quasiequatorial, i.e., when the lone pair of electrons of the nitrogen atom and the $C_{11}C$−H bond are in trans interrelationship and when C has the half-chair conformation. In these circumstances, calculation of the contribution of the diamagnetic anisotropy of the aromatic ring at the NCH_3 protons by Johnson and Bovey's method [14] gives a maximum value of Δδ of +0.50 ppm. This value of the contribution agrees well with the observed experimental difference Δδ = 0.6 ppm for the CS of the NCH_3 group in N-methylpyrrolidine and in substance (I). Thus, the results of a comparison of the CSs of the NCH_3 groups in tetrahydroungerine (I), galanthusine (II), and N-methylpyrrolidine permit the most preferred conformation to be selected as the half-chair conformation for ring C and the β-quasiequatorial orientation for NCH_3, which is located above the plane of the aromatic ring in (I) and (II).



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It must be mentioned that the aromatic protons H_8 and H_1 in (I) and (II) give signals at, respectively, 7.52 and 6.79 ppm (I) and 7.37 and 6.52 ppm (II), while in (III), they are at 6.82 and 6.85 ppm; i.e., when the lactone ring is opened only in (III) does the signal from H_8 shift upfield, and in (I) and (II) it scarcely changes in comparison with ungerine [8]. This can be explained by the different arrangements of the $Ar-CH_2OH$ group relative to H_8 in (I), (II), and (III). Probably, in (I) and (II) H_8 and CH_2-OH are in the syn orientation (a) and are located in the same plane so that the formation of an intramolecular H bond between the O and the H_8 is possible, while in (III) the CH_2-OH conformation is different (b).

When the spectrum of (I) was taken at a temperature of +55°C, the H_8 signal shifted upfield by 0.08 ppm, which confirms the existence of a hydrogen bond between H_8 and the OH group.

Furthermore, calculation of the contributions of the magnetic anisotropy ($\Delta\delta_\chi$) and the electric field ($\Delta\delta_E$) of the OH group at the H_8 proton in conformation a using Zürcher's parameters [15] gives a value of $\Delta\delta = \Delta\delta_E + \Delta\delta_\chi = 0.33$ ppm (downfield), and in the b conformation the contributions of $\Delta\delta_\chi$ and $\Delta\delta_E$ to H_8 are negligibly small.

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