A STUDY OF THE STEREOCHEMISTRY OF ALKALOIDS OF THE GALANTHAMINE TYPE BY NMR SPECTROSCOPY. I

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The structures of galanthamine (I) and epigalanthamine (III) have been studied previously [1–4], but some questions of the conformation of these compounds have hitherto remained debatable. This relates, in particular, to the orientation of the hydroxyl group [2]. In addition, the manner in which rings B and C are fused is not clear. It is obvious that in order to establish the stereochemistry of galanthamine and epigalanthamine unambiguously the use of NMR spectroscopy is extremely important.

The present paper gives the results of a study of the NMR spectra of galanthamine, epigalanthamine, and their O-acetyl derivatives, which has enabled the stereochemistry of their molecules to be refined.

In the NMR spectrum of galanthamine (Fig. 1a), two two-proton signals are found in the weak-field region (τ 3.4–4.2 ppm) which relate to the a and b protons of the aromatic ring A and to the olefinic protons *f* and g of ring B.

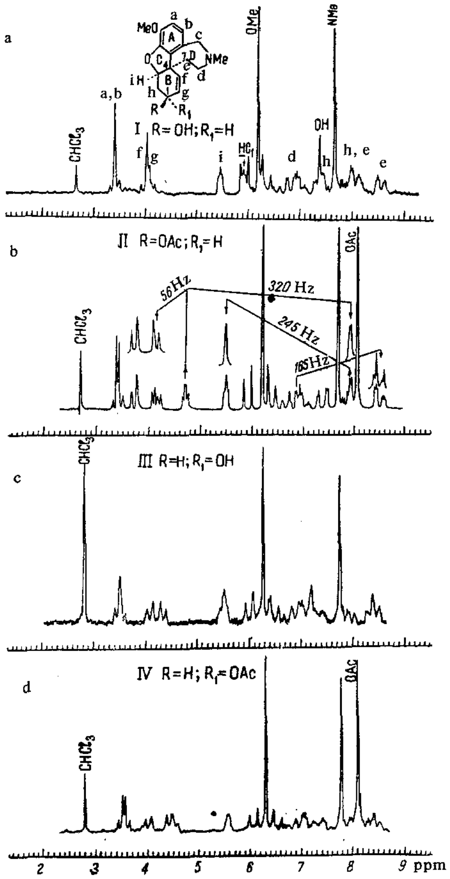


Fig. 1. NMR spectra of galanthamine (a), galanthamine acetate (b), epigalanthamine (c), and epigalanthamine acetate (d).

The aromatic protons a and b form a two-spin AB system; the chemical shifts and the spin-spin coupling constants found are as follows [6]: τ_A 3.44 ppm and τ_B 3.49 ppm with $J_{AB} = 8.5$ Hz. The olefinic protons f and g in I also give a spectrum of the AB type the unsymmetrical nature of the intensities of the central signals of which can be explained by the additional coupling of the proton g with the H proton at C_1.

On comparing the regions of the spectra of compounds I–IV (Fig. 1, a–d) it can be seen that the chemical shifts of the a dnd b and, in particular, the f and g-protons are considerably affected by acetylation and by the orientation of the hydroxyl group attached to the C_1 atom of ring B.

The signal of the i-proton in the spectra of I, II, and IV appears at τ 5.41 ppm in the form of a poorly-resolved one-proton triplet because of vicinal coupling with the h-protons of the methylene group. By using the double-resonance method, the center of the multiplet of one of the protons h was found to be at τ 7.84 ppm.

In the spectrum of epigalanthamine (Fig. 1c), the signal of the proton at C_1 is superposed on signal i and therefore a broad two-proton multiplet is observed at τ 5.48 ppm.

The half-width of the signal of the latter proton, i, in spectra a, c, and d (see Fig. 1), which is determined by the sum of its vicinal spin-spin coupling constants with the h-protons, amounts to 8.0 Hz. This figure is satisfied only by those values of the constants which correspond to the equatorial orientation of this proton i. Since the quasi-axial orientation of the C_4—C_7 bond of ring D has been established [1] and the proton i is equatorial, the proton i and the C_4—C_7 bond are in the cisoid orientation and, accordingly, ring B has the half-chair conformation and has a cis linkage with ring C.

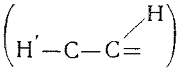
To determine the orientation of the hydroxyl group or the corresponding hydrogen atom on carbon atom 1 of ring B in galanthamine and epigalanthamine, we considered the chemical shifts of the H proton on C_1 and the spin-spin coupling constants of H—C_1 with the neighboring protons h and g.

The signal of the H—COH proton in the spectrum of galanthamine (Fig. 1a) is found at 6.00 ppm, and that of epigalanthamine at 5.48 ppm, i. e,, in I this proton is more highly screened than in II. The correctness of the assignment of the signals at 6.00 and 5.48 ppm to the H—COH proton in compounds I and II is confirmed by their paramagnetic shift in the weak-field direction to τ 4.75 and 4.35 ppm, respectively, on acetylation of the OH group, the H—COAc signal in epigalanthamine being superposed on the signal of the olefinic proton g (see Fig. 1d).

It is known that in the cyclohexane ring the signals of the axial protons are more highly screened and appear in higher fields than in the signals of the corresponding equatorial protons [5, 6]. However, it is hardly possible to use these ideas in order to determine the orientation of the H proton at C_1 in galanthamine and epigalanthamine since its chemical shift depends on the presence of adjacent C—O and C=C bonds. A calculation of the influence of the diamagnetic anisotropy of the benzene ring A on the H proton attached to C_1 in epigalanthamine by Johnson and Bovey's method [7] has shown that the change in the screening of the H—C_1 proton as a result of this influence must be so small that it can be neglected.

We have established the orientation of the H at C_1 in galanthamine and epigalanthamine on the basis of the values of its coupling constants with the neighboring protons h and g.

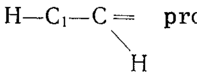
In the spectrum of galanthamine acetate (see Fig. 1b), the signal of the proton at C_1 is a complex triplet with $J_1 = J_2 = 5.0$ Hz and $J_3 = 1.6$ Hz (τ 4.75 ppm). The 5.0 Hz constants correspond to vicinal spin-spin coupling of the H—C_1 proton with the olefinic proton g and also with one of the protons h. It is obvious that the one-proton doublet in the weak field at τ 3.78 ppm, J = 10.5 Hz, in the spectrum of II is due to the proton f and the spectrum of the olefinic proton g forms a quartet with $J_1 = 5.0$ Hz, $J_2 = 10.5$ Hz. The 10.5 Hz constant is due to the spin-spin bond of the g and f-protons, and the additional splitting by 5.0 Hz to the coupling of g with the H—C_1 proton, as is confirmed by double resonance.

Garbisch [8] has shown that the vicinal coupling constant (J) of protons on carbons in sp^3-sp^2 hybridization is connected with the dihedral angles of $\Phi°$  $\left(H'-C-C\overset{\diagup H}{=}\right)$ by a relationship the curve of which is given in Fig. 2.

This relationship for the constant $^3J = 5.0$ Hz, the dihedral angle Φ between the H—C_1 protons and the olefinic proton g in II is approximately 40° (120°), which corresponds to a quasiequatorial orientation of the H—C_1 proton in galanthamine. Consequently, the OH group in galanthamine is quasi-axial, which is in harmony with Barton and

Kirby's conclusion [1].

The spectrum of the olefinic protons f and g of epigalanthamine (see Fig. 1c) give an AB quadruplet with τ_A 4.03 and τ_B 4.27 ppm, $J_{AB} = 10.0$ Hz.

In considering the spectrum, it can be seen that apart from the large constant, the components of the quadruplet are broadened. This broadening of the doublet in the strong field (τ 4.27 ppm) is apparently due to the interaction of $\underline{H}-C_1$ with the olefinic proton g, and the half-width of the lines $\approx$ 3.0 Hz. On the basis of Garbisch's curve (see Fig. 2), the dihedral angle Φ between the  $H-C_1-C(H)=$ protons for $J \approx 3.0$ Hz should be close to 90°, which corresponds to a quasi-axial orientation of the $\underline{H}-C_1$ proton for epigalanthamine.

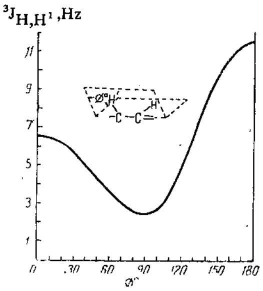


Fig. 2. $J_{CH'-CH=}$(Hz) as a function of the dihedral angle Φ°.

Thus, the results of a consideration of the vicinal spin-spin coupling constants of the $H-C_1$ proton and the olefinic proton g shows the quasi-axial orientation of the hydroxyl group in galanthamine and its quasi-equatorial orientation in epigalanthamine.

At the same time, in these alkaloids inversion of the chemical shift of the $\underline{H}-C_1$ protons takes place, i.e., the signals of the equatorial protons are more highly screened and appear in a relatively stronger field than the signals of the corresponding axial protons. This phenomenon, reported previously in other cases [9], is apparently due to the influence of the diamagnetic anisotropy of the unshared pair of electrons of the oxygen atom and of the C—O bond in ring C and of the double bond in ring B on the $H-C_1$ proton.

In all the spectra given, the signals of the methyl protons of the aromatic OCH_3 groups have the form of narrow three-proton singlets at τ 6.24-6.28 ppm, and those of the NCH_3 groups at τ 7.70-7.71 ppm. Volpp and Bubewa-Iwanowa [3] made the opposite assignment of the signals, which contradicts literature information on the chemical shifts of the OCH_3 and the NCH_3 groups. Our assignment is confirmed by the splitting of the three-proton singlet of NCH_3 (τ 7.71 ppm) in the spectrum of epigalanthamine obtained in CF_3COOH solution into a doublet as a result of the formation of the $-\overset{+}{N}HCH_3$ ion and coupling with the NH proton, and also its shift in the weak-field direction [10]. The $O-COCH_3$ signal in the spectrum of II appeared at 8.04 ppm, and in IV it appeared at 8.01 ppm.

The assignment of the signals of the other methylene protons of rings B and D has been made on the basis of the results of double resonance for galanthamine acetate.

Two multiplets in the strong field with a center at τ 8.45 ppm belong to one of the e-protons, and the second e-proton was found at τ 7.90 ppm. The d-protons give a two-proton multiplet with a center at 6.95 ppm, and the h-protons give signals at 7.84 and 8.05 ppm. The two nonequivalent protons from the $Ar-\underline{CH_2}-N$ methylene group form an AB system and are found in the form of two one-proton doublets with centers at τ 6.00 and 6.28 ppm, $J_{AB}^{gem} = 15.0$ Hz.

It can be seen from a comparison of spectra I–IV (Fig. 1, a–d) that with the isomerization of galanthamine (I), i.e., in epigalanthamine (III) and its acetyl derivative (IV), the signal of one of the e protons undergoes a considerable diamagnetic shift of 0.5 ppm, in consequence of which the spectra III and IV have a two-proton multiplet with a center at τ 8.45 ppm relating to the nonequivalent e protons.

It must be mentioned that to assign the signal of the OH proton we studied the dependence of the NMR spectra of galanthamine on the concentration and the temperature. It was found that τ 7.37 ppm signal is considerably displaced in the strong-field direction when the sample is diluted and heated to +50° C. This signal obviously belongs to the proton of the OH group, and its change with temperature and dilution shows the existence in galanthamine (I) of an intermolecular hydrogen bond, in addition to the intramolecular hydrogen bond between the OH and the O of ring C [1].

The spectra of compounds I–IV were obtained on a JNM-4H-100 instrument with a working frequency of 100 MHz in deuterochloroform solution using HMDS as internal standard. The chemical shifts are given in the τ-scale.

CONCLUSIONS

1. From a consideration of the spin-spin coupling constants of the protons in the NMR spectra of galanthamine, epigalanthamine, and their acetyl derivatives, it has been established that the OH group in galanthamine is quasi-axial and in epigalanthamine it is quasi-equatorial, and ring B has the half-chair conformation in cis fusion with ring C.

2. The axial proton at C_1 in epigalanthamine gives a signal in a weaker field than the corresponding equatorial proton in galanthamine. The dependence of the chemical shift of the signal of the OH proton in galanthamine on the concentration and the temperature show the existence of an intermolecular hydrogen bond between the molecules of the substance in solutions.

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