A STUDY OF THE CONFORMATIONAL STATES OF ANABASINE DERIVATIVES

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The peculiar spatial structure, the existence of several types of lability (inversion of the nitrogen atom, conversion of the rings, rotation about C–C and C–N bonds), and also the proton-donating and proton-accepting groups in the molecules of the alkaloids and derivatives of bipiperidyl permit the assumption that stereospecific effects will be observed in their NMR spectra.

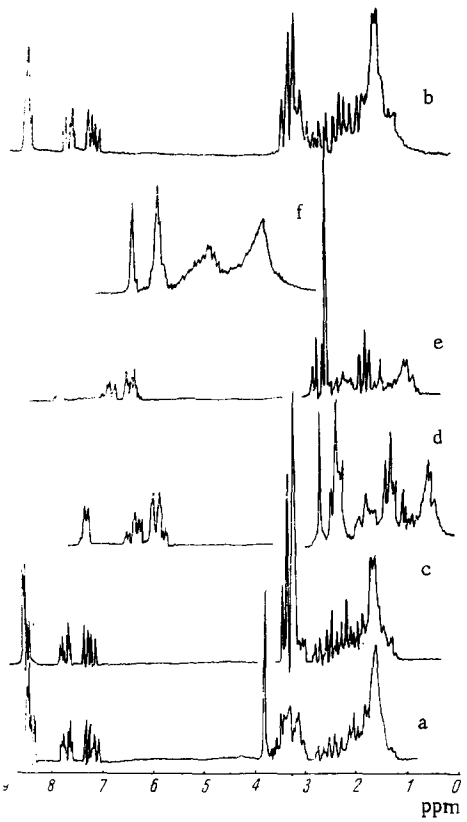

Fig. 1. PMR spectra of N-(β-hydroxyethyl)anabasine (a), N-(β-chloroethyl)-anabasine (b), N-(β-methoxyethyl)-anabasine (c), N-(β-hydroxyethyl)isoanabasine (d), N-(β-methoxyethyl)isoanabasine (e), and N,N'-di(β-hydroxyethyl)-α,β'-bipiperidyl (f).

The present paper gives the results of a study of the N-β-hydroxyethyl and the N-β-methoxyethyl derivatives of anabasine, isoanabasine, and α, β'-bipiperidyl [1, 2], in order to elucidate their conformational states and the influence of dynamic processes on the magnetic parameters of their spectra.

The compounds were obtained by the reaction of ethylene oxide and propylene oxide with the initial alkaloids, followed by the replacement of the hydroxy groups by chlorine, and the conversion of the halogen derivatives with alcoholic alkali into the corresponding ethers.

When the hydroxy group in N-(β-hydroxyethyl)piperidine is replaced by chlorine, a quaternary salt is formed the treatment of which with alcoholic alkali gives not quinuclidine, as we suggested previously [3], but N-(β-methoxyethyl)piperidine, 1,2-dipiperidinoethane, and piperidine [4]. However, in contrast to the reaction with piperidine, the N-β-hydroxyethyl derivatives of anabasine, isoanabasine, and α,β'-bipiperidyl are converted under the same conditions into the N-β-chloroethyl derivatives [5] and not into bisquaternary compounds (see scheme).

In the NMR spectrum of N-(β-hydroxyethyl)anabasine (I) (Fig. 1a), the signal of the OH group at 3.8 ppm shifts slightly with a change in the concentration. Furthermore, the absence of a sharp triplet at 3.5 ppm and the presence of two complex multiplets with δ 2.5 and 2.0 ppm, and also the change in the chemical shifts of the pyridyl radical as compared with N-(β-methoxyethyl)anabasine (III) $\delta H_{\alpha'} = 8.48$; $\delta H_{\alpha} = 8.4$; $\delta H_{\gamma} = 7.72$; $\delta H_{\beta} = 7.72$ ppm permits conformation (I) to be suggested for it. A special feature of this conformation is an intramolecular hydrogen bond of the OH group with the nitrogen atom of the pyridyl radical. The intramolecular hydrogen bond in (I) leads to a nonequivalence of the $-OCH_2$ protons (multiplet at $\delta = 3.3$ ppm in CCl_4, triplet with $\delta = 3.72$ ppm in D_2O and D_2O+HCl).

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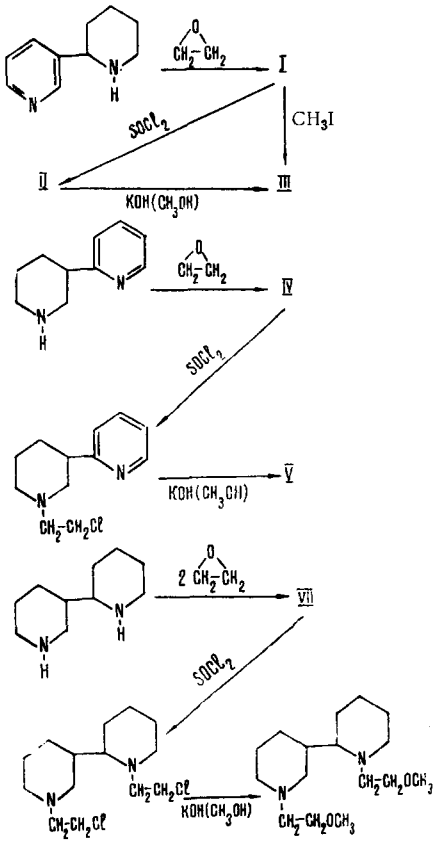
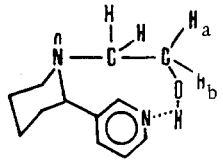
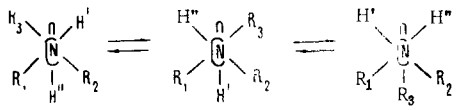
The observed nonequivalence of the $N-CH_2$ protons possibly depends on the presence of nonbound interactions with the α-pyridyl radical, the considerable rigidity of the new ring formed by the intramolecular hydrogen bond, or the specific nature of the distribution of the anisotropic influence of the substituents on the screening of the $N-CH_2$ protons in the rotamers about the C–N bond [7].





In the spectrum of (I) in D_2O, the $N-CH_2$ protons retained their nonequivalence (multiplet of ~12 lines with its center at $\delta = 2.5$ ppm), in contrast to the $-OCH_2$ protons, the signals of which formed a well-defined triplet at 3.72 ppm. Heating (I) in nitrobenzene to 200°C likewise did not eliminate the nonequivalence of the $-N-CH_2$ signals in (I) and (III). Thus, in the rotamers about the $-C-N$ bond the nonequivalence of the anisotropic influence of the unshared pair of the electrons of the nitrogen atom is always retained.



To prove this, the spectra of (I) in strongly acid solutions (D_2O+DCl, Fig. 2) were obtained. The cleavage of the intramolecular hydrogen bond and the protonation of the tertiary nitrogen of the piperidine radical does not lead to the complete equivalence of these $N-CH_2$ groups, while the $O-CH_2$ protons do become equivalent.

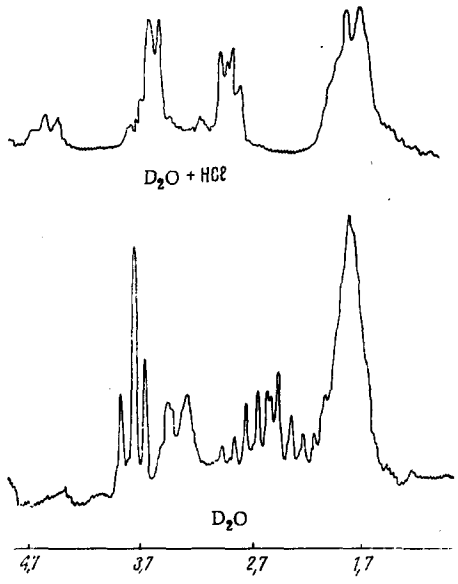
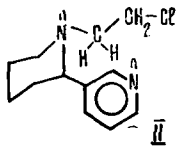
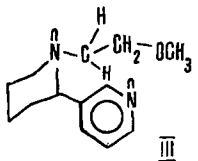


Fig. 2. PMR spectrum of N-(β-hydroxyethyl)anabasine in D_2O and D_2O+HCl.

A similar conclusion was based on the features of the spectra of N-(β-chloroethyl)anabasine (II) (Fig. 1b) and (III) (see Fig. 1c), the tertiary protons of which (at C_6) and those of the OCH_3, OCH_2, and CH_2Cl groups in the δ =3-3.6 ppm region are represented by triplets with J_{vic} = 6 Hz (II) and 6.2 Hz (III). The form of the signals of the $N-CH_2$ fragments indicates the nonequivalence of their geminal protons.



II



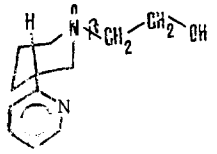
III

In order to confirm the intramolecular interactions between the nitrogen atoms of the pyridyl radical and the substituent on the nitrogen atom of the piperidine in anabasine derivatives, we synthesized isoanabasine [6] [α-(β-piperidyl)pyridine] and N-(β-hydroxyethyl)isoanabasine (IV).

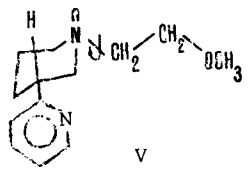
When a solution of the base (IV) was diluted, in its spectrum (see Fig. 1d) the signal of the OH group – at 3.8 ppm – shifted to 3.6 ppm and two triplets appeared clearly at 3.6 and 2.45 ppm which may be ascribed to the $-O-CH_2$ and $-N-CH_2$ protons. The absence of the nonequivalence of the protons in these fragments shows the considerably lower nonequivalent influence of the anisotropy of the substituents about the C–N bond because of the removal of the pyridyl radical in the β position of the piperidine.

It follows from the facts given above and the spectrum of N-(β-methoxyethyl)isoanabasine (see Fig. 1e) that these compounds have the predominant conformations (IV) and (V).

In spite of the fact that the reaction takes place more slowly with propylene oxide, we have succeeded in synthesizing a number of derivatives of anabasine with hydroxypropyl and methoxypropyl substituents on the nitrogen atom of the piperidine (VI). The broad multiplet in the 1.9-2.7 ppm region may show the addition of the propylene oxide to the nitrogen atom of the piperidine nucleus. In these circumstances, rotation around the $N-CH_2$ bond

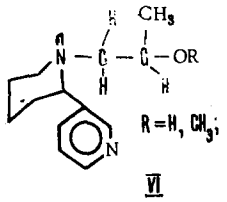


IV



V

is sterically hindered. The change in the spectra when the samples are diluted shows that association takes place between the OH groups and the nitrogen atoms of the piperidine rings. On the basis of the NMR spectra, conformation (VI) may be proposed for the derivatives described.



VI

In a study of the products of the reaction of ethylene oxide with α,β'-bipiperidyl it was found that the ethylene oxide adds to both nitrogen atoms and each piperidine nucleus creates steric hindrance to rotation about the $N-CH_2$ bonds of (VII) (NMR spectra). Since dilution scarcely changes the position of the signal of the OH group (4.05 ppm), while it does lead to a broadened signal at 3.55 ppm ($-OCH_2$) and to a broad

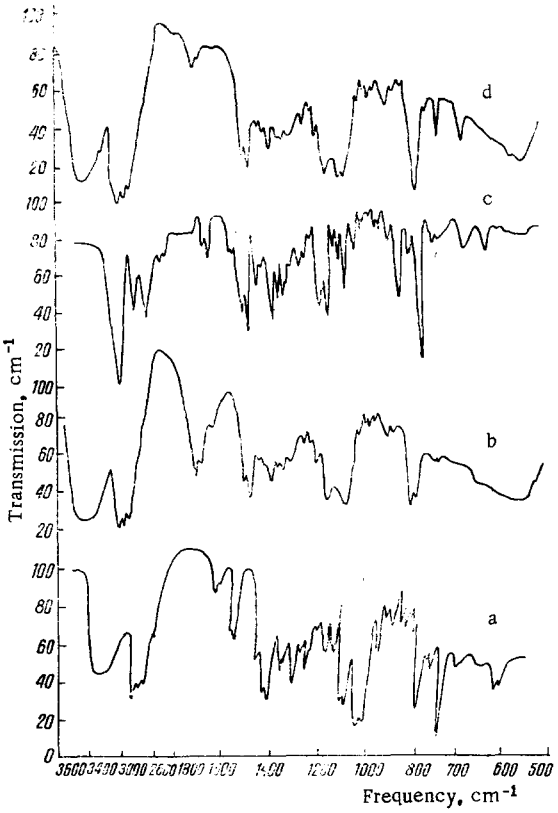
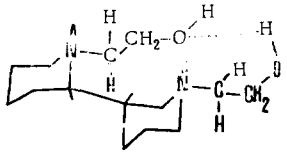


Fig. 3. IR spectra of N-(β-hydroxyethyl)-anabasine (a), N-(β-hydroxyethyl)isoanabasine (b), N-(β-chloroethyl)anabasine (c), and N,N'-di(β-hydroxyethyl)-α,β'-bipiperidyl (d).

signal at 3.2-1.9 ppm (approximately 8-10 hydrogen atoms located in the α positions to nitrogen), the spatial structure of the hydroxyethyl and methoxyethyl derivatives of α,β'-bipiperidyl is apparently characterized by extremely interesting conformational features due to the presence of the substituents on the nitrogen and also to hydrogen bonds and the absence of conversion in the rings (VII) (see Fig. 1f).



VII

The value of $\Delta\delta_{ae}$, of the order of 0.8-1 ppm, for the geminal protons at C_2 of the piperidine radicals according to the results of the integration of the spectra of these compounds, shows the axial orientation of the unshared pair of electrons of the nitrogen [7].

The conformations of the compounds obtained were shown not only on the basis of the NMR spectra but also by their IR spectra in solutions.

The intramolecular hydrogen bond in N-(β-hydroxyethyl)anabasine and N,N'-di(β-hydroxyethyl)-α,β'-bipiperidyl (Fig. 3a, d) is shown in carbon tetrachloride solution by absorption in the 3100-3500 cm^{-1} region (the position and intensity of the bands do not change on dilution). This band disappears in the preparation of the N-β-chloroethyl and the N-β-methoxyethyl derivatives (I and VII) (see Fig. 3c). In N-(β-hydroxyethyl)isoanabasine, the band at 3100-3500 cm^{-1} (Fig. 3b), the intensity of which decreases on dilution, shows the presence of an intermolecular hydrogen bond.

EXPERIMENTAL

Chromatography was performed by the ascending and radial methods of chromatography on paper of type M ["slow"] of the Leningrad No. 2 Mill in the following systems: 1) butanol–hydrochloric acid–water (100 : 15 : 27), and 2) butanol–acetic acid–water (40 : 16 : 70). The chromogenic reagent was Dragendorff's reagent.

Alkoxide from N-(β-Hydroxyethyl)anabasine. A solution of 1.1 g of N-(β-hydroxyethyl)anabasine in 10 ml of dry benzene was treated with 0.12 g of metallic sodium and was heated on the water bath under reflux for 3-4 h. After the end of the reaction, the solvent was distilled off to dryness. This gave 1.5 g (80%) of the alkoxide of N-(β-hydroxyethyl)anabasine in the form of a viscous oil with R_f 0.26 (system 1). Melting point of the picrate 101-102°C (from ethanol).

N-(β-Methoxyethyl)anabasine. To a solution of 1.0 g of the alkoxide of N-(β-hydroxyethyl)anabasine in 10 ml of methanol was added 0.70 ml of methyl iodide, and the mixture was heated under reflux for 3-4 h. After the solvent had been distilled off, 0.81 g (81%) of N-(β-methoxyethyl)anabasine with R_f 0.25 (system 1) was obtained as the main product. Melting point of the picrate 170-172°C (from ethanol). A mixture of the picrate with that which we obtained previously [3] gave no depression of the melting point.

N-(β-Hydroxyethyl)isoanabasine. With cooling and shaking, 5 g (0.11 mole) of ethylene oxide was passed into a solution of 15 g of freshly distilled isoanabasine (0.092 mole) in 70 ml of methanol. The reaction mixture was left at room temperature for 100 h. After the solvent had been evaporated off, the residue was distilled in vacuum. The fraction boiling at 176-178°C (4.5 mm) was collected. The yield of N-(β-hydroxyethyl)isoanabasine was 8 g (61.5%); R_f 0.57 (system 2). Melting point of the picrate 138-140°C (from ethanol).

N-(β-Chloroethyl)isoanabasine. To a solution of 17 g of N-(β-hydroxyethyl)isoanabasine in 170 ml of anhydrous chloroform was gradually added 18.5 g of phosphorus pentachloride. The reaction mixture was heated in the water bath under reflux at 40-50°C for 1.5 h. After cooling, the mixture was made alkaline with lithium carbonate and was extracted with chloroform. After drying and the distillation of the solvent, the residue consisted of N-(β-chloroethyl)isoanabasine in the form of a viscous oil. Yield 17.5 g (94.8%), R_f 0.71 (system 2). Melting point of the picrate 108-110°C (from ethanol).

N-(β-Methoxyethyl)isoanabasine. To a solution of 3 g of N-(β-chloroethyl)isoanabasine in 30 ml of methanol was added 30 ml of 25% methanolic caustic potash. The reaction mixture was heated on the water bath under reflux for 5-6 h. After the solvent had been distilled off, the residue was dissolved in water and extracted with ether. The ethereal solution was dried with anhydrous sodium sulfate. After the solvent had been evaporated off, the N-(β-methoxyethyl)isoanabasine was distilled under vacuum at 135-140°C (4-5 mm). The yield was 1.67 g (57.59%), R_f 0.78 (system 2). The melting point of the picrate was 164-169°C (from ethanol).

N,N'-Di(β-hydroxyethyl)-α,β'-bipiperidyl. With cooling, 9 g (0.2 mole) of ethylene oxide was passed into a solution of 2.2 g (0.086 mole) of α,β'-bipiperidyl in 80 ml of methanol. After the solution had stood at room temperature for 100 h, the solvent was driven off and the residue was distilled in vacuum. The fraction boiling at 220-222°C (4-5 mm) was collected. The yield of the desired compound was 18 g (53.70%), R_f 0.35 (system 2). The monohydriodide had mp 191-192°C (from acetone).

N,N'-Di(β-chloroethyl)-α,β'-bipiperidyl. With cooling and stirring, 15 g of phosphorus pentachloride was gradually added to a solution of 5 g of N,N'-di(β-hydroxyethyl)-α,β'-bipiperidyl in 50 ml of dry chloroform. The mixture was heated on the water bath at 40-50°C under reflux for 1.5-2 h. Then the reaction products were treated as described for N-(β-chloroethyl)isoanabasine. This gave N,N'-di(β-chloroethyl)-α,β'-bipiperidyl in the form of faintly brown crystals with mp 98-100°C, R_f 0.45 (system 2). Yield 3 g (52.45%). The melting point of the picrate was 181-182°C (from ethanol) and of the dihydrobromide 218-220°C; $[\alpha]_D$ +4.61° (ethanol).

N,N'-Di(β-methoxyethyl)-α,β'-bipiperidyl. A solution of 5 g of N,N'-di(β-chloroethyl-α,β'-bipiperidyl in 50 ml of methanol was treated with 30 ml of 25% methanolic caustic potash. The reaction mixture was heated in the water bath for 5-6 h. The solvent was distilled off, and the residue was dissolved in water and extracted with ether. After the drying and evaporation of the solvent, the residue was distilled in vacuum at 140-142°C (2-3 mm). The yield of the desired substance was 1.8 g (38.3%), $[\alpha]_D$ −10.40°, R_f 0.64 (system 2). The melting point of the picrate was 98-100°C (from ethanol).

SUMMARY

1. The condensation of anabasine, isoanabasine, and α,β'-bipiperidyl with ethylene oxide has given N-(β-hydroxyethyl)anabasine, N-(β-hydroxyethyl)isoanabasine, and N,N'-di(β-hydroxyethyl)-α,β'-bipiperidyl.

2. It has been shown that the treatment of N-(β-chloroethyl)anabasine, N-(β-chloroethyl)isoanabasine, N,N'-di(β-chloroethyl)-α,β'-bipiperidyl with alcoholic alkali forms and the methyl ethers of (I, IV, and VII).

3. The conformations of compounds (I, IV, and VII) and their ethers have been established by NMR and IR spectroscopy.

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