# STUDY OF THE CONFORMATIONAL STATES OF AMINO-ALCOHOL DERIVATIVES OF SOME ALKALOIDS AND BASES AND THEIR PROTONATED FORMS AND QUATERNARY SALTS

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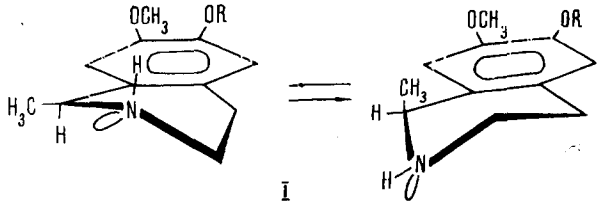
UDC 534.194.536.27

It is known that some N-β-hydroxyalkyl and N-β-chloroalkyl compounds obtained from natural alkaloids possess a directed physiological action. For example, N-(β-hydroxyethyl)cytisine and N-(β-hydroxypropyl)cytisine, obtained by the condensation of cytisine with ethylene oxide [1, 2] and propylene oxide, are far less toxic than cytisine, possess a short-term hypotensive action, and stimulate respiration. N-(β-Hydroxypropyl)cytisine possesses a considerable effect in inhibiting the growth of sarcoma 180 and of Ehrlich's ascitic cancer [3, 4].

Alkylating compounds containing a β-chloroethylamino group have been proposed previously [5] for the treatment of malignant tumors. Well-known alkylating antitumoral compounds containing a β-chloroethylamino fragment are sarcolysine, embikhine, novoembikhine, and others. The properties of these drugs and their medicinal use have been studied by many workers [6-9]. The present paper gives the results of a study of the spatial structure of the products of the interaction of the alkaloids salsoline, salsolidine, ephedrine, and pseudoephedrine and of the bases decahydroquinoline and tetrahydroquinoline with ethylene oxide and also the N-β-chloroethyl derivatives of the bases obtained from the corresponding amino alcohols. Features of the structure of these compounds may be fundamentally connected with the appearance of a specificity of their physiological action, since, in spite of the monotypical nature of the active center, the degree of participation in a biochemical process usually depends on the conformational state of the substrates. Because the saturated ring of salsoline (I, R = H) and salsolidine (I, R = $CH_3$) has two trigonal carbon atoms and a nitrogen atom, in solutions salsoline and salsolidine can exist in two half-chair conformations:




I

The PMR spectrum of salsoline in concentrated hydrochloric acid strongly exhibts the signals of a methyl group (a doublet with a constant $J_{vic} = 7$ Hz at 1.45 ppm), of a hydroxymethyl group (a singlet at 3.6 ppm), and of aromatic protons (a pseudosinglet at 6.5 ppm). The signal of the tertiary α-proton appears in the form of a poorly resolved multiplet at 4.4 ppm. The secondary α-protons form one broad signal at 3.25 ppm and the β-protons, a triplet at 2.8 ppm. On the basis of the equivalence of the chemical shifts of the axial and equatorial α- and β-protons and the magnitude of the splitting of the signal of the β-protons (7.5 Hz) observed in the PMR spectrum, it may be concluded that both isomeric forms of salsoline exist in solution and are rapidly converted into one another.

V. I. Lenin Tashkent State University. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 486-492, July-August, 1974. Original article submitted April 16, 1973.

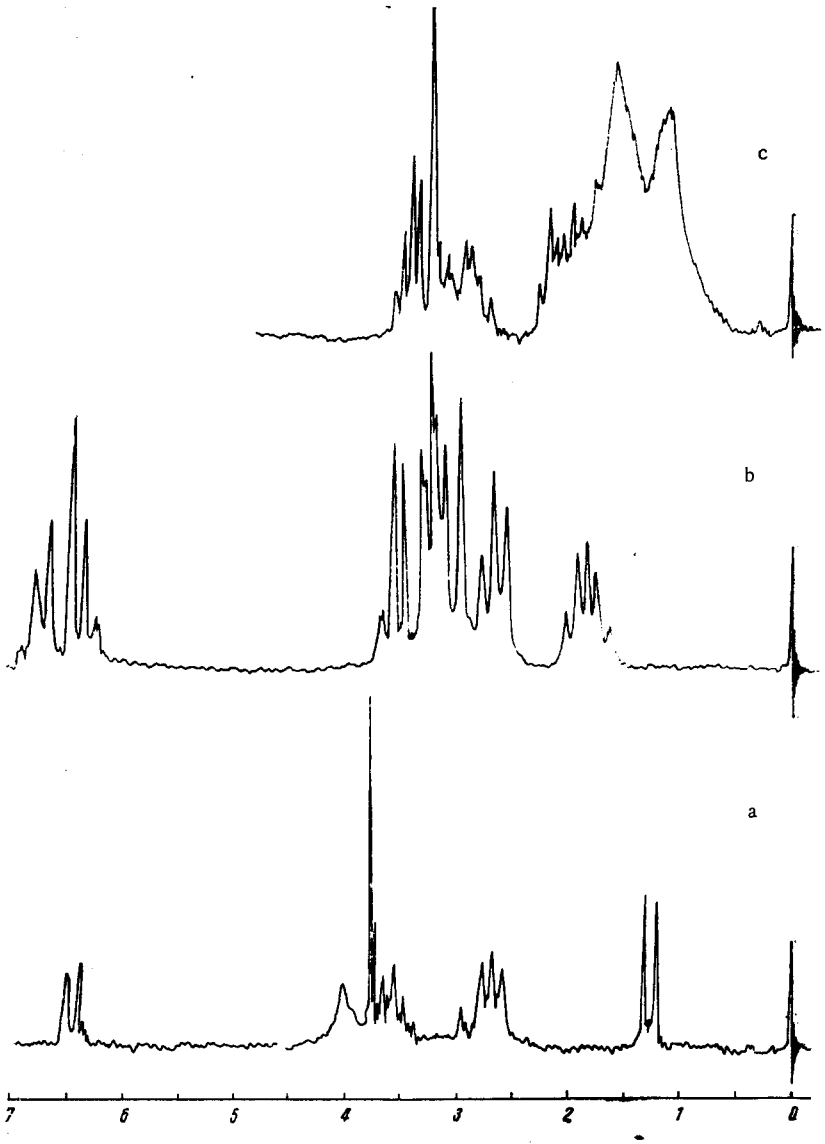



Fig. 1. PMR spectra of N-(β-hydroxyethyl)salsoline in $CHCl_3$ (a), N-(β-hydroxyethyl)decahydroquinoline in $CCl_4$ (b), and N-(β-hydroxyethyl)tetrahydroquinoline in $CCl_4$ (c).

The spectrum of N-(β-hydroxyethyl)salsoline taken in chloroform (Fig. 1a) differs in the form and position of the signals of the analogous groups in the spectrum of salsoline (HCl). The doublet of the methyl group is shifted upfield – 1.3 ppm. The hydroxymethyl group gives a signal at 3.8 ppm, and the aromatic protons form two singlets at 6.4 and 6.55 ppm. At 4.05 ppm appears a new broad signal corresponding to protons of the OH groups. The secondary α-protons of the ring and the protons of the $OCH_2$ group of the substituent give signals in the 3.4-3.8-ppm region. The signals of the secondary β-protons of the ring and the protons of the $>N-CH_2$ group of the substituent are located in the 2.5-3.0-ppm region. Triplets relating to the protons of the methylene groups of the substituent are present. The presence of these triplets shows the equivalence of the methylene protons of the substituent. The signal of the tertiary α-proton is apparently masked by the signals of the protons of the OH and $OCH_3$ groups.

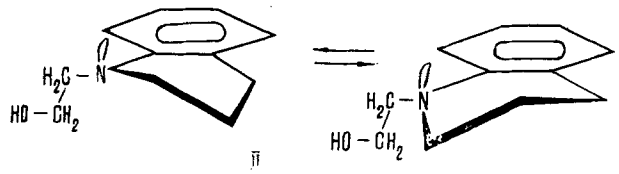
When this compound is protonated in concentrated HCl, two doublets appear, at $\delta = 1.35$ and 1.5 ppm, with coupling constants $J_{vic} = 7$ Hz. On the basis of the ratio of the integral intensities of these doublets (3 : 5), a shift in the equilibrium of the conversion with a small predominance of one of the isomers may be assumed. On iodomethylation, as a result of the introduction of the more voluminous group of the substituent, the equilibrium is more strongly shifted in the direction of one of the isomers, as is confirmed by the presence of only one doublet of a $C-CH_3$ group ($\delta = 1.4$ ppm, $J = 7$ Hz) and the absence of the triplet of the β-protons in the spectrum of N-(β-hydroxyethyl)salsoline methiodide. At a value of the chemical shift

of the $\overset{+}{N}-CH_3$ protons of $\delta = 2.95$ ppm, the predominating conformation of N-(β-hydroxyethyl)salsoline methiodide is the isomer with the axial arrangement of the $\overset{+}{N}-CH_3$ group and the equatorial position of the $C-CH_3$ group [10].

An interesting change in the spectrum is the approach to one another of the signals of the aromatic protons at 6.5 ppm in the protonated forms, which is apparently connected with a disturbance of the delocalization of the unshared pair in the π-orbital of the phenyl system. The latter is confirmed by the results of a comparison of the energy of the $\pi-\pi$ electronic transitions in the free base and its protonated form with the corresponding short-wave shift of the edge of the UV absorption band ($\lambda^{max}_{fr.OCH} = 227$ nm, $\lambda^{max}_{prot} = 223$ nm).

The substitution of the hydroxy group in the aromatic ring by a methyl group does not lead to substantial changes in the spectra. Consequently, the conformational transformations both of salsolidine itself and of N-(β-hydroxyethyl)salsolidine in solution are analogous to the conformational changes of salsoline and N-(β-hydroxyethyl)salsoline, respectively.

In the spectrum in $CCl_4$ of the N-(β-hydroxyethyl)tetrahydroquinoline that we synthesized (Fig. 1b), there are the signals of four aromatic protons in the 6.2-7.0-ppm region. A quintet of the β-protons of the piperidine ring appears clearly at 1.85 ppm, and the γ-protons form a triplet at 2.6 ppm, $J = 7$ Hz. On considering the complex multiplet in the 2.4-3.8-ppm region it is possible to see the following signals: at 3.2 ppm, two overlapping triplets of the α-protons of the piperidine ring and the α-protons of the substituent, and at 2.95 ppm, the clearly shown singlet of the OH group of the substituent. The protons of the $OCH_2$ groups form a triplet at 3.55 ppm. Consequently, as for salsoline, in view of the equivalence of the methylene protons of the piperidine ring and the value of the splitting constant $J_{vic} = 7$ Hz, two rapidly interconverting forms (II) exist in solution:




II

When N-(β-hydroxyethyl)tetrahydroquinoline is protonated, the aromatic part of the spectrum changes substantially. The complex broad multiplet of four nonequivalent aromatic protons changes into a pseudosinglet at 7.1 ppm which, apparently, as in the case of N-(β-hydroxyethyl)salsoline, is formed by the interaction of $H_3O^+$ with the unshared pair of electrons of the nitrogen which causes, thanks to delocalization, a nonuniform distribution of the electron density of the π-electrons in the aromatic ring of the free base. All the remaining signals are somewhat broadened and shifted downfield: the β-protons of the piperidine ring are located at 2.0 ppm, the γ-protons at 2.7 ppm, the proton of the OH group at 3.25 ppm, the four α-protons in the 3.3-3.6-ppm region, and the protons of the $OCH_2$ group at 3.75 ppm. The iodomethylation of N-(β-hydroxyethyl)tetrahydroquinoline also does not lead to a substantial change in the type of spectrum. The retention of the triplet structure of the signal of the γ-protons and the symmetrical form of the β-protons of the piperidine ring show that, in spite of the protonation and iodomethylation of these compounds, similar values of the proportions of the different conformers are characteristic, just as for the free base.

The spectrum of N-(β-hydroxyethyl)decahydroquinoline in $CCl_4$ (Fig. 1c) consists of two complex multiplets: a five-proton multiplet in the 2.7-3.6-ppm region and a 16-proton multiplet in the 1.6-2.3-ppm region. In the low-field multiplet, the signal of the OH group appears distinctly; on dilution it shifts upfield. The dependence of the chemical shift of the OH proton on the concentration shows the absence of intramolecular hydrogen bonds. The signal of the $OCH_2$ protons is located at 3.4 ppm, and this is clearly exhibited in the form of a sharp triplet on protonation. The other lines of the multiplet, corresponding to two protons, are due to the $NCH_2$ group of the substituent. The complex nature of the multiplicity of the signal of the $NCH_2$ protons of the substituent shows their nonequivalence.

The protonation of N-(β-hydroxyethyl)decahydroquinoline does not lead to equivalence of the $NCH_2$ protons of the substituent, from which it may be concluded that the molecules of N-(β-hydroxyethyl)decahydroquinoline and its protonated form are stable or they undergo interconversion, but the equilibrium is strongly shifted in the direction of one isomer. However, the spectrum of N-(β-hydroxyethyl)decahydroquinoline methiodide in DCl shows two signals of the protons of the $\overset{+}{N}CH_3$ group at $\delta = 2.9$ and 2.75 ppm

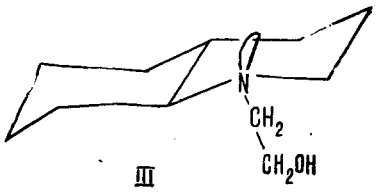
TABLE 1. Physicochemical Constants of the Amino Alcohols Synthesized

| Substance | $R_f$ | mp, °C | bp | $[\alpha]_D$ deg | Hydrochloride | Hydrobromide | Hydriodide | OH stretching vibration ($cm^{-1}$) |
|---|---|---|---|---|---|---|---|---|
| N-(β-Hydroxyethyl)salsoline | 0,57* | 112–113 | – | + 16,85 | 196–197 | 182–183 | 110–112 | 3100–3600 |
| N-(β-Hydroxyethyl)salsolidine | 0,67* | – | Oil | + 36,76 | – | 157–158 | 188–189 | – |
| N-(β-Hydroxyethyl)ephedrine | 0,45* | 50–51 | – | – 17 | 140–121 | 90–91 | 128 | 3200–3580 |
| N-(β-Hydroxyethyl)pseudoephedrine | 0,40† | 45–46 | – | + 15 | | | | 3600 (weak) |
| N-(β-Hydroxyethyl)tetrahydroquinoline | 0,50† | – | 195–197 (5–6 mm) | – | 137–138 | 176–177 | 126 | 3200–3550 |
| N-(β-Hydroxyethyl)decahydroquinoline | 0,86† | – | 145–148 (10–12 mm) | – | – | – | 100 | 3600 (strong) 3150–3600 |
| | | | | | – | – | 121–122 | 3100–3500 |

* Butan-1-ol–hydrochloric acid–water (50 : 7.5 : 13.5) system.
† TLC in the benzene–ether–methanol (10 : 5 : 2) system.

with a ratio of the integral intensities of 1:5. The strong-field signal has the greater intensity. It follows from this that a solution of N-(β-hydroxyethyl)decahydroquinoline in solution consists of a mixture of two isomers differing by the position of the substituent about the nitrogen atom. Since the isomer with the axial arrangement of the $\overset{+}{N}-CH_3$ group usually has the signal in the stronger field [10, 11], we conclude that the hypothesis of the conversion of N-(β-hydroxyethyl)decahydroquinoline with different populations of the isomeric form was correct, and the main form of N-(β-hydroxyethyl)decahydroquinoline methiodide and the corresponding free base is the form of the equatorial arrangement of the hydroxyethyl group of the substituent.

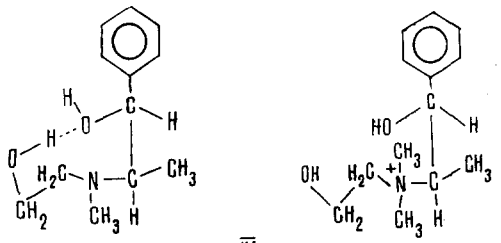
The result obtained above is essentially supplemented by the conclusions drawn from an analysis of the IR spectrum of N-(β-hydroxyethyl)decahydroquinoline. An intense absorption band in the region of frequencies between 2,600 and 2,850 $cm^{-1}$ indicates the predominating trans form of the molecule (III).




III

The PMR spectrum of N-(β-hydroxyethyl)pseudoephedrine in $CCl_4$ shows the following signals: doublet of $C-CH_3$ with a constant J = 7 Hz at 0.6 ppm; singlet of the $N-CH_3$ protons at 2.2 ppm; triplet of the $OCH_2$ protons at 7.15 ppm; and two multiplets at 4.0-4.3 ppm and 2.1-2.8 ppm. The low-field multiplet is formed by a doublet of the proton of the C–Ph fragment and the signals of the two OH protons. The multiplet in the 2.1-2.8-ppm region is composed of the signals of the two nonequivalent protons of the $NCH_2$ group of the substituent and that of a tertiary proton. The nonequivalence of the α-protons of the group of the substituents is due to an intramolecular hydrogen bond.

The presence of an intramolecular hydrogen bond in the amino alcohol of pseudoephedrine follows from an analysis of the IR spectra in the region of the stretching vibrations of hydroxy groups (3000-3650 $cm^{-1}$). In a concentrated chloroform solution of N-(β-hydroxyethyl)-pseudoephedrine (0.5 M) a strong broad band is found at 3200-3600 $cm^{-1}$ which is characteristic for the stretching vibrations of a hydroxy group bound by a hydrogen bond of this type. The stretching vibrations of free hydroxy groups form a line of low intensity in the 3630-$cm^{-1}$ region. With a decrease in the concentration from 0.25 to 0.005 M the relative intensity of the band of the free hydroxyl does not change appreciably. The protonation of N-(β-hydroxyethyl)pseudoephedrine does not lead to substantial changes in its structure, since the PMR spectrum of the protonated form differs from the PMR spectrum of the free base only by a slight broadening of the multiplet of the $OCH_2$ and $NCH_2$ protons of the substituent [12]. However, the introduction of the voluminous $\overset{+}{N}CH_3$ group destroys the intramolecular bond, as a result of which the signal of the $NCH_2$ protons of the substituent becomes a triplet of equivalent protons. The equivalence of the α-protons of the substituent in N-(β-hydroxyethyl)pseudoephedrine methiodide confirms that their nonexistence in N-(β-hydroxyethyl)pseudoephedrine itself cannot be caused by the influence of the asymmetric center. On the basis of these results, the predominant conformations of N-(β-hydroxyethyl)pseudoephedrine and its methiodide are as follows (IV):



IV

In contrast to N-(β-hydroxyethyl)pseudoephedrine, N-(β-hydroxyethyl)ephedrine exists in solutions in different conformations (in comparable concentrations). This follows from the fact that the intensity of the band of the stretching vibrations of the free hydroxy group in the IR spectrum of N-(β-hydroxyethyl)ephedrine (3630 $cm^{-1}$) rises on dilution. Consequently, the solution contains, in addition to a conformer with an intramolecular hydrogen bond, a considerable amount of the amino alcohol of ephedrine with a free amino alcohol group.

The protonation of N-(β-hydroxyethyl)ephedrine leads to a substantial change in the spectrum: the doublet of the proton of the H—C—Ph fragment is distorted and the singlet of the protons of the $NCH_3$ group splits into two doublets. However, the triplet of the equivalent protons of the $OCH_2$ group and the multiplet of the nonequivalent protons of the $NCH_2$ group of the substituent are retained. Consequently, the protonation of N-(β-hydroxyethyl)ephedrine changes the equilibrium of the transition of the isomers into one another, and both isomers clearly appear in the PMR spectrum, although these isomers cannot be seen in the PMR spectrum of N-(β-hydroxyethyl)pseudoephedrine.

When N-(β-hydroxyethyl)ephedrine is iodomethylated, apparently as a result of additional nonbound interaction, only one isomer remains in solution, as follows from the singlet form of the signal of the $\overset{+}{N}CH_3$ protons. In addition, a contraction of the doublet of the proton in the H—C—Ph group and the conversion of the signal of the nonequivalent protons of the NCH group into a triplet of equivalent protons is observed.

Thus, the study of the conformational states of derivatives of the alkaloids salsoline, salsolidine, ephedrine, and pseudoephedrine and of the bases decahydroquinoline and tetrahydroquinoline and their protonated forms and methiodides as examples has shown the existence of an influence of the structure of the bases and of the states of the nitrogen atoms on the intensity and nature of the conformational transformations in monotypical chemical reactions.

## EXPERIMENTAL

Ethylene oxide (8.6 g) was passed into a solution of 25 g of salsoline in 300 ml of ethanol. The reaction mixture was left at room temperature for 3 days and was then heated on the water bath at 60-70°C for 4-5 h, and the solvent was distilled off under vacuum. This gave a mixture of the initial compound and N-(β-hydroxyethyl)salsoline which was separated on a column of alumina. The benzene–ether–ethanol (10 : 5 : 2) solvent system was used. After the solvent had been distilled off, light-yellow crystals of N-(β-hydroxyethyl)salsoline with mp 112-113°C (from ethanol) were obtained. Yield 27.90 g (87.60%); $R_f$ 0.57 paper chromatography in the butan-1-ol–hydrochloric acid–water (50 : 7.5 : 13.5) system; $[\alpha]_D$ + 16.85° (c 0.5%, α ±0.15; ethanol).

The N-(β-hydroxyethyl) derivatives of salsolidine, ephedrine, pseudoephedrine, decahydroquinoline, and tetrahydroquinoline were synthesized under similar conditions. The physicochemical constants of the compounds obtained are shown in Table 1. The PMR spectra were taken on an H-60 spectrometer (Hitachi) at 60 MHz and the IR spectra on a UR-10 instrument (C. Zeiss).

## SUMMARY

1. Salsoline, salsolidine, ephedrine, pseudoephedrine, tetrahydroquinoline, and decahydroquinoline have been condensed with ethylene oxide and the corresponding amino alcohols have been obtained.

2. The conformational states and spatial structures of the compounds synthesized and their protonated forms and methiodides have been studied by IR and PMR spectroscopy. It has been shown that because of the rapid conversion of the saturated parts of the molecules of the bases and inversion processes, several stable spatial forms of the N-derivatives with quarternized nitrogen atoms exist in solutions.

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