SPATIAL STRUCTURE AND CONFORMATIONAL STATE OF DILUPININE ESTERS OF DIBASIC ACIDS

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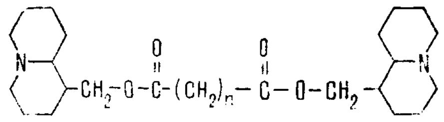
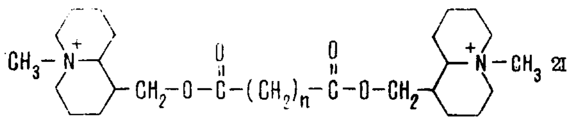
Information on the spatial structure and the direction of the conformational states as functions of the conditions are necessary for explaining the efficiency of the action of muscle relaxants and also for determining the topography of the structure of cholinoreceptors. The combination of these facts together with the biochemical, toxicological, and pharmacological characteristics makes it possible to create a purposefully directed synthesis of bisquaternary compounds, including muscle relaxants, the majority of which are, as is well known, bisquaternary salts.

The activity of curaremimetic compounds [1-4] depends on the degree of screening of the positive charges, the distance between the onium centers, the steroelectronic structure, the chains separating the quaternary nitrogen atoms, lyophilicity, hydrophilicity, etc.

We have previously [5] reported the preparation of bisquaternary derivatives of the alkaloid lupinine. In the present paper we give the results of a study by means of PMR spectra of the conformational states of dilupinine esters of oxalic acid (I, n = 0), malic acid (II, n = 1), succinic acid (III, n = 2), gulatric acid (IV, n = 3), adipic acid (V, n = 4), pimelic acid (VI, n = 5), suberic acid (VII, n = 6), azelaic acid (VIII, n = 7), and sebacic acid (IX, n = 8), their structure (A), and that of their protonated forms and dimethiodides (B).



A



B

In the spectra of the dilupinine esters (I) and (II) in the form of the free bases in CCl_4 there are three groups of signals: a complex multiplet in the 4.1-4.3 ppm region relating to the CH_2O fragment, a multiplet at 2.78 ppm due to the α-H_e (with respect to the nitrogen), and an unresolved signal at 1-2.3 ppm. Taking into account the values of $[\alpha]_D$ (Table 1) and comparing the PMR characteristics of the substances obtained with the PMR spectra of lupinine and epilupinine [6], it may be concluded that, while the α-H_e signals are located at 2.78 ppm, their axial geminal protons resonate at higher fields – about 2-1.8 ppm. Such a difference between the chemical shifts (CSs) is characteristic of a predominant axial–axial direction of the lone pair of electrons of the nitrogen atom. Consequently, it is possible that the predominant conformation of the lupinine skeleton of these esters is "trans–trans" with axial CH_2OR groups. The nature of the multiplicity of the signal at 4.1-4.3 ppm shows the presence in it of rotation about the CH_2O groups, in which, in view of the presence of an asymmetric center, the transitional rotameric forms, which

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TABLE 1

n	$-[\alpha]_D^*$ of the base, deg	Dimethiodides of the dilupinine esters of dibasic acids		
		$+[\alpha]_D^*$	δ-(OCH), ppm	conformation and orientation of CH_2OR in the ring
0	31,2	—	—	—
1	52	11,4	—	—
2	19,4	11,4	3,45	cis—cis (e,e)
3	35,1	11,4	3,45	cis—cis (e,e)
4	15,6	9,4	3,45; 3,95	cis—trans (e,a)
5	25,3	9,1	3,45	cis (e)
6	17,3	7,7	3,45; 3,95	cis—trans (e,a)
7	25,9	8,1	3,95	trans (a)
8	16,4	7,5	3,45; 3,95	cis—trans (e,a)

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* In the measurement of the angles of rotation, methanol was used as the solvent.

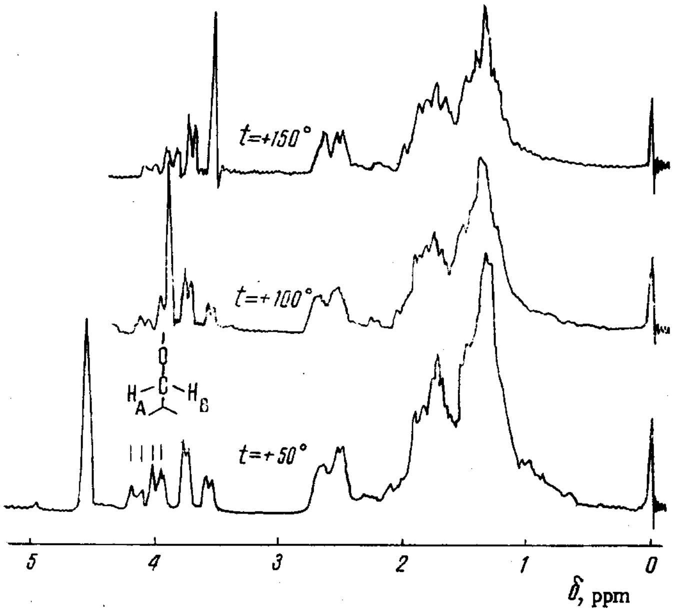

Fig. 1. PMR spectra of lupinine in chlorobenzene at various temperatures.

differ little in energy, are magnetically nonequivalent. The signals of the bridge CH_2 groups are located in the strong field. This shows that the protons considered are not located in the region of the nodal plane of the two π orbitals of the carbonyl groups.*

The presence of nitrogen atoms in the rings permits the suggestion of the possibility of inversion–conversion transformations of the spatial structures; however, in nonpolar solvents one form is predominant, as follows from a comparison of the multiplet of the α-H_e protons of all the dilupinine esters studied with the spectra of lupinine at various temperatures (Fig. 1).

As can be seen, in all cases a splitting of the α-H_e signals is observed through geminal spin–spin coupling and the strong-field location of the signals of the axial protons.

Attack by a hydroxonium ion of the lone pairs of the nitrogen atoms of the bases (I) and (II) affects the state of the conformational equilibrium, since, depending on the concentration of the acid, in acid solutions doublet signals are observed: in (I) three at 3.4, 3.7, and 4.25 ppm, and in (II) two at about 3.7 and 3.55 ppm. The relative intensities of these signals depend on the concentration of acid (Fig. 2). The doublet form of the signal is due to the fact that the $C^7H-C^{11}H_2O$ signals form an ABX system with a small difference δAB. Consequently, the extreme lines of the signals may not always be observed (see Fig. 2).

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* If the CH bond is located in the region of the nodal plane of the group, usually a downfield shift of the signal by 2-1.5 ppm is observed [7].

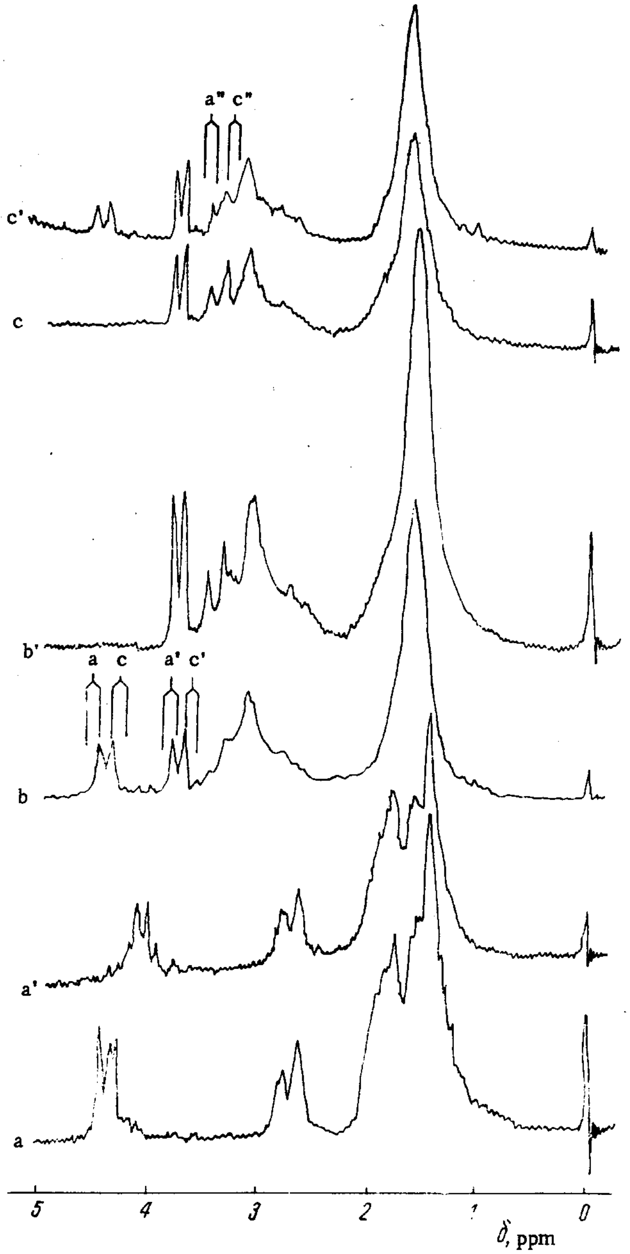
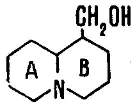


Fig. 2. PMR spectra of (I) (a) and (II) (a') in CCl_4 and of the protonated forms of (I) (b) and of (II) (b') in concentrated HCl and of (I) (c) and of (II) (c') in 18% HCl.

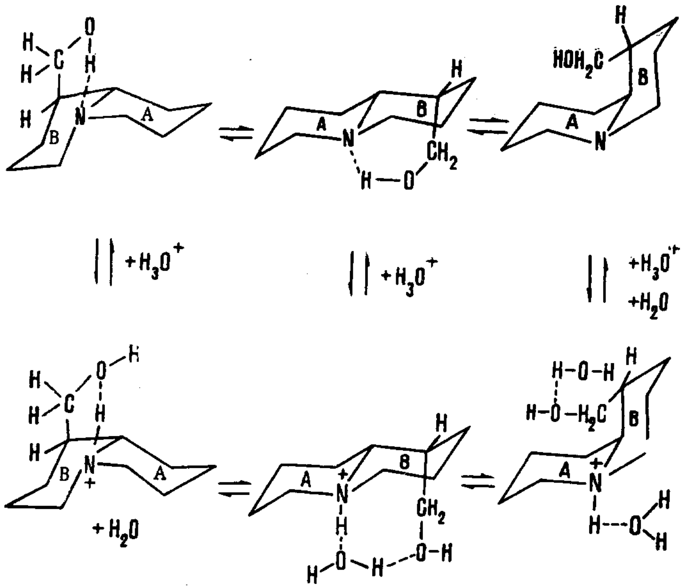
Their unambiguous assignment to the $C^{11}H_2O$ groups follows unambiguously from this; now the α-H_e and α-H_a signals are located in the 2.6-3.3 ppm region thanks to the quaternization of the nitrogen atoms. The results of a comparison of the positions of these signals in the protonated forms of lupinine, epilupinine, and their methiodides [8] permits the conclusion that in acid solutions, depending on the rate of exchange processes, various concentrations of the formations of the ester exist: trans–trans $2CH_2O$ (*a*, *a*), $\delta = 3.2$-3.4 ppm, "cis–cis" $2CH_2O$ (e, e), $\delta = 3.55$-3.7 ppm and 3.2-3.4 ppm, and also cis-a-CH_2O, trans-a-CH_2O, $\delta = 4.2$-4.3 ppm, $\delta = 3.5$-3.7 ppm.

In the spectrum of the dimethiodide of the base (II) a singlet of the $\overset{+}{N}-CH_3$ groups appears at 3 ppm and a doublet of the CH_2O groups at 3.4 ppm. These facts show the axial-equatorial orientation of the $\overset{+}{N}-CH_3$ group (for a,a-$\overset{+}{N}-CH_3$ in quinolizidine systems, $\delta = 2.6$-2.76 ppm [9]) and equatorial CH_2OR groups. Consequently, on iodomethylation the conformational equilibrium shifts to the cis-quinolizidine $\overset{+}{N}-CH_3$ (a, e), e-CH_2O conformation.

The spectrum of the base (III) does not differ fundamentally from (I) and (II), and the predominant conformation, according to the PMR spectrum, is similar to that of the bases (I) and (II).



Since in lupinine, rings A and B are not equivalent, the conformational equilibrium must represent a minimum between three forms differing in the orientation of the lone pair, of the substituent on the nitrogen atom, and of the conformation of the bicyclic system itself:



i j k

It has been found that when the base (III) is protonated, all these forms can be detected. In the PMR spectrum of this base in HCl there are three doublet signals at 4.15, 3.72, and 3.38 ppm. The relative intensities of these doublets change with a decrease in acidity (Fig. 3). Since these forms are present in HCl solutions and in the spectra of lupinine there are only two forms [8], it may be assumed that an important factor for the stabilization of these conformational forms is the appearance of an intramolecular hydrogen bond between the carbonyl group and the $\overset{+}{N}-H$ bond in HCl solutions with a low H_2O activity [10]. With an increase in the activity of the water, these complexes are destroyed, thanks to which the concentration of the least stable form falls and the concentrations of the other conformations rise. From a consideration of the PMR spectra of the base (III) at various concentrations of HCl it is possible to detect a decrease in the form of δCH_2O at 4.25 ppm and a gradual increase in the concentration of the form having the signal of the protons of the hydroxymethyl group at 3.4 ppm. These facts permit the conclusion that in acid aqueous solutions a complex conformational equilibrium exists the state of which is determined by the relative rates of inversion of the lone pairs of the nitrogen in forms i, j, and k (see above), the rate of proton exchange, the stability of the complex with the intramolecular bond, and also nonbound interactions between the substituents in the quinolizidine system.

Since for monosubstituted quinolizidines three nonequivalent conformations i, j, k are possible and in the PMR spectrum of (III) in HCl three CH_2OH multiplets are observed, then, allowing for the fact that the ethers contain two quinolizidine radicals, a minimum of six forms is present in acid solution: the symmetrical ii, jj, and kk and the unsymmetrical ij, ik, and jk, between which there are equilibria with the participation of H_2O and H_3O^+.

The results of a comparison of the spectra of the methiodides of lupinine and of epilupinine, and also other methiodides of dilupinine esters with those given in the present paper show that in the methiodide of this base the signal of the CH_2O group is a doublet at 3.4 ppm and that of the $\overset{+}{N}-CH_3$ group is a singlet at 3.05 ppm. Consequently, the conformational equilibrium has been displaced in the direction of the cis form.

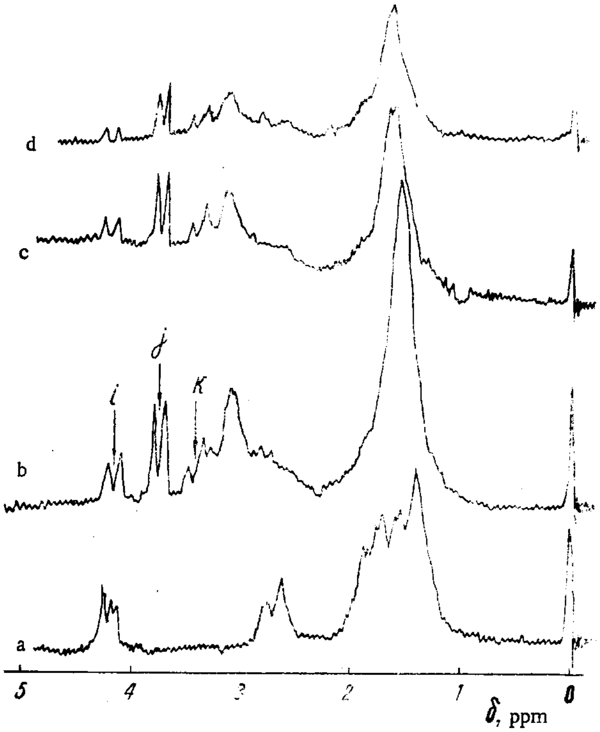


Fig. 3. PMR spectra of (III) in CCl_4 (a), in 36% HCl (b), in 18% HCl (c), and in 9% HCl (d).

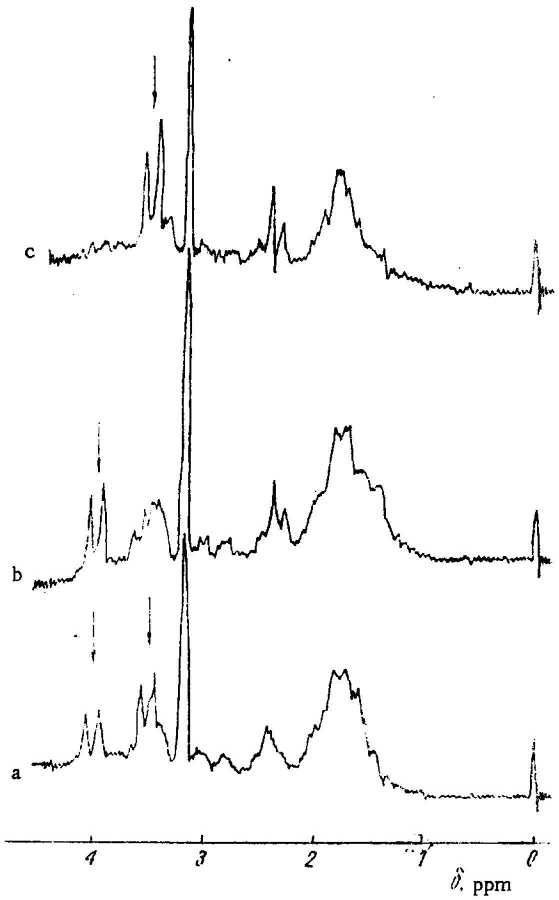


Fig. 4. PMR spectra of the dimethiodides (V) (a), (VI) (b), and (IV) (c) in 10% HCl.

The spectra of the bases, beginning with (IV), do not differ substantially in the nature of the multiplets at 4.1-4.3 ppm, 2.6-2.8 ppm, and 1-2.1 ppm, but in contrast to the bases (I), (II), and (III) they include a multiplet in the 2.1-2.3 ppm region relating to the signals of the four protons of the bridge methylene groups. These signals obviously belong to the signals of a CH group bound to a C=O group, the splitting of which is due to the protons of the neighboring methylene groups. The presence of the latter in a weaker field than in the spectra of the bases (II) and (III) shows that in such compounds the signals appear in the region of the nodal plane of the electrons of the two carbonyl groups and the population of the conformational states of the different orientations of the C=O groups relative to one another depends on the number of methylene groups between the two quinolizidine fragments. This phenomenon is also confirmed by measurements of $[\alpha]_D$ for the dibases studied (see Table 1). The oscillating nature of this relationship with even and odd numbers of bridge methylene groups shows that in the predominating conformation the vectorial sum of the transition moments changes regularly. In view of the form of the signals of the OCH_2 protons (AB part of an ABX system), characterizing the influence of the asymmetric centers thanks to the nonequivalence of the rotamers about the C_7-CH_2-O bond, these facts can be interpreted as the result of the fact that, in agreement with Rosenfel'd's formula [11],

$$[\alpha] = A \sum_{a} R \frac{\nu^2}{R\nu k^2 - \nu^2} \cdot \frac{n^2+2}{3},$$

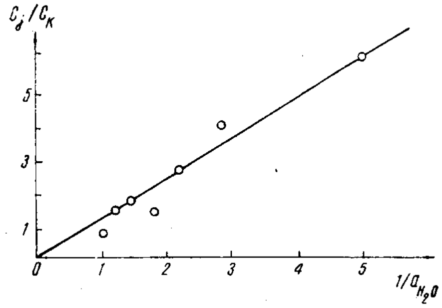


Fig. 5. Dependence of the ratio c_j/c_k on the activity of water $1/a_{H_2O}$.

TABLE 2

HCl, %	H_0^*	a_{H_2O}	$\frac{c_j}{c_k}$	$\frac{1}{a_{H_2O}}$
36	−4,35	0,2	5,6	5
28,34	−3,28	0,35	3,9	2,85
25	−2,90	0,45	2,60	2,20
21,30	−2,30	0,55	1,40	1,81
16,43	−1,68	0,77	1,80	1,43
11,30	−1,17	0,82	1,60	1,22
6,93	−0,61	0,9	0,68	1,11

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* The values of H_0 and of a_{H_2O} were taken from a paper by M. I. Vinnik [12] (Fig. 5).

the sum of the partial forces of rotation depends on whether the number of members in the total is odd or even. The value of $[\alpha]_D$ is less when the number is even, which shows the mutual compensation of the vectorial components of the sums. Thus, in spite of the low rotation barrier about the polymethylene bridge, these results permit the conclusion that predominant forms of rotamers about the bridge $-CH_2-CH_2-$ bonds exist in solutions. It follows from the PMR spectra that the predominant conformation of the dilupinine esters with n from 3 to 8 in nonpolar media is the trans–trans form with axial CH_2OR groups. In dilupinine systems with n > 3 an interesting influence of the conformational transitions of one of the bound residues of the dibasic acids of the quinolizidine system on the other is also observed. In the free bases, this may be shown in a synchronization of the processes of inversion about the nitrogen atom, and in reactions it may be shown in a change in the direction of the displacement of the conformational equilibrium.

In a consideration of the PMR spectra of the dimethiodides of the bases (IV–IX) three groups of signals are possible:

a) Two doublets of the hydroxymethyl protons at 3.95–4.0 ppm and 3.45 ppm, n = 4, 6, 8, signal of $\overset{+}{N}-CH_3$ broadened – δ = 3.21 ppm, $\Delta\nu_{1/2}$ = 3.5 Hz (Fig. 4a);

b) only one signal in the weak field with n = 5, 7 at 3.9 ppm, $\delta_{\overset{+}{N}-CH_3}$ = 3.2 ppm, $\Delta\nu_{1/2} \simeq$ 1.5 Hz (Fig. 4b);

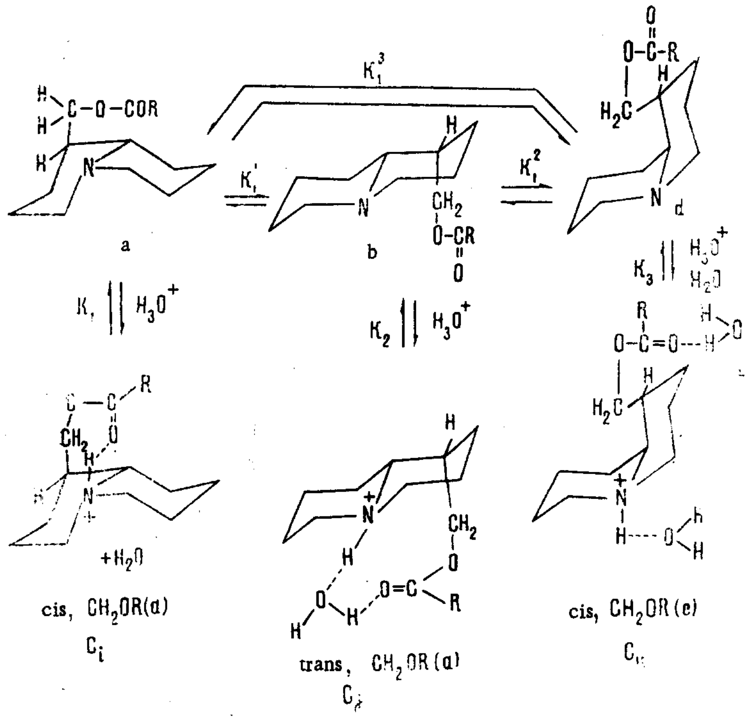
c) one strong-field signal at 3.45 ppm with n = 2, 3, $\delta_{\overset{+}{N}-CH_3}$ = 3.12 ppm, $\Delta\nu_{1/2} \simeq$ 1.5 Hz (Fig. 4c).

Thus, the conformational transition of the trans-quinolizidine system in the iodomethylation reaction differs fundamentally according to the length of the $-(CH_2)_n-$ bridge, namely: where there is only a weak-field doublet of the hydroxymethyl group, the conformation of the dimethiodide is trans–trans: $-CH_2O-$ (a, a), $\overset{+}{N}-CH_3$ (a, a); when, however, only a strong-field doublet is observed, the dimethiodide of the bis-quaternary form possesses the cis,cis conformation: $-CH_2-$ (e, e), $\overset{+}{N}-CH_3$ (a, e); in those cases where both signals are present and they are of similar intensities, the conformation of the dimethiodide is such that one nucleus has the cis form with $-CH_2O-$ (e), $\overset{+}{N}-CH_3$ (e, a) and the other nucleus is present in the trans conformation with $-CH_2O-$ (a) and $\overset{+}{N}-CH_3$ (a, a). This conclusion is in harmony with the fact that in the methiodide of cis$-CH_2O-$(e)-lupinine and in the methiodide of trans$-CH_2O-$(e)-epilupinine the CSs of the hydroxymethyl protons are δ = 3.45 ppm [6, 8].

As we have seen above, on protonation (see Fig. 2) and when exchange processes take place in HCl solutions, the dilupinine esters form a mixture of conformers with various cis- and trans-linkages of the quinolizidine fragments the concentration of which depends on the activity of the water, the acidity of the medium, and the rate of proton exchange. A larger amount of water in the solvate shell is necessary for the stability of the k form than for the i and j forms. This shows that a rise in the rate of exchange with an increase in the activity of H_2O favors a shift of the equilibrium from the first form to the second because of the lower stability of the ring with the intramolecular hydrogen bond and the lower degree of solvation with water molecules in this cis system – i. What has been said above can be represented by a scheme to which the following equations correspond

$$k_1 = \frac{c_i \cdot a_{H_2O}}{h_0 \cdot a}; \quad (1) \quad k_2 = \frac{c_j}{h_0 \cdot b}; \quad k_3 = \frac{c_k}{h_0 \cdot a_{H_2O} \cdot d}; \qquad (2)$$

$$c_i = \frac{k_1 \cdot h_0 \cdot a}{a_{H_2O}}; \quad (3) \quad c_j = k_2 \cdot h_0 \cdot b; \quad c_k = k_3 \cdot h_0 \cdot a_{H_2O} \cdot d$$



a+b+d=A (concentrations of the bases taken)

$$a = b\cdot k_1;\quad b = d\cdot k_1^2;\quad a = d\cdot k_1^3$$

$$\frac{c_j}{c_k} = \frac{k_2\cdot h_0\cdot b}{k_3\cdot h_0\cdot a_{H_2O}\cdot d} = \frac{k_2}{k_3}\cdot\frac{b}{d\cdot a_{H_2O}} = \frac{k_2}{k_1}\cdot k_1^2\,\frac{1}{a_{H_2O}}, \tag{4}$$

where c_i is the concentration of the cis conformation with an axial CH_2-OR ($\delta = 4.2$ ppm); c_j is the concentration of the trans form with an axial CH_2OR group ($\delta = 3.75$ ppm); and c_k is the concentration of the cis form with an equatorial CH_2OR group ($\delta = 3.45$ ppm).

To check the correctness of the quantitative description of these conformational changes, we have studied the degree of change of the concentrations of two forms of lupinine at different acidities h_0 and water activities. Beginning from some value of h_0 it is possible to neglect the presence of the c_i form, since the equation

$$\frac{c_j}{c_k} \simeq \frac{k_2}{k_3}\cdot k_1^2\,\frac{1}{a_{H_2O}}$$

is valid, i.e. the ratio of the concentration of the trans CH_2OR-axial conformations to the concentration of the cis conformation with an equatorial CH_2OR must decrease in inverse proportional to the activity of the water.

Table 2 gives the values of c_j/c_k, which were determined by the integration of the PMR spectra as a function of H_0 (acidity function) and a_{H_2O} (activity of water) for C-lupinine ($4.8\cdot 10^{-1}$ M).

As can be seen from Fig. 5, the value of c_j/c_k decreases in agreement with Eq. (4), which confirms our proposed scheme of changes in the conformational states of the quinolizidine fragment of lupinine as a function of the activity of water, the acidity of the medium, and the concentration of the base.

CONCLUSIONS

1. The conformational states of dilupinine esters of dibasic acids and their protonated forms, and also their dimethiodides, have been studied by PMR spectroscopy.

2. It has been shown that the nature of the conformational transformations of the trans-quinolizidine system of lupinine and of the dilupinine esters of dicarboxylic acids depends fundamentally on the acidity of the medium, the activity of water, the strength of intramolecular bonds, and the concentration of bases.

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