A COMPARATIVE STUDY OF THE IR SPECTRA OF ALKALOIDS CONTAINING PIPERIDINE AND QUINOLIZIDINE RINGS IN THE 2500-2830 cm^{-1} REGION

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It is well known that intensive absorption in the 2500-2830 cm^{-1} region in the IR spectrum of a base containing an aliphatic nitrogen atom in a ring shows the stereospecific interaction of the electrons of the unshared pair of this atom with the neighboring $\alpha-CH$ bonds. Bohlmann [1] and others [2-4] have made wide use of this phenomenon to establish the direction of the axial anticoplanar α-protons with respect to the unshared pair, which, in its turn, has enabled the trans configuration of the quinolizidine, hydroisoquinoline, and other fragments of complex natural compounds to be determined [5, 6].

However, it can be seen from our preceding papers [7, 8] that the appearance of absorption in the region under investigation is connected with an extremely complex electron-vibrational process including the delocalization and the polarization interaction of the electrons of the unshared pair with the α-protons, the parameters of which also depend, apparently, on the interaction of the transitional dipole moments of the stretching vibrations during the inversion-conversion transformations of the conformations. This phenomenon is due to the absence of types of vibrations of $N-CH_2$ and $N-CH$ fragments which are characteristic with respect to shape and intensity (and, to a smaller extent, to frequency). The present paper gives the results of an experiment permitting this assumption to be substantiated.

In order to establish the features of the conformations of the bases of the piperidine, cytisine, sparteine, and matrine series, we have studied the characteristics of the vibrational spectra in the 2500-2830 cm^{-1} region of the solid and liquid states of anabasine (I), N-methylanabasine (II), anabasamine (III), cytisine (IV), N-methylcytisine (V), tetrahydrocytisine (VI), aphylline (VII), *l*-lupanine (VIII), pachycarpine (IX), lupinine (X), 17-oxosparteine (XI), α-isoaphylline (XII), matrine (XIII), allomatrine (XIV), matridine (XV), allomatridine (XVI), sophoridine (XVII), isosophoridine (XVIII), isosophoridane (XIX), sophoramine (XX), isosophoramine (XXI), and sophocarpine (XXII).

The samples for investigation in the solid state were obtained in the form of tablets prepared from 2 mg of the base and 200 mg of KBr; the solutions had a concentration of 0.2 M in CCl_4, and a NaCl cell 0.12 mm thick was used for spectrophotometry. In addition, the spectra of the liquid bases (I, II, VII-IX) were recorded in solid solution in heneicosane ($C_{21}H_{44}$), for which the solid matrix was prepared by fusing 2 mg of the base with 5 mg of heneicosane. The IR spectra were recorded on a UR-10 (K. Zeiss) instrument with a LiF prism at a rate of recording of 50 cm^{-1}/min with a scale of 32 mm/100 cm^{-1}.

The areas of the trans bands (S) were determined with a planimeter both for the solid bases and for the liquid bases in the solid matrix. The spectral band of isosophoridine (XVIII), which does not absorb in the 2500-2830 cm^{-1} region was used as the base line.

Table 1 gives the values of the total integral intensities (A) of the bases in solution calculated by Bourgin's formula [9] with a summation step of $\Delta\nu = 6$ cm^{-1} in the ln (T_0/T) scale and the values of S (area in cm^2) for the solid bases, and Fig. 1 gives the spectra of bases in the liquid and solid states.

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TABLE 1

Compound	Area and frequency of transitions (cm^{-1}) of the trans band		Chemical shift* of the feebly polar α-protons with respect to the nitrogen, ppm
	in the solid (S, cm^2)	in solution ($A \times 10^4$, $mol^{-1} \cdot liter \cdot cm^{-2}$)	
I	11,5† 2680, 2700, 2750, 2800	1,113 2690, 2725, 2775, 2820	δHtert $= 3,2$ $\delta H_2^e = 2,95;$ $\delta H_2^a = 2,44$
II	24,6 2580, 2620, 2670, 2700, 2720, 2780	1, 723 2665, 2700, 2720, 2775	δH tert $= 2,58$ $\delta H_2^e = 2,79;$ $\delta H_2^a = 1,93$
III	20,9 2630, 2660, 2700, 2720, 2780	1,59 2680, 2700, 2720, 2780	δH tert $= 2,82$ $\delta H_2^e = 3,03;$ $\delta H_2^a = 2,05$
IV	18,0 2620, 2630, 2680, 2710, 2740, 2800	1,65 2635, 2700, 2715, 2780	$\delta H_{11,12} = 2,9 - 3,0$
V	24,5 2580, 2650, 2695, 2720, 2745, 2760, 2780	2,02 2680, 2700, 2730, 2785	$\delta H_{11,13}^e = 2,9 - 3.0$ $\delta H_{11,13}^a = 2,3$
VI	—	—	$\delta H_{11}^e = 3,3;$ $\delta H_{11}^a = 2,3$ $\delta H_{13}^e = 3,0$ $\delta H_{13}^a = 2,3$
VII	20,5 2610, 2635, 2665, 2710, 2730, 2760, 2800, 2810	0,5 2760 (weak), , 2810	$\delta H_{17}^e = 2,45;$ $\delta H_{17}^a = 2,99;$ $\delta H_2^a = 2,17:$ $\delta H_2^e = 4,56$ $\delta H_6 = 3,14$
VIII	22,5 2680, 2730, 2765, 2815	1,95 2700, 2750, 2810	$\delta H_{17}^e = 2,65$ $\delta H_{17}^a = 1,85$ $\delta H_{10}^a = 2,3;$ $\delta H_{10}^e = 4,35$
IX	31,55 2590, 2630, 2685, 2730, 2760, 2800	3,4 2680, 2760, 2800	δH_8 tert $= 3,15$ $\delta H_{10}^e = 2,4;$ $\delta H_{10}^a = 1,95$ $\delta H_{15}^e = 2,56$ $\delta H_{15}^a = 1,83$ $\delta H_{17}^e = 2,53$ $\delta H_{17}^a = 2,21$
X	34 2600, 2620, 2680, 2695, 2770, 2800	2,4 2680, 2700, 2760, 2810	$\delta H_{2,10}^e = 2,9$ $\delta H_{2,10}^a < 2$

TABLE 1. (Continued)

Compound	Area and frequency of transitions (cm^{-1}) of the trans band		Chemical shift* of the feebly polar α-protons with respect to the nitrogen, ppm
	in the solid (S, cm^2)	in solution (A × 10^4, $mol^{-1} \cdot liter \cdot cm^{-2}$)	
XI	$\frac{34{,}8}{2530,\ 2580,\ 2610,\ 2660,\ 2670,\ 2750,\ 2795}$	$\frac{2{,}00}{2650,\ 2680,\ 2725,\ 2765,\ 2815}$	$\delta H_{10}^{e} = 2{,}68$ $\delta H_{10}^{a} = 2{,}14$ $\delta H_{2}^{e} = 2{,}58$ $\delta H_{2}^{a} = 1{,}78$
XII	$\frac{30{,}1}{2570,\ 2590,\ 2630,\ 2640,\ 2650,\ 2670,\ 2720,\ 2730,\ 2755,\ 2795}$	$\frac{2{,}35}{2590,\ 2670,\ 2700,\ 2720,\ 2770,\ 2800}$	$\delta H_{17}^{e} = 2{,}79$ $\delta H_{17}^{a} = 1{,}96$ $\delta H_{15}^{e} = 2{,}6$ $\delta H_{15}^{a} = 1{,}8$
XIII	$\frac{29{,}8}{2630,\ 2650,\ 2660,\ 2700,\ 2730,\ 2740,\ 2760,\ 2795}$	$\frac{2{,}00}{2690,\ 2700,\ 2750,\ 2795}$	$\delta H_{2,10}^{e} = 2{,}68$ $\delta H_{2,10}^{a} = 1{,}8$
XIV	$\frac{30{,}6}{2570,\ 2590,\ 2610,\ 2630,\ 2680,\ 2710,\ 2760,\ 2810}$	$\frac{2{,}35}{2640,\ 2670,\ 2710,\ 2760,\ 2810}$	$\delta H_{2,10}^{e} = 2{,}8 - 2{,}9$ $\delta H_{2,10}^{a} = 2{,}15$
XV	$\frac{40{,}55}{2530,\ 2600,\ 2620,\ 2630\ \ 2640,\ 2680,\ 2690,\ 2740,\ 2780,\ 2810,\ 2820}$	$\frac{4{,}15}{2680,\ 2690,\ 2700,\ 2740,\ 2750,\ 2770,\ 2800,\ 2820}$	$\delta H_{2}^{e}\ \delta H_{10}^{e}$ δH_{17}^{e} $\delta H_{13}^{e} \sim 2{,}0$
XVI	$\frac{4{,}95}{2610,\ 2640,\ 2670,\ 2680,\ 2690,\ 2740,\ 2760,\ 2780,\ 2790,\ 2805,\ 2820}$	$\frac{4{,}41}{2620,\ 2680,\ 2690,\ 2740,\ 2760,\ 2780,\ 2800,\ 2820}$	δH_{2}^{e}, δH_{10}^{e} δH_{11}^{e}, $\delta H_{13}^{e} \sim 2{,}6$
XVII	$\frac{28{,}1}{2640,\ 2670,\ 2710,\ 2750,\ 2795}$	$\frac{1{,}90}{2640,\ 2720,\ 2790}$	$\delta H_{2,10}^{e} = 2{,}65$ $\delta H_{2,10}^{a} = 2{,}08$
XVIII	—	—	—
XIX	$\frac{34{,}0}{2580,\ 2620,\ 2640,\ 2670,\ 2680,\ 2730,\ 2750,\ 2810}$	$\frac{2{,}81}{2630,\ 2670,\ 2720,\ 2740,\ 2760,\ 2800}$	δH_{2}^{e}, δH_{2}^{a}, δH_{10}^{e}, δH_{10}^{a}, δH_{11}^{e} δH tert = 3—2 ppm
XX	$\frac{17{,}0}{2610,\ 2680,\ 2690,\ 2740,\ 2760,\ 2810}$	$\frac{2{,}30}{2620,\ 2680,\ 2690,\ 2750,\ 2770,\ 2810}$	$\delta H_{2,10}^{e} = 2{,}8$ $\delta H_{2,10}^{a} = 2{,}2 - 2{,}1$
XXI	$\frac{21{,}5}{2700,\ 2740,\ 2760,\ 2800}$	$\frac{1{,}95}{2600,\ 2690,\ 2760,\ 2815}$	$\delta H_{2,10}^{e} = 2{,}82$ $\delta H_{2,10}^{a} = 2{,}04$
XXII	$\frac{21{,}5}{2620,\ 2630,\ 2690,\ 2740,\ 2750,\ 2760,\ 2790,\ 2810}$	$\frac{1{,}90}{2630,\ 2700,\ 2740,\ 2760,\ 2810}$	$\delta H_{2,10}^{e} = 2{,}67$ $\delta H_{2,10}^{a} = 1{,}83$

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* For the alkaloids of the quinolizidine series, the chemical shift in the 2-3.2 ppm region was determined by the INDOR method at a frequency of 100 MHz (Varian HA-100).

† The numerator gives the area and the denominator the frequency of the transitions of the trans band.

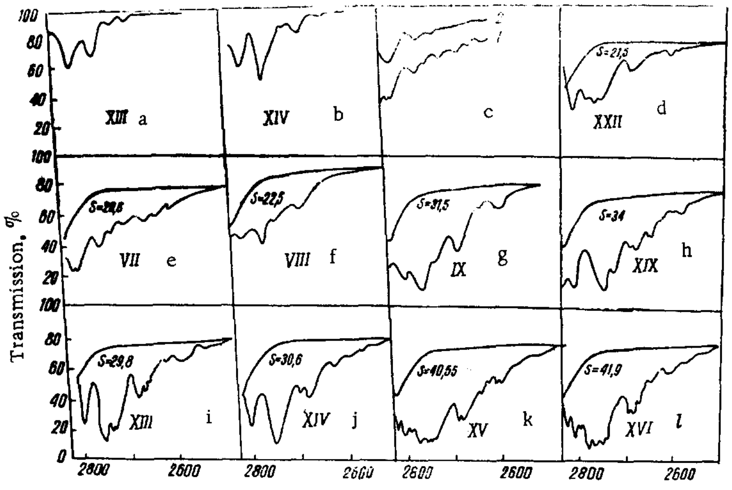


Fig. 1. IR spectra of compounds in solution: matrine (a), allomatrine (b), and aphylline in acetonitrile (1) and in carbon tetrachloride (2) (c); in the solid state: sophocarpine (d), aphylline (e), lupanine (f), pachycarpine (g), isosophoridane (h), matrine (i), allomatrine (j), matridine (k), and allomatridine (*l*).

On comparing the spectra, it can be seen that a transition in the solid phase changes the intensity and number of permitted absorption bands of almost all the alkaloids with different spatial structures. While for the bases with a labile conformation in solutions, such as piperidine [10, 11] and (I-III), these facts are quite natural, for rigid structures containing trans-quinolizidine fragments (VII-XI, and others), the spectral changes clearly show a considerable conformational instability of the nitrogen-containing moieties of these molecules in solutions. For example, in the spectrum of (XIII) (Fig. 1i) in the solid state the absorption at 2700 cm^{-1} is greatly reduced and that in the 2760 cm^{-1} region is considerably increased, while several new bands appear clearly (2630, 2650, 2660, 2730, and 2740 cm^{-1}).

Since all the bases differ from one another by the number of closely adjacent labile centers, and in some cases by the conformation of the whole structure, in solutions specific interactions in the process of successive inversion transformations are observed which affect the intensity of the vibrational transitions. A proof of the influence of this type of transformations is given by the changes in the intensity of the infrared transitions in the 2500-2830 cm^{-1} region with a change not only of the phase state but also of the polarity of the solvent.

Under the influence of the reaction field of the medium — a polar solvent, acetonitrile, reducing the rate of inversion [12] — the intensity of absorption of the IR bands of (VII) falls and, in addition, the band at 2800 cm^{-1} and the weak band at 2720 cm^{-1} shift by 10 cm^{-1} in the low-frequency direction (Fig. 1c, curves 1 and 2).

Compounds (VI) and (XVIII), just like (VII), exhibit scarcely any absorption bands in solution, but, in contrast to the latter, they do not absorb in the solid phase, either. This shows the lability of the conformations of (VII), the considerable spatial stability of (VI) and (XVIII), and the noncoplanar direction of the unshared pair and of the α-CH bond. The reason for this is the fixing of the A/B cis moiety of (XVIII) by the C ring and the unfavorable nature of intermediate conformations with a parallel direction of the α-CH bond and the unshared pair.

The base (VI) possesses the most stable conformation with an equatorial unshared pair. The absence of lability in the nitrogen-containing part of the molecule is due to steric hindrance of the inversion of the A/B moiety. The decrease in this hindrance in (IV) and (V) [the existence of inversion at N_1 in the product of the complete hydrogenation of (VI)] leads to dynamic transformations the intermediate forms of which contain an unshared pair parallel with the α-CH bond. The bases of the sparteine series differ from (VI) and (XVIII) by lability in rings A and D.

On comparing the results on the relative intensities of related structures, it may be concluded that the total integral intensity of the "Bohlmann region," which is used to determine the predominant direction of the unshared pair and the number of α-protons [2-4], is sensitive to the state of aggregation, the number of protons, and the shape of the potential surface on inversion, and also to distortions of the conformations in the solid phase which may be expressed in a very slight change in the dihedral angles between the directions of the unshared pair and the corresponding α-trans-C—H bonds.

In the group of bases (X, XI-XIV, and XIX), the total integral intensity is proportional to the number of axial protons with an accuracy of 5%.

In order to establish the number of feebly polar equatorial α-CH protons adjacent to the unshared pair of the nitrogen, the PMR spectra of all the bases listed were recorded on an H-60 (Hitachi) instrument in CS_2 solution (10%).

The number of geminal α-equatorial protons determined by integrating the signals of the PMR spectra in the 3.2-2.0 ppm region (see Table 1) corresponds to the number of axial protons found from the IR spectra.

The IR spectra of (VII) and (VIII) in the solid phase are identical, which is probably due to the fact that they have the same number of protons of similar nature. The close values of the areas of the IR bands of (XX, XXI, XXII) on the one hand, and (VII and VIII) on the other hand, in spite of the fact that the numbers of feebly polar protons are different, according to the PMR results, show the cis configuration of the C/D ring linkage in (VII) and (VIII) and the trans configuration of the A/B rings in (XX-XXII).

Consequently, the number of α-protons trans to the unshared pair can be determined by studying the IR spectra in the solid phase in association with the PMR results, where the positions of the signals of the feebly polar protons are less sensitive to the nature of these labile transformations.

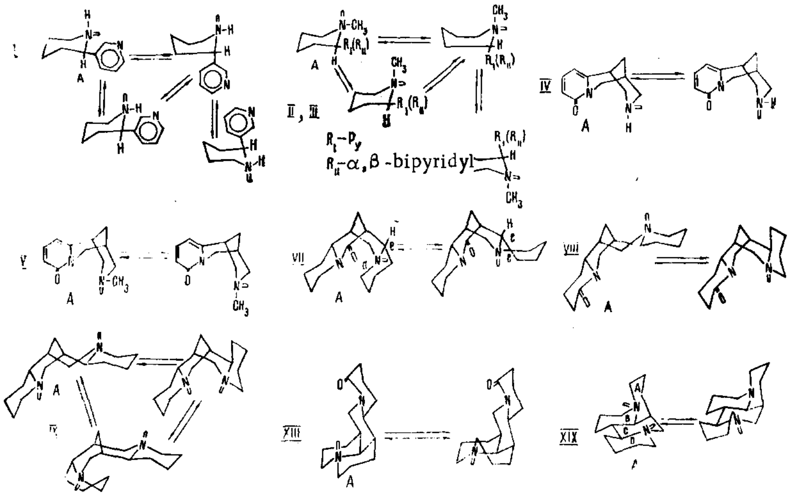
The linear relationship between the number of α-axial C—H protons and the total intensity (S) found for compounds with two quinolizidine rings is absent (for example, $S_{XIII} = 29.8$ cm^2, $S_{XV} = 40.55$ cm^2, $S_{XIV} = 30.6$ cm^2, and $S_{XVI} = 41.9$ cm^2 (Fig. 1, i, j, k, and *l*). A similar phenomenon has been reported [3] for solutions of sparteine (S = 34 cm^2) and α-isosparteine (S = 40.1 cm^2). Wiewiorowski et al. [3] consider that sparteine has a stable conformation with ring C in the boat form in which there must be six parallel axial protons. Our experiments show that this conclusion is not accurate, since

a) with an increase in the number of parallel α-axial protons S rises more slowly;
b) the values of S_{IX} and S_{XIX} in the solid state are similar (31.6 and 34.5 cm^2, respectively) (Fig. 1, g, h); and
c) the results of a comparison of intensities in the solid state for (VII) (S = 20.5 cm^2) and (VIII) (S = 22.5 cm^2) (Fig. 1, e, f) and integration in the 3.2-2.0 ppm region of the PMR spectra show the presence of four feebly polar α-protons, i.e., the conformations of the bases in solution may differ only by the nature of the inversion process in the C/D linkage.

On comparing the values of the total intensity of absorption, it can be seen that compounds of the matridine series and also bases with double bonds (XX, XXI, XXII) in the C/D ring system are characterized by reduced values of S (Fig. 1d). These changes are connected with the influence of remote nonbound interactions or with a deviation of the conformations of the unsaturated fragments from the normal chair-shaped state. According to the change in the intensity of the transition, these features of the structure of the bases may affect the geometry and state of the electrons of the unshared pair of the angular nitrogen in the A/B moiety.

On the basis of what has been said, the following types of labile conformational transitions including a change in the direction of the axis of the electron distribution of the unshared pair of the nitrogen atoms and some distortion of the geometry of the cyclic systems may be suggested (A represents the predominant conformation). (See scheme on following page.)

Taking into account the consequences of the Curtin-Hammett principle [13], the types of equilibrium that have been established due to the lability of the nitrogen-containing parts of the molecules of bases of the piperidine, cytisine, sparteine, and matrine series, permit the prediction of the direction of isomerization in the production of their stable N-derivatives (N-oxides, protonated forms, methiodides, etc.).



Thus, a consideration of the dynamic inversion processes with a simultaneous consideration of the magnetic parameters and the features of the IR spectra of alkaloids of the piperidine and quinolizidine series makes it possible to investigate in more detail the conformational states of nitrogen-containing heterocyclic bases.

SUMMARY

1. A comparative method of studying the conformational states of alkaloids of the piperidine and quinolizidine series by comparing the intensities of the IR bands in the 2500-2830 cm^{-1} region in the solid and liquid states has been proposed.

2. It has been shown that the process of inversion and other labile conformational transformations affect the number, frequency, and intensity of the vibrational transitions in the "Bohlmann region."

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