INVESTIGATION OF THE LABILITY OF THE CONFORMATIONS OF SOME ALKALOIDS OF THE QUINOLIZIDINE SERIES

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The investigation of the spatial structure of natural bases containing piperidine and quinolizidine fragments is connected with the study of the conformational properties of these systems due to the labile centers in the molecule. While for piperidine at least two types of transformations can be isolated [1] (the conversion of the ring and the inversion of the unshared pair of the nitrogen), for the complex molecules of the alkaloids of the C_{15} series a greater diversity of these transformations must be assumed in view of the number of types of lability and the possibility of the inhibition of conversion and inversion processes.

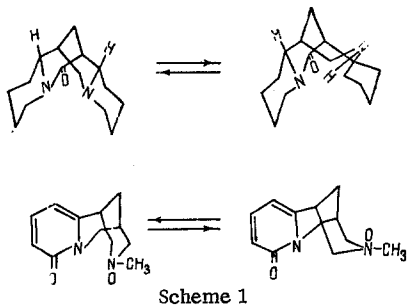
Thus, in a paper by Anisimova, Kost, et al. [2], the hypothesis was put forward that the IR spectra of piperidine, N-methylpiperidine, and N-dueteropiperidine in the liquid state show the bands of the vibrations of two conformations, while when they are frozen they show the vibrational spectra characteristic for a single configuration. The bonds that disappear at low temperatures were ascribed to the vibrations of the *a* conformation (axial N–H bond).

In order to determine the lability of the conformations of the quinolizidine alkaloids, we considered the IR spectra of lupinine (I), epilupinine (II), N-methylcytisine (III), isoaphylline (IV), α-isolupanine (V), and aphyllidine (VI) in the solid and dissolved states. In these cases, the changes in the spectra may depend on the specific interaction of the bases with the molecules of the solvent, changes in the conformations during the phase transition, and the presence of new conformations, the appearance of which is a consequence of complex inversion transformations which are impossible in the solid state.

The IR spectra of the alkaloids were recorded on a UR-10 (K. Zeiss) instrument at a recording rate of 50 cm^{-1}/min. The samples were crystalline, in the form of tablets (3 mg of base in 300 mg of KBr) or in solutions with a concentration of 0.4 M with a thickness of the NaCl cell of 0.15 mm. Purified CS_2 was used as the solvent.

As can be seen from Table 1, the disturbance of the crystal lattice by the solvent leads to the appearance of a series of new bands and to changes in the frequencies of some bands ascribed mainly to complex deformation and pulsation vibrations of these cyclic molecules.

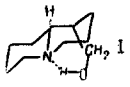
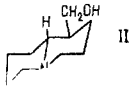
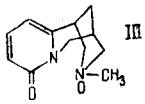
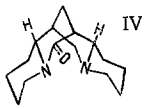
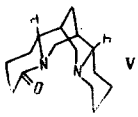
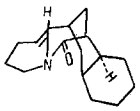
The present paper gives the results of a study of bases which, unlike piperidine and N-methylpiperidine do not participate in processes accompanied by exchange between axial and equatorial C–H bonds.



Scheme 1

V. I. Lenin Tashkent State University. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 49-54, January, 1971. Original article submitted May 26, 1970.

TABLE 1. Change in the Absorption Bands in the IR Spectra of CS_2 Solution (0.4 M) as Compared with the Spectra of the Solid Phase

Compound	Bands in solution, cm^{-1}	
	disappearing	arising
 I	555, 585, 655, 750, 875, 955, 980, 1000, 1255, 1305, 1345	565—700 (broad band), 720, 740, 770, 790, 865, 885, 940, 1020, 1220, 1265
 II	545, 750, 970, 1050, 1160, 1205, 1225	540 (broadening band) 630, 670, 715, 970, 980, 1210, 3630 (free OH group)
 III	515, 720, 770, 810, 1290, 1455	730, 740—765, 825, 845, 970, 1325
 IV	515, 545, 565, 790	605, doublet 960 and 965, 1370
 V	525, 550, 575, 1360	500—525 (broad band) 675—700 (broad band) 785, 1100, 1350
 VI	525, 640, 800, 1200	520—540 (broad band) 640, 655, 675, 800, 830, 1220

The only form of lability which molecules acquire after dissolution is possible by the inversion of the bonds and the unshared pair of electrons about the nitrogen atom. In the liquid phase at the normal temperature trough-shaped forms of the molecules may arise (Scheme 1), since the potential barrier to inversion in tertiary amines is 7.46-9.2 kcal/mole [3].

This transition takes place through vibrations increasing the angle between the C—N bonds and lengthening them. It is obvious that these movements are restricted in the crystal, i.e., in the crystals the frequencies of these types of vibrations must rise and their intensities must decrease.

For cyclic trialkylamines such bands are the C—N stretching vibrations at 827 cm^{-1} and the deformation vibrations at 365 cm^{-1} [3]. The inhibition of inversion in the solid phase is shown in a change of more than two vibrational coordinates and, therefore, the calculation of the inversion barrier by means of the simple formula $V = \frac{3}{2}[k_1(\Delta l)^2 + k_2(\Delta\alpha)^2]$ for these structures is not obligatory even in the case of the introduction of spectroscopic masses in place of cyclic alkyl radicals.

The difference is observed most clearly in the change of the vibrational characteristics for lupinine and epilupinine (Fig. 1). The spectrum of solid epilupinine has three bands: 545 (narrow), 607, and 705 cm^{-1}, while in solution the 540 cm^{-1} band is broadened, the 705 cm^{-1} band is shifted to 715 cm^{-1}, and two strong bands appear at 630 and 670 cm^{-1}. In lupinine in the solid phase there are four bands: 525, 585, 655, and 705 cm^{-1}.

In the liquid state, bands at 550 and 710 cm^{-1} are clearly traced, and the other vibrations form two broad overlapping bands in the 500 and 570-650 cm^{-1} regions.

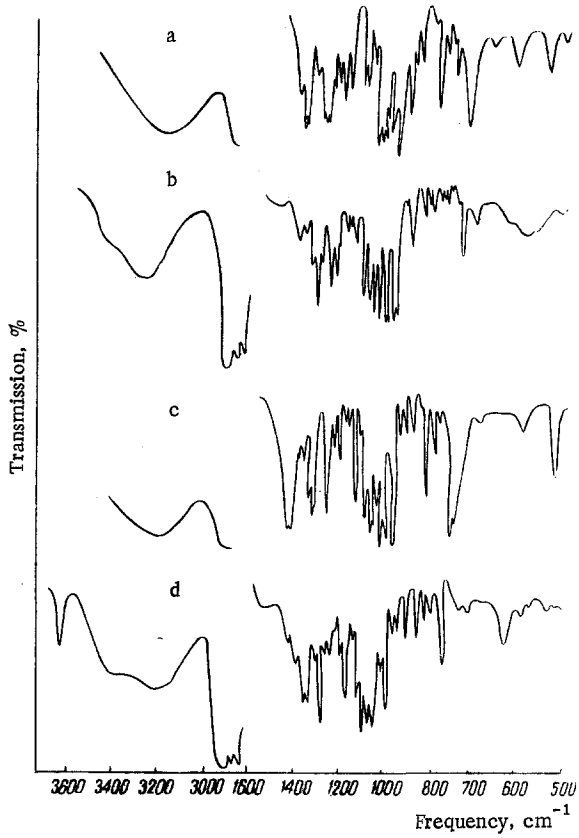


Fig. 1

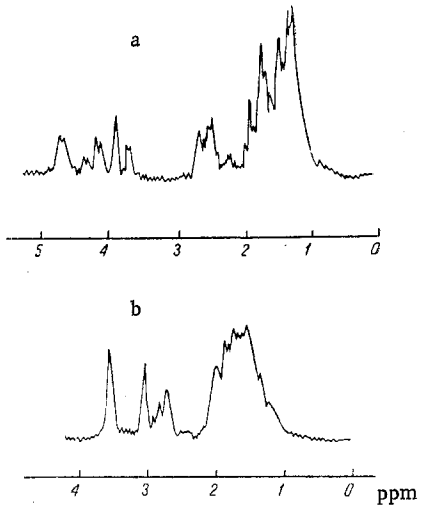


Fig. 2

Fig. 1. IR spectrum of lupinine and epilupinine in the solid phase (a, c) and in CS_2 solution (b, d).

Fig. 2. NMR spectrum of lupinine (a) and that of epilupinine (b) in C_6H_6 (10%) at 60 MHz.

In the spectra of all the bases there is a band at 740, 770 cm^{-1} which is shifted in the low-frequency direction in solution ($\Delta\nu$ 10-20 cm^{-1}). The band at 800-820 cm^{-1} behaves similarly. The changes in the frequencies of epilupinine and (III) are similar. In solid (III) bands are seen clearly at 515, 535, 570, 615, 660, 705, and 720 cm^{-1}. Substances (IV), (V), and (VI) behave similarly, with the exception of some details (see Table 1).

The differences in the changes in the vibrational characteristics of lupinine on passing from the crystalline state to the dissolved state can be explained by the formation of a comparatively stable additional ring through an intramolecular hydrogen bond of the $-CH_2OH$ axial group with the axial unshared pair of the nitrogen. The presence of an intramolecular hydrogen bond in lupinine has been shown previously [4-7] and is confirmed by our results (weak band at 3630 cm^{-1} of a free hydroxyl, the relative intensity of which does not rise on dilution, and the shape of the band at 3100-3500 cm^{-1} in comparison with the case of epilupinine) (see Fig. 1).

The additional ring in lupinine is possibly fairly stable and therefore in solutions its formation has a considerable influence on the pulsation and deformation vibrations of the quinolizidine ring. To confirm this, we recorded the NMR spectra of 10% solutions of lupinine and epilupinine in CCl_4 and C_6H_6 on H-60 (Hitachi) (Fig. 2) and HA-100 (Varian) (Fig. 3) instruments.

In the spectrum of epilupinine (C_6H_6) there are the signals of two equivalent protons at 3.5 ppm, of a hydroxy group at 3 ppm, of two equatorial α-protons located in the α position to the nitrogen atom at 2.72 ppm, and those of the other protons at 1-2.2 ppm. In contrast to epilupinine, lupinine (benzene solution) has the signal of the OH proton at 4.65 ppm (same concentration as for epilupinine) and the methylene protons of the CH_2OH fragment form the AB part of an ABXY system, proton A giving δ 4.0 ppm, J_{AB} = 11.6 Hz, J_{AX} = 6 Hz. Proton B gives a signal at 3.65 ppm with J_{AB} = 11.6 Hz and J_{BX} = 3 Hz. This multiplet structure is not disturbed when the sample is diluted.

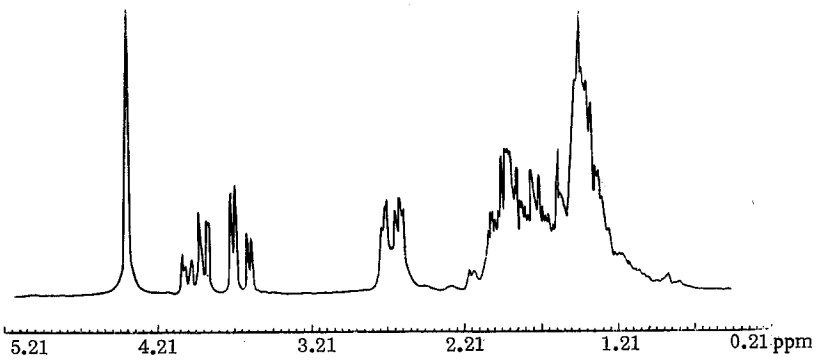


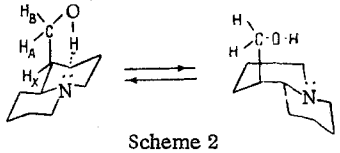
Fig. 3. NMR spectrum of lupinine at 100 MHz.

A comparison of the spectrum taken on the H-60 instrument with that obtained at 100 MHz, although the general pattern is preserved, reveals new details, namely long-range spin-spin coupling (≃1 Hz) of the H_A proton, apparently with the axial proton at C_8 of the quinolizidine ring. Since long-range couplings between H and the C_6 proton are not shown, this, together with the relative values of the vicinal constants J_{AX}, J_{BX}, shows a departure from the purely chair conformation of the intramolecular hydrogen bond of the ring.

Consequently, in lupinine the position of H_A is pseudoaxial and that of H_B pseudoequatorial. The third proton of the quinolizidine ring H_X at C_7 is pseudoequatorial with respect to this new ring.

The two equatorial α-protons have a chemical shift of 2.82 ppm, and the signal of the axial protons is resolved to a better extent than in epilupinine (1.6-2.2 ppm).

The formation of an intramolecular hydrogen bond in lupinine leads to a fall in the rate of inversion. In actual fact, if the lability of this center of lupinine is expressed in a change in the direction of the unshared pair together with the corresponding rotation of the C–N bond, this process must lead to a disturbance of the intramolecular hydrogen bond and of the ring, for which an additional consumption of energy of 3-4 kcal/mole is required (Scheme 2).



Scheme 2

However, the low value of the inversion barrier in this case makes it impossible to investigate this process in more detail by using low-temperature technique. Consequently, a comparative study of the IR and NMR spectra of a group of nonconverting bases of the quinolizidine series enables some features of the process to be determined in dependence on the details of the structure of the molecules.

SUMMARY

The IR and NMR spectra of lupinine, epilupinine, and a series of other alkaloids of the quinolizidine series have been studied.

It has been shown that the inhibition of the inversion processes in the molecules of the alkaloids in the solid phase is revealed in a change in the nature of the absorption in the 500-1200 cm^{-1} region.

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