CONFORMATIONAL TRANSFORMATIONS OF THE ALKALOIDS LUPININE AND TROPINE ON THE FORMATION OF THEIR N-OXIDES

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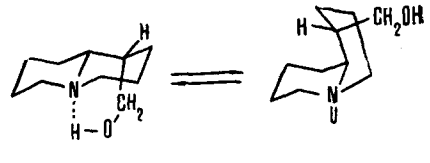
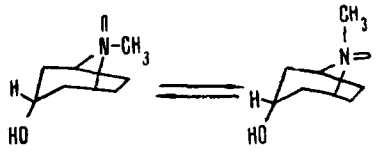
Chemical investigations have shown the fairly high conformational stability of the trans-quinolizidine system of lupinine [1] and of the bicyclic system of tropine [2], but the presence of a nitrogen atom with an invertible lone pair of electrons permits the assumption that it is possible to obtain from these bases isomeric derivatives the concentrations (yields) of which will, to a first approximation, be directly proportional to the lifetimes of the invertomers and to the rate of the reaction of the reagent with them.

In actual fact, if it is assumed that the process of inversion of lupinine leads to a change in the direction center from "a, a" to "e, a," and in tropine from "a" to "e," then because of steric hindrance in the attack by the reagent of the "a, a" and "a" forms, in spite of the considerable predominance of these conformations in solution in accordance with the Curtin–Hammett rule [3], it will be possible to isolate the isomeric compounds corresponding to the "e, a" and "e" forms in considerable relative amounts.

We have obtained the N-oxides of lupinine and tropine under mild conditions by mixing the initial bases with 5% H_2O_2 in water at room temperature. Lupinine formed two isomeric N-oxides (I and II), the separation of which was effected by solubilities, their individualities being checked by chromatography in a thin layer of Al_2O_3 [benzene–ether–methanol (5 : 2 : 1) system].



a,a e,a



a e

In the mass spectrum of the lupinine N-oxide (I) (Fig. 1a) there is the peak of the molecular ion with m/e 185, and the strongest peaks are those at 168, 138 (100%), 136, and 83; in the spectrum of the lupinine N-oxide (II) (Fig. 1b) there are peaks with m/e 185, 152, 136 (100%), 110, 97, and 83. On comparing the mass spectra of the two lupinine N-oxides it can be seen that the differences in the conformation affect the routes of decomposition of the isomers.

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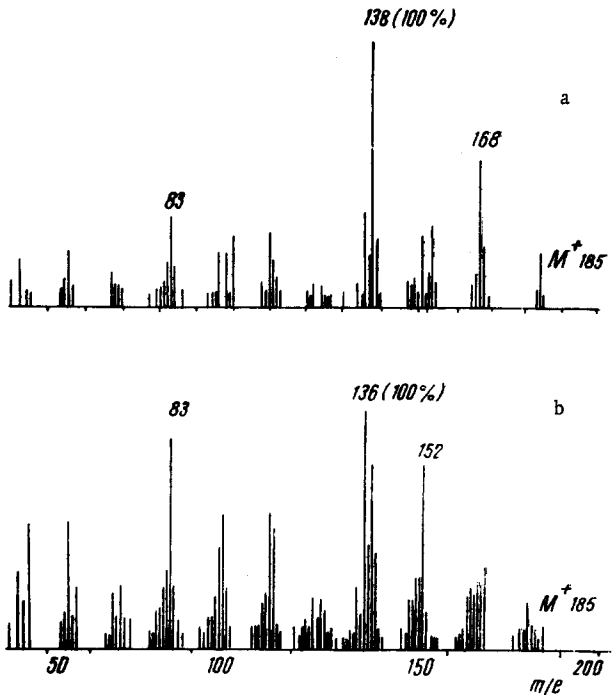
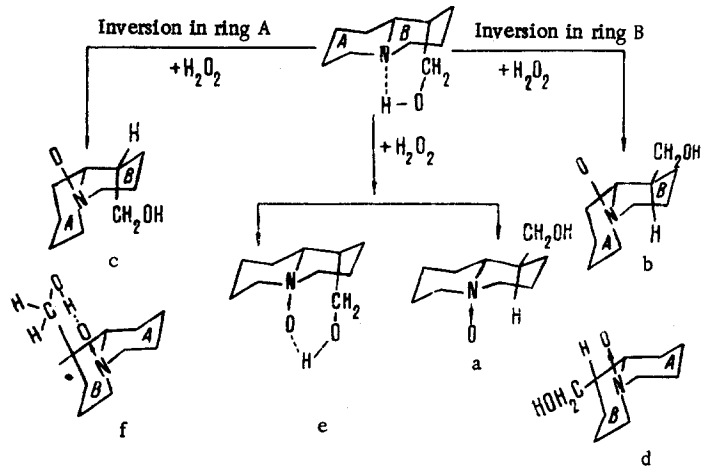


Fig. 1. Mass spectra of the N-oxides of lupinine (I) (a) and (II) (b).

The IR spectra of the lupinine N-oxides differ from one another, especially in the 500-1200 cm^{-1} region which is characteristic for the pulsation and skeletal vibrations of the ring. The spectrum of the lupinine N-oxide (I) has an N → O band in the 950 cm^{-1} region, while in (II) this band is split into three (930, 940, and 950 cm^{-1}). In the 3200-3600 cm^{-1} region the first isomer shows a strong broad band relating to the stretching vibrations of a hydroxy group involved in an intramolecular hydrogen bond, and in the second it appears in the 3350-3600 cm^{-1} region. No band of a free hydroxy group is observed even at a concentration of the base of 0.002 M (cell thickness 0.60 mm). In tropine N-oxide, the N → O band is found in the form of a doublet in the 930, 950 cm^{-1} regions.

The existence of isomeric lupinine N-oxides is explained by an inversion equilibrium between the spatial forms of the bases.



Theoretically, the existence of six isomers of lupinine N-oxide in the all-chair conformation is possible, form "a" arising on epimerization at C_1, forms "c" and "f" on the inversion of ring A, and forms "b" and "d" through the inversion of ring B. The isomers "e" and "f" may have an intramolecular hydrogen bond.

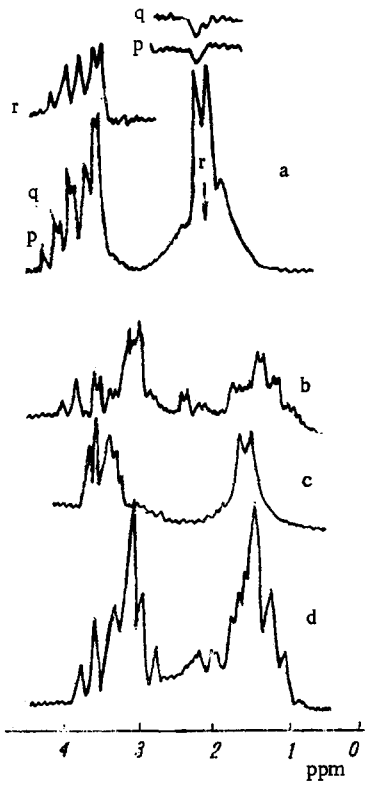


Fig. 2

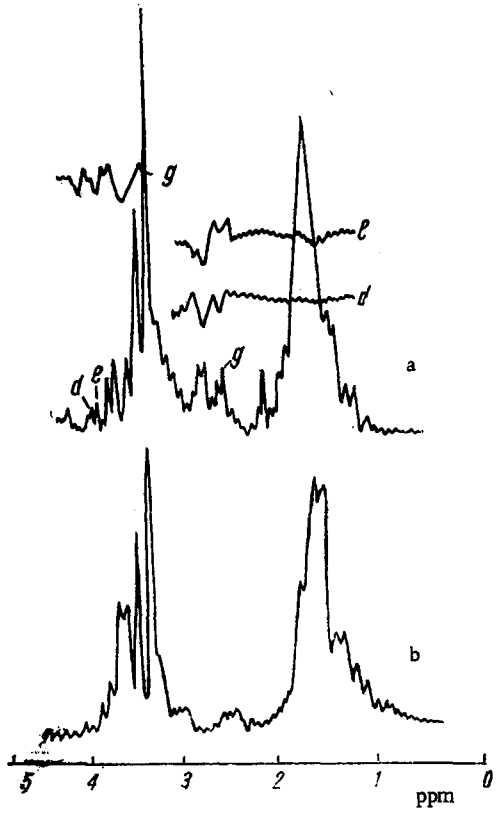
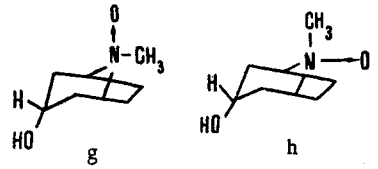


Fig. 3

Fig. 2. PMR spectrum of lupinine N-oxide (I) in D_2O (a), in conc. HCl (b), in pyridine (c), and in chloroform (d), and INDOR spectra in D_2O (p, q, r) (r – total resonance).

Fig. 3. PMR spectra of lupinine N-oxide (II) in D_2O (a) and in conc. HCl (b), and the INDOR spectra in D_2O (g, d, e).



Two forms of tropine N-oxide are possible in solution, differing by the spatial position of the methyl group ("g" and "h").

To determine the spatial structure of the lupinine and tropine N-oxides obtained, we studied their PMR spectra. The PMR spectrum of lupinine N-oxide (I) in D_2O (Fig. 2a) differs considerably from the spectrum of the initial base [4], in particular by the fact that there is a larger number of protons in the weak field. A multiplet of the AB part of a ABXY system of nonequivalent protons of a hydroxymethylene group clearly appears at 4.1 and 3.8 ppm, and the hydroxy group of this system forms an intramolecular hydrogen bond with the N-oxide group. The presence of a hydrogen bond is shown by the conversion of the multiplet mentioned into a doublet at 3.7 ppm with $J_{vic} = 6$ Hz after the breakage of the intramolecular hydrogen bond $>N \rightarrow O \ldots H$ in conc. HCl (Fig. 2b). Integration shows that in this region there are five other protons occupying the α positions about the $N \rightarrow O$ group. The identity of the sign of the angle of rotation of lupinine N-oxide (I) with that of the initial base ($[\alpha]_D$ of lupinine is $-21°$), the results of integration, and the existence of an intramolecular hydrogen bond (not destroyed in pyridine, Fig. 2c) permit the conclusion that this isomer contains an axial $N \rightarrow O$ bond with respect to the A and B rings and an axial CH_2OH group.

The spectrum in chloroform (Fig. 2d) shows the presence of one molecule of water of hydration (9.0 ppm), the retention of the nonequivalence of the CH_2-OH protons, and the symmetrical action of the

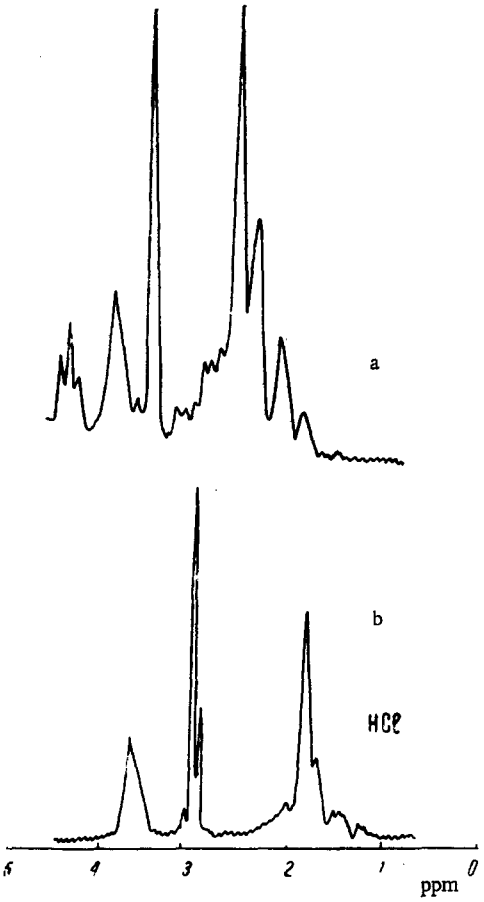


Fig. 4. PMR spectra of tropine N-oxide in D_2O (a) and in conc. HCl (b).

field of the N → O group on the α-CH_2 protons at C_5 and C_6. Thus, the conformation of the isomer under consideration corresponds to form "e."

By the method of INDOR double resonance at the lines of the feebly polar protons (Fig. 2p, q) of the hydroxymethylene group at 4.2 and 4.0 ppm the presence of the signals of a tertiary proton at C_1 was established (2.1-2.2 ppm). Complete decoupling from the signal of the C_1 proton (Fig. 2r) showed the contraction of the lines of the multiplet of the nonequivalent hydroxymethylene protons.

In the PMR spectrum of lupinine N-oxide (II) (Fig. 3a), again an intramolecular double bond appears as in shown by the AB multiplet from the ABXY system at 4.1 and 3.8 ppm. In the same region are located the signals of the protons α to the nitrogen atom, which are fewer judging from integration than in the first isomer. One of the α-protons to N → O is found in the strong-field region at 3.0 ppm with $J_{gem} = 12$ Hz. The protonation of lupinine N-oxide (II) (Fig. 3b) shifts the signal of the proton to 3.3 ppm. A multiplet with $\delta = 2.6$ ppm and a width of 30 Hz corresponds to the tertiary proton at C_1.

The unsymmetrical action on the α-CH_2 protons of the N → O group, the position of the signal of the tertiary proton at C_1, the intramolecular hydrogen bond, and the change in the sign of the angle of rotation as compared with lupinine permit the conclusion that conformationally this isomer belongs to the cis series with a N → O group axial to the B ring and equatorial to the A ring, and an axial CH_2–OH. The isomer corresponds to form "f."

The INDOR experiment with respect to the lines of the quartet of the feebly polar proton of the hydroxymethylene group showed responses in the 2.8 ppm region. These confirm the position of the tertiary proton at C_1.

The signal of one of the equatorial protons is found in the region under consideration, as follows from another INDOR experiment on the resolution of the lines at 2.6 ppm, which gave a response at about 4.17 ppm with $J_{gem} = 12$ Hz (Fig. 3g, d, and e).

Two N-oxide forms were detected in the spectrum in conc. HCl of the tropine N-oxide obtained (Fig. 4b). The protons at C_6, C_2, and C_4 were represented by an unresolved signal at C_6, C_2, and C_4 were represented by an unresolved signal at 4.2 ppm, and the protons of the methylene bridge, and at C_3 and C_5 by signals in the 1.5-2.7 ppm region. At 3.4 ppm there were two narrow singlets (3.3 and 3.4 ppm) with an intensity ratio of 1: 2.6. These two singlets are the signals of the protons of axial and equatorial methyl groups of the isomeric tropine N-oxides.

In the spectrum of tropine N-oxide in D_2O (Fig. 4a), the chemical shifts of the methyl groups almost coincided at 3.2 ppm, and the protonation of the oxygen of tropine N-oxide increased the difference in the descreening of these protons. Furthermore, the equatorial proton at C_4 is represented by a pseudotriplet at 4.3 ppm, the protons at C_2 and C_6 are located at 3.8 ppm, and the others in the 1.8-3.1 ppm region.

An additional proof of the equivalence of the methyl groups in the nonprotonated forms is their magnetic equivalence in a quaternary salt [5]. In the protonated form of tropine N-oxide in solution the isomer with the axial CH_3 group apparently predominates.

Thus, the formation of derivatives in reaction involving the nitrogen atom in the bicyclic systems of quinolizidine and tropane with the introduction of groups of which the van der Waal's volume is smaller than that of CH_3 permits the presence of equilibrium conformational transitions in them in solutions to be detected chemically. Steric hindrance and the formation of intramolecular hydrogen bonds are factors determining the structure of the end-products and the predominant direction of the shift of the inversion-conformation equilibrium in solution.

EXPERIMENTAL

The IR spectra were taken on a UR-10 instrument (C. Zeiss) in the form of tablets with potassium bromide and in solutions and concentrations of 0.2 and 0.002 M (thickness of the NaCl cells 0.39 and 0.60 mm). Purified chloroform was used as the solvent.

The PMR spectra were recorded on an H-60 instrument (Hitachi) with a working frequency of 60 MHz.

Preparation of the N-Oxides of Lupinine and Tropine. A. Lupinine (4 g) was dissolved in 80 ml of 5% H_2O_2, and the reaction mixture was left for three days. The water was distilled off from the mixture under water-pump vacuum at a temperature not exceeding 40-50°C. The residue, which consisted of a mixture of the two lupinine N-oxides, was boiled with ether. The concentrated ethereal mother solution deposited white acicular crystals of lupinine N-oxide I with mp 83-84°C, $[\alpha]_D^-$ 19.84° (c 1.003%; methanol). Yield 0.8 g (25.9%).

The residual crystals that had not passed into the ethereal solution were treated repeatedly with boiling dry acetone. The acetone mother solution yielded lupinine N-oxide II with mp 193-195°C; $[\alpha]_D^+$ 29.8° (c 1.026%; methanol). Yield 3.0 g (68.65%).

B. Under the conditions for obtaining the lupinine N-oxides, 3 g of tropine gave tropine N-oxide with mp 102-103°C.

SUMMARY

1. It has been shown that in the chemical reactions for obtaining the N-oxides of lupinine and tropine the bicyclic systems of quinolizidine and tropane exhibit a conformational lability due to inversion.

2. On the basis of IR and PMR spectra the structure and conformation of the isomeric N-oxides of lupinine and tropine have been determined.

LITERATURE CITED

1. F. Galinovsky and H. Nesbadba, Monatsh. Chem., 85, 1300 (1954).
2. G. Fodor, J. Toth, and J. Vincze, J. Chem. Soc., 1955, 3504; G. Fodor, and O. Kovacs, J. Chem. Soc., 1953, 724.
3. E. Eliel, Stereochemistry of Carbon Compounds, McGraw-Hill (1962).
4. T. K. Yunusov, A. I. Ishbaev, V. B. Leont'ev, and A. S. Sadykov, Khim. Prirodn. Soedin., 49 (1971).
5. G. Closs, J. Amer. Chem. Soc., 81, 5456 (1959).