DETERMINATION OF THE CONFIGURATION OF QUINOLIZIDINE ALKALOIDS WITH A LACTAM GROUP

A. I. Begisheva, Kh. A. Aslanov,
Z. U. Petrochenko, and A. S. Sadykov

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One of the most convenient methods for determining the configuration of quinolizidine alkaloids is the IR spectroscopic method of Bohlmann et al. [1, 2]. However, this method does not permit the determination of the nature of the linkage of a quinolizidine nucleus containing a lactam group.

By blocking the noninert nitrogen atom and subsequent reduction of the lactam group in the second quinolizidine nucleus it is possible to obtain products, the IR spectroscopic investigation of which shows the configuration of this fragment of the molecule.

The lithium aluminum hydride reduction of the lactam groups in the methiodides of allomatrine [3], isosophoridine [4], aphylline [5], and 17-oxosparteine [6] (the configurations of which have been definitively established and are not subject to doubt) leads to the corresponding desoxo derivatives (Table 1).

The IR spectra of the methiodides have the bands of the lactam carbonyl (1640 cm^{-1}), and absorption in the 2800-2700 cm^{-1}, which is characteristic for trans-quinolizidine, is absent. In the spectra of the reduction products, the band of the lactam carbonyl has disappeared and in each case the 2800-2700 cm^{-1} region corresponds to the type of quinolizidine compound determined previously (Fig. 1). The results obtained show that this method can be applied successfully to the determination of the configuration of the lactam-containing moiety of the quinolizidine alkaloids.

We have used this method to study the configuration of the C/D linkage of sophoridine [7], as a result of which the cis-C/D configuration (I) reported previously [8-10] was confirmed. Kamalitdinov et al. [11] proposed configuration II (ring C in the boat form) for sophoridine on the basis of the fact that the dehydrogenation of sophoridine with mercury acetate forms 5-hydroxy-6,7-dehydromatrine (V), which is also formed from matrine (III) where the C/D rings have the trans linkage. Let us consider the formation of one and the same 5-hydroxy-6,7-dehydro compound from matrine and allomatrine.

In the molecule of matrine (III), the hydrogen atom attached to C_5 has the e-,a orientation (A/C) and the 1,3 e,a mutual arrangement with the free electron pair of N_1, while in allomatrine (IV) it has the a-,a orientation (A/C) and is 1,3-diaxial with the free pair of the nitrogen atom. The hydrogen atoms at C_{11}, although they are axial-axial in both cases, are nevertheless located on different sides of the plane in relation to the π electrons of N_1. Since on dehydrogenation both isomers give the same product, it must be assumed that the deformation of the rings as a result of the formation of the double bond (in the central por-

TABLE 1

Base	Methiodides		Products of the reduction of the methiodides	
	mp, °C	$[\alpha]_D$, deg	mp, °C	$[\alpha]_D$, deg
Allomatrine	295,0	+49,28	235,0	+58,90
Isosophoridine	317,0	+64,52	234,0	+25,14
Aphylline	204,5	+62,22	194,0	+56,04
17-Oxosparteine	212,0	+73,19	193,0	+14,49
Sophoridine	237,0	−43,52	234,0	−22,55

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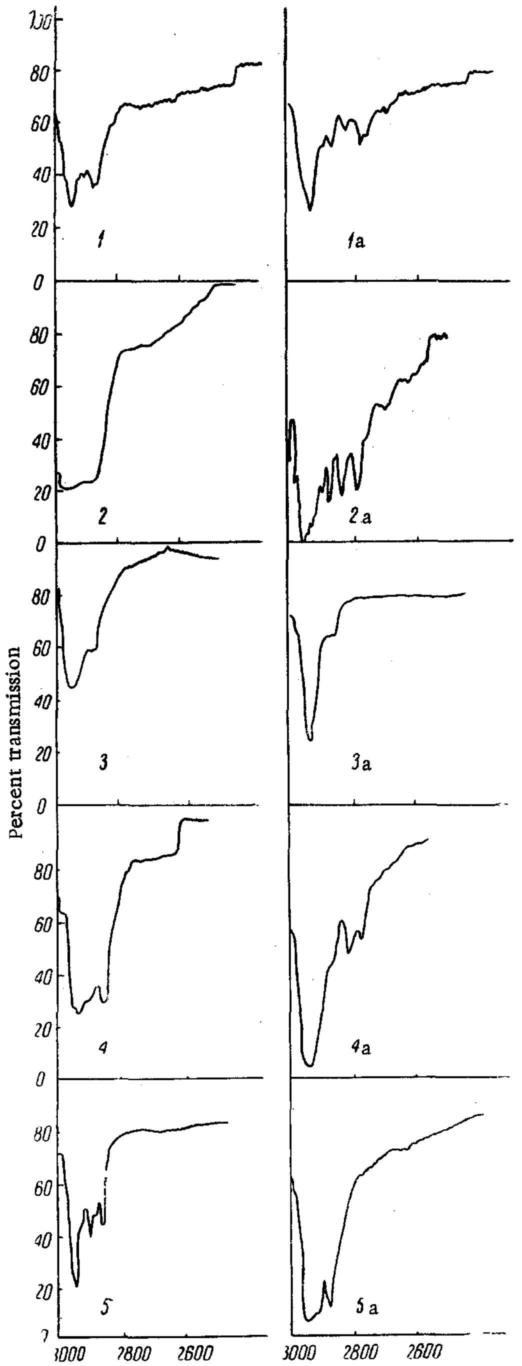
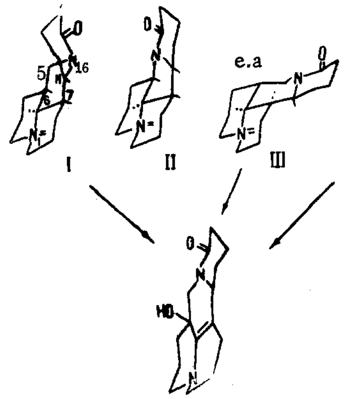


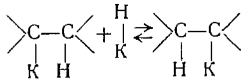
Fig. 1. IR spectra of the methiodides of the corresponding reduction products of the methiodides (a): 1) allomatrine; 2) isosophoridine; 3) sophoridine; 4) aphylline; 5) 17-oxosparteine.

tion of the molecule) leads to a change in the orientation of the bonds at the α-carbon atoms, i.e., at C_5 and C_{11}.



These statements agree with the configuration of the bonds at the α-carbon atoms established for cyclohexene [12]. The formation from sophoridine of a dehydro product identical with 5-hydroxy-6,7-dehydromatrine can be explained in the same way.

In the paper by Kamalitdinov et al. [11], the mechanism that we proposed for the isomerization of the matrine alkaloids [10] is categorically subjected to doubt. A distinction must be made between the mechanisms of the isomerization of the quinolizidine bases over Pt/H_2 in acetic acid and that of their hydrochlorides on fusion. In the latter case, the process takes place only when in a cis-quinolizidine system there is a nitrogen atom capable of forming a salt, since isomerization under the conditions of catalytic hydrogenation is specific with respect to the arrangement of the neighboring hydrogen atoms and the possibility (condition) for a reversible process in the stage



$$>\underset{K}{C}-\underset{H}{C}< + \overset{H}{\underset{K}{|}} \rightleftarrows >\underset{H}{C}-\underset{K}{C}<$$

and it does not depend on the degree of basicity of the nitrogen in the quinolizidine fragments. This is shown by an enormous number of facts from the study of the stereochemistry of catalytic reactions, especially over Pt/H_2, of derivatives of decalin, perhydroanthracenes, steroid compounds, etc. [13], where acetic acid is also one of the best solvents for performing the reaction, although there is no nitrogen in these molecules.

In heterocyclic compounds, however, the role of the heteroatom in these reactions consists only in the fact that it may affect the mobilities of the atoms of the neighboring points in dependence on its state. Kamalitdinov et al. [11] consider that in the catalytic reaction over Pt/H_2 the "dominating role" is played by the nitrogen and, since in sophoridine N_{16} is inert, the C/D linkage cannot change the configuration. These authors endeavored to support their conclusions by the fact that 17-oxosparteine remains unchanged under these conditions. According to this, in the reaction under consideration aphylline should be isomerized (there is no lactam in the cis nucleus), but it does not in fact isomerize. It will be erroneous simply to consider two completely different structures, the matrine and sparteine structures, since in the latter there is a "rigid" bridge system which ensures the specificity of the results of the dehydrogenation and hydrogenation of these systems and, consequently, their isomerization as well. The significance of the lactam group in the C/D linkage of the matrine alkaloids, as mentioned above, consists in a certain influence which it has on the mobility of the protons.

This is clearly seen from our previous paper [10], where it is shown that sophoridine (containing a lactam group) is isomerized completely to isosophoridine over Pt/H_2 in glacial CH_3COOH, while its lactam-free derivative remains unchanged.

Thus, all the facts completely confirm the hypothesis which we put forward concerning the reactivity of lactam-containing quinolizidine systems in isomerization reactions.

EXPERIMENTAL

The IR spectra were taken on a UR-10 instrument (tablets with potassium bromide). The melting points were determined on a Kofler block and the $[\alpha]_D$ values in ethanolic solutions. The analyses of the compounds corresponded to the calculated figures.

The methiodides of allomatrine, isosophoridine, sophoridine, aphylline, and 17-oxosparteine were obtained by boiling the corresponding bases with a small excess of methyl iodide in acetone. The methiodides were washed with acetone and were then recrystallized from acetone–ethanol (1 : 1) (see Table 1).

Products of $LiAlH_4$ Reduction. The appropriate methiodide (1 g) was finely dispersed in 100 ml of absolute ether and was reduced with 0.6 g of $LiAlH_4$ in 100 ml of absolute ether. The reaction mixture was shaken for 30-40 min and was then boiled for 4 h. After cooling, the excess of $LiAlH_4$ was decomposed with water. The ethereal layer was separated off and the residue (a curd-like mass) was washed repeatedly with absolute ethanol. After the elimination of the solvent, the residue, which contained the reduction product and a very small amount of the initial methiodide, was chromatographed on columns of Al_2O_3 (activity grade II), the products being eluted with a mixture of acetone and ethanol (1 : 1).

Elimination of the solvent from the fractions containing the pure reduction product gave the latter in the crystalline state. The composition of the product of the reduction of sophoridine methiodide was $C_{16}H_{29}N_2I$.

SUMMARY

A method has been proposed for the determination of the configuration of lactam-containing quinolizidine alkaloids.

LITERATURE CITED

1. F. Bohlmann, Chem. Ber., 91, 2157 (1958).
2. F. Bohlmann, W. Weise, D. Rahtz, and C. Arndt, Chem. Ber., 91, 2176 (1958).
3. K. Tsuda and H. Mishima, Pharm. Bull. (Tokyo), 5, 285 (1957).
4. F. Rulko, Zh. Obshch. Khim., 32, 1695 (1962).
5. A. I. Ishbaev, A. S. Sadykov, and Kh. A. Aslanov, Zh. Obshch. Khim., 35, 194 (1965).
6. A. P. Orekhov, I. I. Kabachnik, and P. Ya. Kefeli, Dokl. Akad. Nauk SSSR, 31, 334 (1941).
7. A. I. Begisheva, Z. U. Petrochenko, Kh. A. Aslanov, and A. S. Sadykov, Khim. Prirodn. Soedin., 455 (1969).
8. F. Rulko and N. F. Proskurnina, Zh. Obshch. Khim., 32, 1690 (1962).
9. A. I. Begisheva, Kh. A. Aslanov, and A. S. Sadykov, Khim. Prirodn. Soedin., 371 (1968).
10. Kh. A. Aslanov, A. S. Sadykov, V. B. Leont'ev, and A. I. Begisheva, Khim. Prirodn. Soedin., 93 (1969).
11. D. D. Kamalitdinov, S. Iskandarov, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 409 (1969).
12. E. Eliel, N. Allinger, S. Angyal, and G. Morrison, Conformational Analysis, Interscience, New York (1965).
13. E. Eliel, Stereochemistry of Carbon Compounds, McGraw-Hill, New York (1962).