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ISOMERIZATION OF THE ALKALOIDS OF THE MATRINE SERIES OVER Pt/H_2

Kh. A. Aslanov, A. S. Sadykov, V. B. Leont'ev, and A. I. Begisheva

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Results of a comparison of the stereochemical behavior of polycyclohexane compounds and ali-heterocyclic compounds show that the extension of the main principles of conformational analysis [1, 2] to the latter requires the introduction of corrections because of the specific influence of the heteroatom. A heteroatom, especially nitrogen, in saturated rings may, in addition to exerting the usual inductive influence, interact specifically with the neighboring bonds, namely: 1) in the case of a planar arrangement of the axis of the electron cloud of a sp^3 unshared pair and an α-C–H bond, the passage of the electrons of the nitrogen to the antibonding orbital of this bond is possible, as is found in the IR and NMR spectra of the quinolizidine alkaloids [3, 4]; (because of this interaction, there must be a decrease in the energy of α-trans-axial C–H bonds), and 2) the repulsion of the electrons of the unshared pair from the electrons of the neighboring groups or bonds must have a definite influence on the configuration of the molecule.

To determine the influence of these features of the nitrogen atom in complex alicyclic systems, we have used the isomerization of the alkaloids of the matrine series over Pt/H_2 in acetic acid.

Base	Products obtained
Allomatrine	Allomatrine
Matrine	40% of allomatrine + 60% of matrine
Sophoridine	Isosophoridine
Isosophoridine	Isosophoridine
Allomatridine	Allomatridine
Matridine	40% of allomatridine + 60% of matridine
Sophoridane	Sophoridane
Isosophoridane	Isosophoridane

As the subject of investigation we took the lactam-containing alkaloids of the matrine series (allomatrine, matrine, sophoridine, isosophoridine) and the oxygen-free compounds corresponding to them.

Allomatrine was obtained by isomerizing matrine as described by Tsuda and Mishima [5], isosophoridine by the isomerization of sophoridine as described by Rulko [6], and the oxygen-free products by the reduction of the corresponding lactam-containing bases with lithium aluminum hydride. The results of the reactions were confirmed by the chromatography of the products in a thin layer of alumina in the acetone–water (40 : 2) and ether systems.

It can be seen from the results obtained that matrine and matridine are converted only partially into allomatrine and allomatridine, respectively, and sophoridine is converted completely into isosophoridine, while neither sophoridane nor isosophoridane are isomerized at all. The difference in the behavior of sophoridine and sophoridane under the conditions of catalytic hydrogenation shows that a change in the nature of the nitrogen in the cis-C/D linkage leads to a substantial difference in the reactivities of the molecules of the isomers.

On considering the possible directions of the conversions of these compounds from the point of view of the mechanism of isomerization over Pt, one must take into account the fact that these reactions proceed via a stage of cis-molecular elimination and hydrogenation of the intermediate dehydro products or compounds of the bases with the catalyst, while in the hydrogen addition stages, cis-addition must be ensured [7]. However, performing the reaction for a long time in an acid medium favors the reverse transition of the intermediate product of incomplete hydrogenation into the adsorbed form of the base [8] and migrations of the cis-added catalyst, which requires the presence of neighboring hydrogen atoms capable of cis-addition to one of the K–C bonds (where 2K represents the catalyst Pt$<$). Consequently, in the majority of known cases [5, 9] the most stable isomer predominates in the reaction mixture if hindrance caused by electronic and steric effects is absent. Several intermediate products (A, B, and C) can be formed by cis cleavage from sophoridine.

I

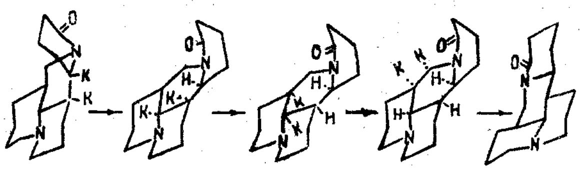
A

B

C

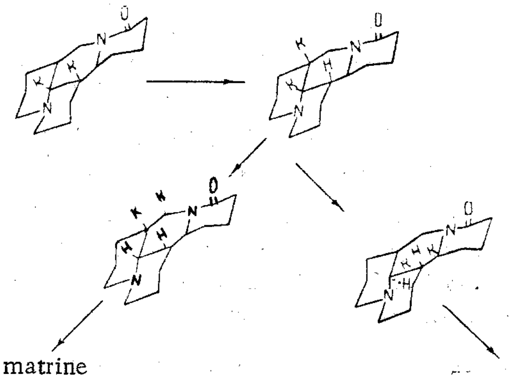
The most probable is product B in view of the greater mobility of the tertiary hydrogen atoms. Partial hydrogenation of product B at the *a*–b bond may give a cis-C/D and a trans-B/C linkage, which would lead to the initial compound, or a trans-C/D and a cis-B/C linkage. In the latter case, ring D assumes the boat form which is then restored to the chair form in the subsequent hydrogenation of points e, c, and d.

Since the initial compound was not isolated from the reaction product, only the second case (trans-C/D) applies, one of the bonds of the catalyst readily migrating to point e, the hydrogen at which is now in the cis-position with respect to it. The hydrogenation of the newly-formed bond with the catalyst (*a*–e) leads to trans-B/C and cis-A/C linkages, and the catalyst migrates to points c–d, the hydrogenation of which leads to the return of the boat form of ring D originally produced to the stable chair form. Thus, we obtain trans-C/D, cis-A/C, trans-B/C, and cis-A/B linkages (on the basis of geometrical considerations and the conversions of ring A), i.e., isosophoridine.



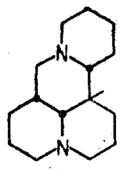
The correctness of this approach to the explanation of the isomerization of sophoridine must be confirmed, and it will prove true if by means of it it is possible to understand the reason for the partial conversion of matrine into allomatrine and of matridine into allomatridine.

The isomerization of matrine into allomatrine also takes place through the cis detachment of two hydrogen atoms. On partial hydrogenation of the intermediate product formed, the catalyst migrates into the neighboring cis position. The hydrogenation of this product with the addition of hydrogen from the frontal direction must lead to the initial compound, and addition from the reverse direction after migration of the catalyst to point d and subsequent hydrogenation must lead to allomatrine, as is observed in experiment.

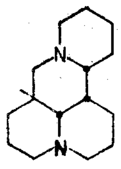


In our opinion, the isomerization of sophoridine takes place because, in view of the conjugation of the carbonyl group with the free pair of electrons of the nitrogen atom in the C/D linkage, the N—C bonds have a partial double-bond nature, which leads to an increase in the mobility of the hydrogen atoms at points b and d. The results given show that this effect is very substantial in the isomerization of sophoridine, since sophoridane does not isomerize under these conditions.

The mechanism of the transition of sophoridine into isosophoridine described confirms its syn-cis configuration [10]. In view of the trans-arrangement of all the tertiary hydrogen atoms to one another, the anti-cis form would not isomerize over platinum. This also makes it possible to choose between the two configurations proposed by F. Rulko for isosophoridine—II and III.



II



III

The isomer II with the trans-C/D, trans-B/C, cis-A/C, and cis-A/B linkages should correspond to isosophoridine, while III, with a trans configuration of the C/D rings should have ring C in the boat form and be unstable, which is not the case for isosophoridine.

Consequently, the isomerization of sophoridine and compounds similar to it containing cis-quinolizidine groupings but no lactam group (isosophoridane and isosophoridine, cis-A/B) is unlikely under the conditions given. It is possible that a change in the conditions [11] which could increase the mobility of the secondary hydrogen atoms and also of the α-cis hydrogen atoms would lead to positive results.

Conclusions

The isomerization of the alkaloids of the matrine series over Pt/H_2 has been studied.

It has been shown that sophoridine, isosophoridane, and isosophoridine, which contain cis-quinolizidine systems, do not isomerize under the conditions in which sophoridine isomerizes.

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Tashkent State University