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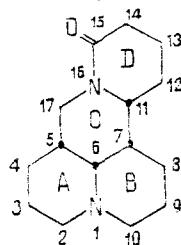
#### STEREISOMERISM OF THE MATRINE ALKALOIDS

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The stereoisomerism of compounds of the matrine series is considered on the basis of the authors' own x-ray structural studies of these alkaloids. A corrected series of eight stereoisomers has been drawn up. It has been shown that the numbers of theoretically possible stereoisomers of matrine is thirty-two.

The molecule of the alkaloid matrine has four asymmetric carbon atoms — C(5), C(6), C(7), and C(11) [1, 2].



This makes the investigations of eight pairs of racemates theoretically possible. The stereoisomerism of these eight alkaloids was first considered in a paper by F. Bohlmann et al. in 1958 [3], and the stereoisomers were subdivided into representatives of the trans and cis series according to the type of linkage of rings A and B.

In 1975, Japanese workers isolated a new stereoisomer of matrine and subsequently established its structure and absolute configuration by x-ray structural analysis [4]. Taking this new compound — (+)-isomatrine — into account, as well, they arranged all the known stereoisomers in the series shown in Fig. 1.

We have previously studied the three-dimensional structures of six stereoisomers (matrine, allomatrine, isosophoridine, sophoridine, tetrahydroneosophoramine, and cis-matrine) by x-ray structural analysis [5-9]. On the basis of the results obtained, a more detailed consideration of the stereoisomerism of the alkaloids of the matrine series is possible.

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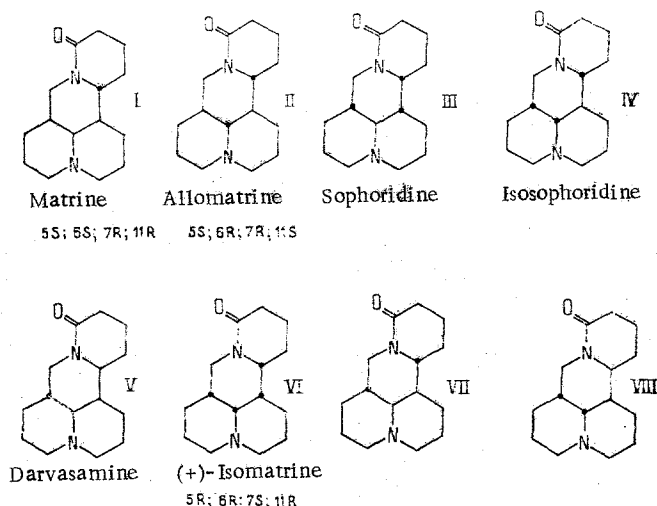


Fig. 1. Series of stereoisomers of matrine.

Ueno et al. [4] ascribed structure (III) in Fig. 1 to sophoridine on the basis of L. I. Begisheva's incorrect results, while the NMR investigations of F. G. Kamaeva [10] and the results of our investigations [6] show that it is represented by structure (VII) shown in the same figure.

Apparently, tetrahydroneosophoramine (THNS), obtained by T. E. Monakhova et al. [11] by the hydrogenation of the alkaloid neosophoramine was unknown to Ueno et al. [4], and therefore they did not consider it. For this A/B-cis stereoisomer of matrine, Monakhova et al. [11], on the basis of chemical facts, proposed a configuration accurately coinciding with that of darvasamine [12] and subsequently confirmed by our x-ray structural investigations [8]. However, the physical constants of THNS and of darvasamine differ sharply, which shows the nonidentity of these compounds. In view of this, it may be assumed that either the configuration of darvasamine has been determined incorrectly or, if it is correct, this is a special case of conformerism — different conformations will correspond to one and the same configuration. Since the structure of darvasamine has not so far been studied by the method of x-ray structural analysis, we shall consider its configuration to be undetermined and put THNS in the series of stereoisomers in place of darvasamine.

In the paper of Ueno et al. [4], the absolute configurations of matrine, allomatrine, and (+)-isomatrine are given in the Cahn-Prelog-Ingold system of symbols [13]. The results that we have obtained indicate that the configuration of the C(7) asymmetric center of these compounds has been determined incorrectly — in matrine and allomatrine it should be S and in (+)-isomatrine it should be R. The C(11) asymmetric center of allomatrine also has the incorrect S configuration.

We have determined the relative configurations of all the stereoisomers studied, taking the configuration of the C(5) asymmetric center as the S configuration. The configurations of the other centers were established relative to the configuration of this center (relative configurations). Consequently, the configurations found correspond to the structures of the actual stereoisomers or to their optical antipode.

Thus, the correct series of matrine stereoisomers consists of six isomers and has the form shown in Fig. 2. In this series, the first four compounds form a trans series with respect to the linkage of rings A and B and the other a cis series.

The series of stereoisomers includes the still unknown compounds (VII) and (VIII). Their theoretical structures and relative configurations (Table 1) can be predicted on the basis of the structures of the known isomers. The system of denoting the conformations — chair C, boat B, and half-chair H — have been adopted from Schwartz [14]. For each of the compounds (VII) and (VIII), the A/B and the A/B-trans configurations are possible.

Table 1 gives the shortened contacts between valence nonbound atoms of the molecule for the given conformation. The conformation with the trans and cis linkages of the A/B rings of compounds (VII) and (VIII) are obtained from the conformations of allomatrine and isoso-

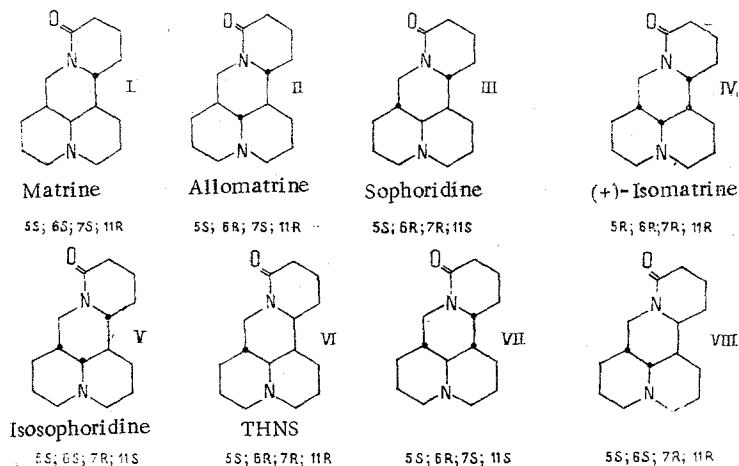


Fig. 2. New series of matrine stereoisomers.

TABLE 1. Theoretically Possible Conformations for the Two Still Unknown Stereoisomers (VII) and (VIII)

Iso- mer	A/B linkage	Ring			Shortened contacts
		A	B	C	
VII	cis	${}^5C_2$	${}^{7,10}B$	$B_{6,16}$	C(6)...C(12) C(3)...C(10) C(5)...C(10)
	trans	${}^5C_2$	${}^7C_{10}$	$B_{6,16}$	
VIII	trans	${}^5C_2$	${}^{10}C_7$	${}^{6,15}B$	C(6)...C(12) C(3)...C(7) C(2)...C(9) C(4)...C(7)
	cis	${}^5C_2$	${}^7C_{10}$	$B_{7,17}$	C(6)...C(12) N(1)...C(17)

phoridine, respectively, by the inversion of the hydrogen atom at the C(11) atom. Consequently, these conformations differ from the conformations of the corresponding precursors by the fact that ring C in them has the boat form.

The (VIII) molecule with the A/B-cis linkage is very labile — the conformations given in the table can easily pass into one another, for example, into conformations with  ${}^{2,5}B$ ,  $B_{7,10}$ ,  ${}^{6,16}B$  or  ${}^{1,4}B$ ,  $B_{7,10}$ ,  $B_{7,17}$ . In this molecule, in addition to the steric hindrance characteristic of the isosophoridine molecule a shortened C(6)...C(12) contact appears. In the A/B-cis linkage of (VII), likewise, the C(6)...C(12) contact is shortened, but there are other shortened contacts as well: C(3)...C(10) and C(15)...C(10). The molecule of compound (VIII) in the A/B-trans form has two shortened contacts — C(6)...C(12) and N(1)...C(17).

A quantitative evaluation of the stresses in these molecules shows that they are no greater than the stresses in the molecule of cis-matrine [9]. The existence of the latter molecule indicates that from the energy point of view the possibility of the existence of the predicted stereoisomers (VII) and (VIII) is not excluded, either. The conformations of the isomers (VII) and (VIII) can serve as a structural basis for their direct synthesis or their preparation by isomerization from other bases of this series.

The new stereoisomer of matrine that we have detected — cis-matrine [9] — does not fall within the eight-membered series considered. cis-Matrine is the first stereoisomer in which rings C and D have the cis type of linkage. Its configuration differs from that of ordinary matrine only by the configuration of the bonds of the N(16) nitrogen atom.

This indicates that in considering the stereoisomerism of the alkaloids of the matrine series it is necessary to take into account not only the asymmetry of the four carbon atoms but also the asymmetry of the N(1) and N(16) nitrogen atoms. Then the six chiral centers give  $2^6 = 64$  stereoisomers in the form of 32 pairs of enantiomers.

It must be mentioned that the N(16) nitrogen atom in the ideal conjugation in the "lactam fragment" — C(11), N(16), C(15), C(14) — of the matrine alkaloids has the plane-trigonal coordination. In the real molecules of the matrine series, the delocalization of the unshared pair of electrons of the N(16) nitrogen atom is incomplete, and this nitrogen atom departs from the plane of the three atoms surrounding it C(11), C(17), and C(15) in the direction of the unshared electron pair. By determining the direction of departure of this nitrogen atom and of the hydrogen atom at C(11) it is possible to establish the type of linkage of rings C and D. The type of linkage can also be established by determining the sign of the torsional angles around the C(11)—N(16) bond in rings C and D: In the case of the trans linkage the signs are different and in the case of the cis linkage they are the same. The linkage of rings C and D of the matrine alkaloids would be more correctly called quasi-trans and quasi-cis.

Thus, the family of matrine alkaloids considered hitherto is incomplete; it forms a subfamily of an expanded family of 32 members. The first representative of the new family outside this subfamily is known — it is cis-matrine. It is possible that some other representatives of it exist and will become known in the near future.

#### CONCLUSION

The stereoisomerism of the matrine alkaloids has been considered on the basis of x-ray structural results. The stereoisomerism of the eight-membered matrine series has been refined. The eight-membered series of stereoisomers has been expanded into a 32-membered series.

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