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STRUCTURE OF TETRAHYDRONEOSOPHORAMINE

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Tetrahydroneosophoramine is a new stereoisomer of matrine in which the linkages of rings A/B and B/C are cis and of A/C trans. It is obtained by the hydrogenation of neosophoramine over platinum oxide in ethanolic solution [1]. Stereoisomerism of the matrine alkaloids has been discussed by Japanese workers [2] and exactly the same configuration is given for darvasamine [3]. However, the physicochemical constants of tetrahydroneosophoramine and darvasamine differ sharply.

In view of this, to elucidate the stereochemistry of these alkaloids we have studied the three-dimensional structure of tetrahydroneosophoramine by x-ray structural analysis. Tetrahydroneosophoramine is the second, after isosophoridine [4], of the cis isomers of matrine that has been studied by this method.

The crystallographic parameters of tetrahydroneosophoramine measured in a precession camera and refined in a syntex-$P2_1$ diffractometer are as follows:

$a = 8,211\,(1)$ Å $M = 248$
$b = 14,021\,(2)$ Å $\rho_{calc} = 1,24$ g/cm³
$c = 6,002\,(1)$ Å $Z = 2$
$\gamma = 105,9°$ Space group $P2_1$
$V = 664,63$ Å³

The intensities of 1283 reflections were measured by $\theta/2\theta$ scanning in CuK_α radiation (graphite monochromator) to $2\theta \leq 120°$ on the diffractometer mentioned, and 1072 reflections with $I \geqslant 2\sigma$ were used in the calculations.

The model of the structure was found by the multivariant tangent method using the programs of the "Rentgen-75" group [5] and was refined by the method of least squares by the programs of the "Kristall" group [6]. The hydrogen atoms were located geometrically. The final value of the R factor was 0.062.

The conformation of the tetrahydroneosophoramine molecule is shown on Fig. 1. Rings A, B, and C have the chair form, and the form of D is close to the half-chair. The linkages of rings A/B and B/C are cis and of A/C and C/D trans. Such a configuration can be obtained from the configuration of isosophoridine [4] by changing the positions of rings A and B rela-

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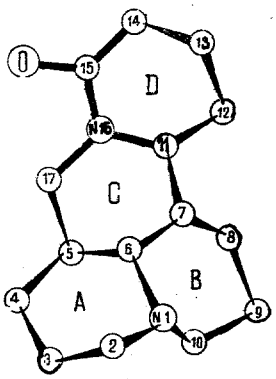

Fig. 1

tive to rings C and D. The deviations of the geometric parameters of the chairs of rings A, B, and C from the parameters of an ideal chair in tetrahydroneosophoramine and in isosophoridine are similar. An exception is the deviation of the C(12) and C(13) atoms of ring D from the plane of the remaining atoms of the ring. In this ring only the C(13) atom deviates by 0.48 Å, which shows the coplanarity of the other five atoms, while as in isosophoridine, the C(12) and C(13) atoms deviate in opposite directions by 0.15 and 0.52 Å, respectively.

The plane of ring C makes angles of 4 and 54°, respectively, with the planes of rings A and B, and the other angles are identical in tetrahydroneosophoramine and isosophoridine. The identical value of the angle between the planes of rings A and B in the two compounds — 51° — leads to the appearance of approximately identical stresses in the molecules. On comparing the information on the lengths of the shortened contacts in the molecules given below and in the preceding paper [4], it is possible to convince oneself of the correctness of this statement. The shortened lengths of the contacts in the tetrahydroneosophoramine molecule are as follows (R_i and R_j are the van der Waals radii of atoms i and j, respectively, and δ is the overlapping of van der Waals spheres that is acceptable for normal contacts):

Contact	Length of the contact, Å	$2\sqrt{R_iR_j}$, Å	$2\sqrt{R_iR_j}-\delta$, Å
C(8) — C(12)	3,12	3.42	3,27
C(5) — C(10)	3,12	3,42	3,27
C(3) — C(10)	3,13	3,42	3.27
C(5) — C(8)	3,17	3,42	3.27
O — C(17)	2,74	2.97	2,82
H_a(3) — H_a(16)	2,01	2,31	2,01
H_a(5) — H_a(8)	2,00	2,31	2,01

Figures given in the literature [7] were used as the normal and shortened values of the lengths of the nonbond contacts. According to this paper, in the tetrahydroneosophoramine molecule there are four shortened and three very shortened contacts.

Because of the strain of the molecule the valence angles in the molecule, particularly in rings A and B, are increased to 113-114°C. The lengths of the valence bonds are normal in comparison with the other stereoisomers [4, 8] with the exception of the C(12)-C(13) interatomic distance, which is 1.43 Å. The decrease in this bond length and the flattening of ring D as compared with the same ring of isosophoridine [4] and the increase, as a result of this, in the valence angles at the C(12) and C(13) atoms apparently take place as a consequence of the intensive thermal vibrations of these atoms. The C(15)—O interatomic distance is 1.22 Å.

The coordination of the N(1) atom is pyramidal and of the N(16) atom plane-trigonal because of conjugation in the lactam fragment of the molecule.

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SYNTHESIS OF METHIONINE-5-ENKEPHALIN

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There has recently been a report of the isolation from animal brain of a group of peptides having affinity for the opiate receptor [1]. One of these peptides, which has acquired the name of methionine-5-enkephalin, is a new pentapeptide of structure (I) (all the asymmetric amino acids have the L configuration):

$$H\text{-}\overset{1}{Tyr}\text{-}Gly\text{-}Gly\text{-}Phe\text{-}\overset{5}{Met}\text{-}OH \qquad (I)$$

Structure (I) was shown by a complete amino acid analysis, the cleavage of the natural peptide by the Edman method, and mass spectrometry [1], and has also been confirmed by synthesis [2, 3]. We have developed a new method for the total chemical synthesis of methionine-5-enkephalin (I) in solution. The synthesis is performed by a 4 + 1 scheme providing for the use as starting materials of the pentafluorophenyl ester of N-tert-butoxycarbonyl-O-benzyl-L-tyrosine (II), the pentafluorophenyl ester of N-tert-butoxycarbonylglycine (III), N-tert-butoxycarbonylglycine (IV), the p-nitrobenzyl ester of L-phenylalanine (V), and the sodium salt of L-methionine (VI).

The intermediate compounds in this synthesis are the previously unknown p-nitrobenzyl ester of N-tert-butoxycarbonylglycyl-L-phenylalanine (VII), the p-nitrobenzyl ester of glycyl-L-phenylalanine (VIII), the p-nitrobenzyl ester of N-tert-butoxycarbonylglycylglycyl-L-phenylalanine (IX), the p-nitrobenzyl ester of glycylglycyl-L-phenylalanine (X), the p-nitrobenzyl ester of N-tert-butoxycarbonyl-O-benzyl-L-tyrosylglycylglycyl-L-phenylalanine (XI), and the N-hydroxysuccinimide ester of N-tert-butoxycarbonyl-L-tyrosylglycylglycyl-L-phenylalanine (XII).

To eliminate the benzyl and o-nitrobenzyl protective groups from compound (XI) we used catalytic hydrogenation in the presence of palladium black. The last stage of the synthesis consisted in the elimination of the tert-butoxycarbonyl protective group from N-tert-butoxycarbonyl-L-tryosylglycylglycyl-L-phenylalanyl-L-methionine (treatment with a 15% solution of HCl in dioxane for 40 min at 20°C).

Methionine-5-enkephalin (I). mp 190-194°C (decomp.), R_f 0.40 (butan-1-ol—acetic acid—water (4:1:1)), 0.32 (ethyl acetate—pyridine—acetic acid—water (60:20:6:11)) (TLC on silica gel, spots revealed with ninhydrin), $[\alpha]_D^{20}$ +32.0° (c 1.0; methanol). Amino acid analysis: Tyr 1.06, Gly 2.00, Phe 1.10, Met 0.96.

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