MOLECULAR AND CRYSTAL STRUCTURE OF TETRAHYDRONEOSOPHORAMINE

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UDC 548.737

The structure of tetrahydroneosophoramine has been studied by x-ray structural analysis. Rings A, B, and C have the chair conformation, and ring D the half-chair conformation. On the basis of a semiquantitative analysis it has been shown that the strains in the molecules of tetrahydroneosophoramine and of matrine are of the same order of magnitude.

A structure for tetrahydroneosophoramine (THNS) has been given by Monakhova et al. [1] in which the ring linkages are A/B-cis, B/C-cis, and A/C-trans. The structure of another matrine stereoisomer — darvasamine — is characterized by just the same linkages of the rings [2]. In order to answer the question of configurational ambiguity, we have made an x-ray structural investigation of tetrahydroneosophoramine. Preliminary results obtained in this investigation have been reported previously [3]. In the present paper the geometry of the tetrahydroneosophoramine molecule is discussed in more detail.

In the tetrahydroneosophoramine molecule (Fig. 1) the C(10) atom occupies the axial and C(7) the equatorial position with respect to ring A. The A/C-trans linkage of the rings takes place by mutually diequatorial bonds, while the B/C-cis linkage is effected by axial (C(5) atom) and equatorial (C(11) atom) bonds with respect to ring B. The conformation of ring A is ${}^{5}C_{2}$-chair, of B ${}^{10}C_{7}$-chair, and of ${}^{6}C_{16}$-chair. Ring D in the ${}^{12}H_{13}$ half-chair form is trans-linked with ring C.

Figure 1b shows a projection of the tetrahydroneosophoramine molecule which resembles the mutual arrangement of rings A, B, and C in matrine if we exclude from consideration ring D and in place of the trans-linkage of rings A/B of matrine we consider the likewise trans-linked rings A/C of tetrahydroneosophoramine. With this arrangement, ring B of tetrahydroneosophoramine corresponds to ring C of matrine, and the tetrahydroneosophoramine molecule proves to be similar to the matrine molecule with respect to the relative positions of the rings, which permits the structures of these two molecules to be compared on the basis of the structure of matrine, which is well known to us [4]. A similar method has been used previously in the consideration of the conformation of the isosophoridine molecule [5].

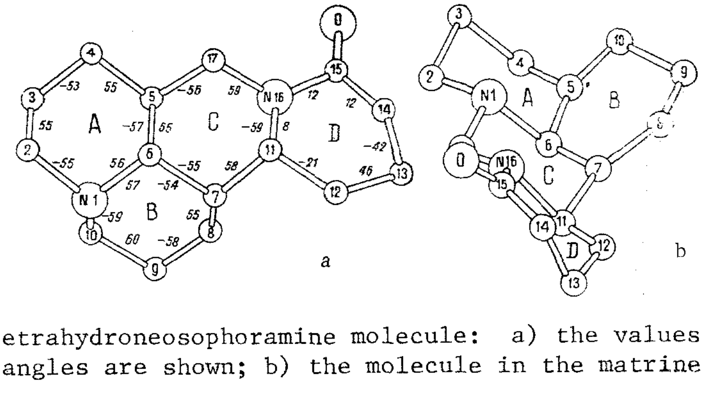

Fig. 1. Tetrahydroneosophoramine molecule: a) the values of the torsional angles are shown; b) the molecule in the matrine "arrangement."

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0009-3130/81/1706-0546$07.50

TABLE 1. Shortened Intramolecular Nonvalent Contacts in the Tetrahydroneosophoramine Molecule

Contact	The same contact in the "matrine" arrangement	Length of the contact, Å	Normal value, Å
C (8) . . . C (5)	C (11) . . . N (1)	3,16	3,42
C (8) . . . N (16)	C (11) . . . C (9)	3,16	3,20
C (10) . . . C (3)	C (17) . . . C (3)	3,13	3,42
C (10) . . . C (5)	C (17) . . . N (1)	3,12	3,42

TABLE 2. Coefficients of the Equations of the Planes and Deviations δ of the Atoms from these Planes in the Structure of Tetrahydroneosophoramine

Plane	Atom	Coefficients of the equations of the planes				δ, Å
		A	*B*	*C*	*D*	
I (ring *A*)	N (1)	—6,54	4,88	—3,54	—5,23	0,002
	C (3)					—0,002
	C (4)					0,002
	C (6)					—0,002
	C (2)*					—0,635
	C (5)*					0,678
II (ring *B*)	N (1)	0,84	2,19	5,86	4,30	—0,010
	C (6)					0,009
	C (8)					—0,009
	C (9)					0,009
	C (7)*					0,667
	C (10)*					—0,699
III (ring *C*)	C (5)	6,86	—4,57	3,25	5,13	0,002
	C (7)					—0,002
	C (11)					0,002
	C (17)					—0,002
	C (6)*					0,659
	N (16)*					—0,659
IV (ring D)	C (11)	—3,29	11,45	—3,29	3,16	—0,026
	N (16)					0,054
	C (15)					—0,052
	C (14)					0,023
	C (13)*					0,479
	C (12)*					—0,044

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*Atoms not included in the calculation of the equation of the plane.

TABLE 3. Bond Lengths in Tetrahydroneosophoramine (standard deviations in parentheses)

Bond	Bond length, Å	Bond	Bond length, Å
N (1)—C (2)	1,478 (6)	N (1)—C (6)	1,468 (6)
C (2)—C (3)	1,548 (7)	C (7)—C (11)	1,539 (6)
C (3)—C (4)	1,532 (7)	C (11)—C (12)	1,531 (7)
C (4)—C (5)	1,539 (7)	C (12)—C (13)	1,426 (10)
C (5)—C (6)	1,537 (6)	C (13)—C (14)	1,451 (10)
C (6)—C (7)	1,526 (5)	C (14)—C (15)	1,504 (7)
C (7)—C (8)	1,544 (6)	C (15)—N (16)	1,344 (6)
C (8)—C (9)	1,524 (7)	N (16)—C (17)	1,476 (6)
C (9)—C (10)	1,511 (7)	N (16)—C (11)	1,492 (6)
N (1)—C (10)	1,496 (6)	C (15)—O	1,219 (6)
		C (5)—C (17)	1,513 (7)

Let us separate the tetrahydroneosophoramine molecule into left (the C(10) atom and ring A) and right (the C(8) atom and rings C and D) parts. The N(1) nitrogen atom is present in the left part, and ring D in the right part, i.e., in the tetrahydroneosophoramine molecule the right and left parts of the isosophoradine molecule in the matrine "arrangement" have changed places. Taking this difference into account, the conformation of the tetrahydroneosophoramine molecule can be considered on the basis of the conformation of isosophoridine [5].

TABLE 4. Ellipsoids of the Thermal Vibrations of the Nonhydrogen Atoms and Their Orientation Relative to the Crystallographic Axes in the Structure of Tetrahydroneosophoramine (lengths of the semi-axes of the ETVs multiplied by 10^3)

Atom	Semi-axes of ETV, Å	Angle, deg			Atom	Semiaxes of ETV, Å	Angle, deg		
		a, j	*b, j*	*c, j*			*a, j*	*b, j*	*c, j*
N (1)	413	63	135	49	C (10)	464	173	70	85
	367	114	53	41		405	84	73	20
	320	38	68	89		334	92	154	71
	494	65	129	43		429	55	149	68
C (2)	400	113	46	47	C (11)	346	47	62	76
	337	145	109	87		322	116	77	27
	500	57	127	46		563	56	148	66
C (3)	380	83	37	60	C(12)	405	59	59	60
	334	147	87	59		354	130	84	40
	467	60	121	39		693	74	133	43
C (4)	383	69	39	79	C (13)	407	63	53	62
	311	143	68	54		343	148	65	60
	367	62	139	54		428	54	124	46
C (5)	340	138	75	48	C (14)	398	117	50	45
	330	62	53	63		351	132	121	83
	368	69	157	67		422	163	57	89
C (6)	325	124	73	35	C (15)	355	82	70	24
	323	41	74	65		286	105	141	66
	390	87	151	64		394	40	124	59
C (7)	348	160	69	71	N (16)	343	80	37	57
	314	70	72	33		323	130	102	49
	462	104	114	33		422	48	108	43
C (8)	352	38	79	62	C (17)	357	107	147	84
	331	125	26	74		328	133	62	48
	471	103	103	22		515	45	134	61
C (9)	404	46	66	69	O	402	131	94	45
	344	133	28	86		318	78	44	58

Numerical values of the ETVs to be read on three lines.

TABLE 5. Values of the Valence Angles in Tetrahydroneosophoramine (standard deviations in parentheses)

Angle	Value of the angle, degrees	Angle	Value of the angle, degrees
N (1) C (2) C (3)	113,6 (4)	C (11) N (16) C (17)	112,9 (3)
C (2) C (3) C (4)	110,2 (4)	N (16) C (17) C (5)	110,8 (4)
C (3) C (4) C (5)	110,9 (4)	C (17) C (5) C (6)	110,0 (4)
C (4) C (5) C (6)	109,3 (4)	N (16) C (11) C (12)	113,2 (4)
C (5) C (6) C (7)	112,1 (3)	C (1) C (12) C (13)	114,7 (5)
C (6) C (7) C (8)	111,2 (3)	C (12) C (13) C (14)	117,4 (6)
C (7) C (8) C (9)	108,4 (4)	C (13) C (14) C (15)	115,2 (5)
C (8) C (9) C (10)	111,5 (4)	C (14) C (15) N (16)	117,5 (4)
C (9) C (10) N (1)	108,4 (4)	C (15) N (16) C (11)	125,9 (4)
C (10) N (1) C (6)	113,3 (3)	C (14) C (15) O	119,9 (4)
C (6) N (1) C (2)	110,3 (3)	N (16) C (15) O	122,6 (5)
N (1) C (6) C (7)	110,7 (4)	C (15) N (16) C (17)	119,3 (4)
C (5) C (6) N (1)	113,9 (4)	C (4) C (5) C (17)	110,9 (4)
C (6) C (7) C (11)	109,7 (4)	C (7) C (11) C (12)	114,0 (4)
C (7) C (11) N (16)	109,8 (4)	C (8) C (7) C (11)	115,3 (4)

The length of the C(8). . .N(16) contact (3.16 Å) (Table 1) in the right part of the tetrahydroneosophoramine molecule is somewhat greater than the corresponding C(4). . .N(16) contact (3.08 Å) in isosophoridine. This increase in the C(8). . .N(16) distance is apparently due to the repulsion of the adjacent C(8) and C(12) atoms to 3.12 Å. At the same time, the exocyclic angles at the C(7) and C(11) atoms increase to 115 and 114°, respectively The interaction of the C(8) and C(5) atoms forming the second shortened contact in the right part of the molecule somewhat increases the C(5) C(6) C(7) valence angle (112°).

The increase to 112-114° of the C(2) N(1) C(10), C(3) C(2) N(1), C(10) N(1) C(6), and C(5) C(6) N(1) valence angles is due to the interaction of the C(10) atom with the C(3) and C(4) atoms. As a result of this interaction, ring A is deformed more than ring B and C. It

TABLE 6. Coordinates and Parameters of the Anisotropic Thermal Vibrations of the Nonhydrogen Atoms in the Structure of Tetrahydroneosophoramine (all values multiplied by 10^4; standard deviations given in parentheses)

Atom	x/a	y/b	z/c	B (11)	B (22)	B (33)	B (12)	B (23)	B (13)
N (1)	3534 (4)	8913 (3)	2051 (8)	147 (6)	63 (2)	349 (17)	20 (6)	—30 (12)	22 (19)
C (2)	5097 (6)	8863 (4)	893 (2)	167 (9)	78 (3)	476 (25)	11 (9)	—65 (18)	64 (28)
C (3)	4765 (6)	8195 (4)	—1206 (12)	185 (10)	79 (4)	438 (23)	27 (10)	—59 (17)	156 (28)
C (4)	3659 (6)	7158 (4)	—602 (10)	175 (9)	72 (3)	400 (22)	56 (9)	—54 (15)	146 (25)
C (5)	2028 (5)	7217 (3)	585 (9)	153 (7)	55 (3)	280 (16)	39 (7)	—20 (12)	4 (21)
C (6)	2493 (5)	7912 (3)	2607 (9)	141 (7)	58 (3)	255 (16)	40 (7)	—20 (12)	2 (19)
C (7)	933 (5)	7958 (3)	3935 (9)	159 (8)	66 (3)	258 (16)	54 (7)	—42 (13)	—40 (20)
C (8)	9914 (6)	8573 (3)	2698 (11)	180 (9)	63 (3)	433 (22)	84 (8)	—82 (15)	—92 (25)
C (9)	1104 (6)	9591 (4)	2179 (12)	214 (10)	66 (3)	496 (25)	102 (8)	—39 (18)	—51 (31)
C (10)	2591 (7)	9510 (3)	786 (11)	276 (11)	54 (3)	369 (21)	43 (9)	35 (15)	2 (29)
C (11)	9914 (6)	6904 (3)	4607 (9)	169 (8)	71 (3)	271 (16)	27 (8)	—40 (13)	50 (22)
C (12)	8376 (7)	6871 (5)	6078 (12)	223 (11)	112 (5)	388 (23)	9 (12)	—83 (19)	141 (31)
C (13)	6782 (7)	6541 (5)	4975 (15)	190 (11)	133 (6)	744 (35)	52 (13)	—307 (25)	146 (36)
C (14)	6500 (6)	5668 (4)	3573 (11)	185 (9)	66 (3)	395 (21)	27 (9)	—7 (15)	41 (27)
C (15)	8980 (6)	5618 (3)	2146 (9)	205 (9)	45 (2)	276 (17)	5 (8)	34 (13)	28 (24)
N (16)	9484 (4)	6267 (3)	2583 (8)	170 (7)	55 (2)	284 (14)	31 (6)	—7 (10)	67 (8)
C (17)	993 (6)	6200 (3)	133 (10)	187 (9)	58 (3)	389 (19)	54 (8)	—17 (13)	108 (23)
O	7781 (4)	5012 (2)	643 (8)	241 (7)	68 (2)	393 (15)	—11 (6)	107 (11)	45 (19)

TABLE 7. Coordinates and Isotropic Thermal Parameters of the Hydrogen Atoms in the Structure of Tetrahydroneosophoramine (values of coordinates multiplied by 10^3)

Plane	x/a	y/b	z/c	B_j	Atom	x/a	y b	z/c	B_j
H_2(1)	576	963	36	5,72	H_{10}(1)	215	910	−78	5,23
H_2(2)	583	861	204	5,72	H_{10}(2)	345	22	39	5,23
H_3(1)	416	853	−253	5.94	H_{11}(1)	78	655	554	4,47
H_3(2)	601	815	−187	5.94	H_{12}(1)	824	628	730	6.83
H_4(1)	334	672	−214	4,93	H_{12}(2)	863	758	693	6,83
H_4(2)	437	681	49	4.93	H_{13}(1)	569	664	614	6,92
H_5	127	755	−61	3.91	H_{13}(2)	673	731	378	7.92
H_6	330	766	368	3,84	H_{14}(1)	633	506	482	4.97
H_7	137	833	550	4,32	H_{14}(2)	538	552	254	4,97
H_8(1)	940	820	110	5.04	H_{17}(1)	55	575	−22	4.82
H_8(2)	884	863	370	5.04	H_{17}(2)	177	586	228	4,82
H_9(1)	640	5	117	5,56					
H_9(2)	152	1	369	5.56					

can be seen from the values of the torsional angles (Fig. 1a) that the deformations of ring B and C are similar. The maximum decreases in the torsional angles as compared with the ideal value of ±60° [6] amount to 5-6°, and they are identical in both A/B-cis stereoisomers of matrine. However, on the whole, the deformation of ring B in tetrahydroneosophoramine is somewhat smaller than that of the corresponding ring A in isosophoridine. The deviation of the "angular" atoms of the chairs of tetrahydroneosophoramine have decreased to different degrees in comparison with the ideal value (Table 2). In ring D the C(12) atom is coplanar with the C(11), N(16), C(15), and C(14) atoms. The deviation of the C(13) atom from the plane of these atoms is 0.48 Å. Consequently, it is possible to describe the conformation of ring D of tetrahydroneosophoramine as a "sofa" conformation, in contrast to the half-chair conformation in the other matrine alkaloids [7-10].

The mean length of the $C(sp^3)$–$C(sp^3)$ bonds is 1.52 Å (Table 3), which is somewhat less than the mean value in the other alkaloids of the matrine series. This decrease is determined by the substantial decrease in the lengths of the C(12)–C(13) and C(13)–C(14) bonds, which are 1.43 and 1.45 Å, respectively. It is, apparently, the intensive thermal vibrations of the C(12) and C(13) atoms that leads to this shortening of the bond lengths. The lengths of the semi-axes of the ellipsoids of the thermal vibrations (ETVs) of the C(12) and C(13) atoms of tetrahydroneosophoramine are 0.56 and 0.69 Å (Table 4). In other matrine alkaloids, in which the length of the bonds under consideration have normal values, the lengths of the semi-axes of the ellipsoids of the thermal vibrations of the C(12) and C(13) atoms are in the interval of 0.4-0.5 Å [7-10].

The lengths of the bonds involving the N(1) atom in tetrahydroneosophoramine differ somewhat from one another in comparison with isosophoridine in which all the N(1)–C bonds have the same length (1.47 Å) and the N(16)–$C(sp^3)$ bonds are somewhat lengthened on comparison with the same bonds in isosophoridine. The lengths of the N(16)–C(15) bonds are the same in the two compounds with an accuracy of three standard deviations in the determinations of the lengths of the bonds in tetrahydroneosophoramine (see Table 3), and the length of the C(15)–O double bond (1.22 Å) remains unchanged in all the bases of the matrine series considered.

The values of majority of valence angles at the tetrahedral carbon atoms are close to the usual values (Table 5). The reason for the increase in some angles in rings A, B, and C has been stated above. All the angles at the tetrahedral atoms of ring D are increased, especially the angle at the C(13) atoms, which has a value of 117°. The distribution of the angles at C(15) in tetrahydroneosophoramine is the same as in isosophoridine, while the endocyclic C(17) N(16) C(11) angle is decreased in comparison with the same angle in isosophoridine, the C(15) N(16) C(11) and C(17) N(16) C(15) angles remaining the same to an accuracy of 3 standard deviations (see Table 5).

Thus, the comparative consideration of the conformations of the tetrahydroneosophoramine and isosophoridine molecules reduced to the matrine "arrangement" that has been carried out, permits us to judge the degree of relative strain of the molecules. The numbers and lengths of the short intramolecular contacts, and also the numbers and values of the increased valence angles in matrine and two if its A/B-cis stereoisomers show that the strains present in these three compounds are of the same order of magnitude.

EXPERIMENTAL

The parameters of the elementary cell of tetrahydroneosophoramine crystals grown from solution and petroleum ether were measured in a precision camera and were refined by the method of least squares with respect to 12 reflections in a Syntex-$P2_1$ diffractometer. The crystallographic parameters of tetrahydroneosophoramine, $C_{15}H_{24}ON_2$, are as follows: a = 8.211(2), b = 14.023(3), c = 6.003(1), γ = 105.9(3)°; space group $P2_1$; Z = 2; ρ_{calc} = 1.23 g/cm^3.

The intensities of 1283 reflections were measured in the diffractometer mentioned by the $\theta/2\theta$-scanning method. CuK_α radiation monochromatized by reflection from a graphite crystal was used. In the subsequent calculations, 1072 reflections with $I \geqslant 2\sigma$ were used. No correction was introduced for absorption.

The model of the structure was found by the direct method using the programs of the Rentgen-75 complex [10]. The structure was assigned by the method of least squares using the programs of the Kristall complex [11]. After a series of refinements by the method of least squares in the approximations of isotropic (R = 0.138) and anisotropic (R = 0.100) thermal vibrations of the atoms, the positions of the hydrogen atoms were found geometrically. Taking as the initial values of B_j of the hydrogen atoms the isotropic thermal parameters of the carbon atoms to which the H atoms were attached, the positional and isotropic thermal parameters were refined. The final value of the R factor was 0.062.

Table 6 gives the coordinates and anisotropic thermal parameters of the nonhydrogen atoms and Table 7 the coordinates and isotropic thermal parameters of the hydrogen atoms in the structure of tetrahydroneosophoramine.

SUMMARY

The structure of a stereoisomer of the alkaloid matrine — tetrahydroneosophoramine — has been studied by x-ray structural analysis Rings A, B, and C have the chair form, and ring D the half-chair form. It has been shown on the basis of a semiquantitative analysis that the strains in the molecules of tetrahydroneosophoramine and matrine are of the same order of magnitude.

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