AN X-RAY STRUCTURAL INVESTIGATION OF cis-MATRINE — A NEW STEREOISOMER OF MATRINE

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UDC 548.737

In an investigation of the three-dimensional structure of the alkaloid matrine by x-ray structural analysis, a new stereoisomer of it has been detected, which has been called cis-matrine. In cis-matrine rings C and D are cis-linked, while the configurations of the A, B, and C fragments in cis-matrine and in ordinary matrine are identical. The cis-matrine molecule is characterized by a greater degree of strain than the molecule by ordinary matrine.

In order to obtain high-quality single crystals of matrine for investigating its spatial structure by x-ray structural analysis, we recrystallized a new portion of the substance under conditions not differing appreciably from those used previously (petroleum ether, room temperature). The crystallographic parameters of the crystals from the new batch indicated that it belonged to the monoclinic system, unlike the crystals belonging to the rhombic system found previously [1].

Kondo [2] has determined the physicochemical constants of three crystalline forms of matrine without performing a special crystallographic investigation permitting these modifications to be identified. We therefore considered that we were apparently dealing with two of them — rhombic and monoclinic. The packing of the matrine molecules in the monoclinic and rhombic crystalline forms would be different and therefore the crystal field would act differently on the molecules. The possibility of the realization of different conformers in the different crystal modifications was not excluded. Of course, the matrine molecule, which possesses a rigid skeleton, is hardly capable of a conformational rearrangement under the action of the crystal field. However, the possibility of the conformational rearrangement in some sparteine alkaloids [3] indicates that the probability of the conformational rearrangement of the matrine molecule is not zero. In short, having interpreted the structure of monoclinic matrine it would be possible to answer the question to what extent the conformation of the molecule is retained on passing from one crystalline form to another.* If the three dimensional structures of the molecules in the two modifications were identical, we should obtain an additional source for the estimation of the standard deviations in the determinations of the geometric parameters. Finally, by comparing the structures of the molecule in the two crystals with the aid of a program for the quantitative comparison of conformations which has already been used in the study of the three-dimensional structure of sophoridine N-oxide [4], we should obtain such a value of s for identical conformations upon which it would be possible to base ourselves in the subsequent comparisons of the conformations of the matrine alkaloids.

After the refinement of the structure of the monoclinic modification, quantitative comparison of the conformations of the matrine molecule in the two crystals was performed on a computer [5]. A very high value of the criterion s was obtained (0.39 Å), which showed a difference in the conformations of the molecules in the polymorphic modifications. A subsequent analysis of a model, and also the values of the valence and torsional angles, showed that a new stereoisomer of matrine had been discovered. This compound, in which rings C and D have the cis-linkage, is the first C/D-cis isomer of matrine. We have called it cis-matrine.

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*It is possible to speak of two crystalline modifications of matrine only if the conformations of the molecules in them are the same but they differ from one another by the type of packing of these molecules.

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0009-3130/81/1705-0432$07.50

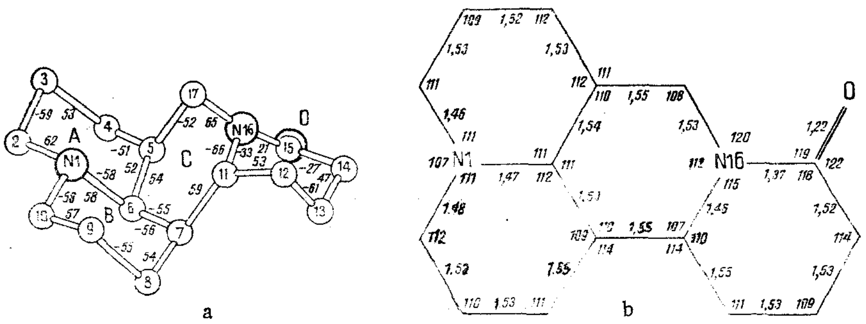

Fig. 1. The cis-matrine molecule; a) conformation in the crystal (the values of the torsional angles are given); b) bond lenghts and magnitudes of valence angles.

The structure of cis-matrine is shown in Fig. 1. The forms of rings A, B, and C are $^{2}C_{5}$, $^{10}C_{7}$, and $^{6}C_{16}$ chairs, respectively [6]. The ring-D configuration resembles the $^{12}H_{13}$ subchair. The configuration of the part of the molecule consisting of rings A, B, and C is the same as in matrine: A/B-trans, A/C-cis, B/C-cis, but the conformations of the other moiety in ordinary matrine and cis-matrine differ. A comparison of these fragments of the matrine and cis-matrine molecules gives a fairly high value of 0.22 Å for the criterion s. As already mentioned, a feature of the structure of cis-matrine by which it differs from ordinary matrine is the cis linkage of rings C and D, which imparts the shape of a step to the molecule. Such a configuration leads to the appearance of steric hindrance in the C/D part of the molecule together with substantial differences in the remaining part of it. The distances between the nonbound atoms of the cis-matrine molecule, which are shortened in comparison with the normal distances [7], are given below:

Contact	Length of the contact, Å	Normal value according to [7], Å
C (3)...C (17)	3,14	3 42
C (3)...C (11)	3,15	3,42
N (1)...C (17)	3,08	3,20
N (1)...C (11)	3,07	3,20
C (5)...C (15)	3,27	3,42
C (7)...C (13)	3,16	3,42
C (7)...C (15)	3,30	3,42

In the A,B,C part of the molecule of cis-matrine and of ordinary matrine [1], the same contacts are shortened, but in the first compound the length of the N(1)...C(11) and N(1)...C(17) are equal (3.07 and 3.08 Å) while in matrine there is a difference between them of 0.12 Å.

The interaction between the atoms of rings C and D worsens the coplanarity of the atoms in the "lactam fragment" – C(11), C(14), C(15), and N(16) (Fig. 1 and Table 1) – in comparison with their coplanarity in all the other compounds of the matrine series that have been considered [1, 4, 8, 9]. The C(12) and C(13) atoms of ring D depart by 0.42 and 0.30 Å in opposite directions from the plane of the ring. The plane of ring D is inclined at an angle 70.8° to the plane of ring C with the $^{6}C_{16}$ chair conformation.

The angles between the planes of rings A, B, and C are practically in cis-matrine and in ordinary matrine; the planes of rings A and B in cis-matrine are parallel (0.5%), and the plane of ring C is almost perpendicular, to the planes of rings A and B, the corresponding angles being equal to 81.3° and 80.9°. The deviations of the "angular" atoms of the chairs are less than the ideal value of ±0.73 Å [10] and are between 0.63 and 0.71 Å (Table 1). A feature of ring C is the greater deviation of the N(16) atom from the plane of ring C (0.71 Å) than that of the C(6) atom. This feature is also reflected in the values of the torsional angles in ring C in which the N(16) atom participates: The angles of rotation around the C(17)–N(16) and the C(11)–N(16) bonds have values greater than 60° (Fig. 1a), while in all other matrine alkaloids they are less than 60°. The mean and maximum deviations of the torsional angles from the ideal value of 60° in rings A, B, and C, especially

TABLE 1. Coefficients of the Equations of the Planes and the Deviations of the Atoms, δ, from These Planes in the Structure of cis-Matrine

Plane	Atom	Coefficients equation of the plane				δ, Å
		A	*B*	*C*	*D*	
I (ring *A*)	N(1)	—6,65	8,62	1,45	1,47	0.0096
	C(3)					—0.0093
	C(4)					0 0091
	C(6)					—0,0 94
	C(5)*					0,6278
	C(2)*					−0,6869
II (ring *B*)	N(1)	—6 67	8,64	1,41	1 43	0,0035
	C(6)					—0,0035
	C(8)					0,0033
	C(9)					−0,0033
	C(7)*					0,6799
	C(10)*					−0,6662
III (ring *C*)	C(5)	2,77	—3,65	5,00	3 23	0,0079
	C(7)					—0,0079
	C(11)					0,0082
	C(17)					—0,0082
	C(6)*					0,6682
	N(16)*					—0,71 8
IV (ring D)	C(11)	—5,05	6,53	3,73	5,09	0,0410
	N(16)					0,0885
	C(15)					−0 0838
	C(14)					0 0372
	C(12)*					0,4234
	C(13)*					—0,2955

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*This denotes the atoms not included in the calculation of the plane.

in the last, are greater than the deviations in matrine because of the greater steric hindrance observed in the cis-matrine molecule.

The $C(sp^3)-C(sp^3)$ bond lengths vary from a minimum value of 1.52 Å to a maximum of 1.55 Å, with a mean value of 1.53 Å, and the lengths of the $N(1)-C(sp^3)$ bonds have a mean value of 1.46 Å, which agrees well with the values for other alkaloids of this class. The C(15) – O and N(16) – C(15) bond lengths of 1.22 Å and 1.37 Å, respectively, also agreeing with the values in other alkaloids of the matrine series, show a delocalization of the electrons in the "lactam fragment."

The valence angles at the $C(sp^3)$ atoms have the usual values. The endocyclic angles C(6)C(5)C(17) and C(6)C(7)C(11), which are increased in matrine, have the normal values in cis-matrine. This is apparently explained by the competing repulsions between the sterically hindered atoms of rings A, B, and C, on the one hand, and of rings C and D on the other. A feature of the valence angles of this compound is an increase in the exocyclic angles at the C(11) and C(7) atoms to 115 and 114°. The valence angles at the C(15) atom are close to 120° but at N(16) they differ considerably from this value. The sum of the angles at the N(16) atom amounts to 357°, which shows a worsening of the coplanarity of the bonds at this atom as compared with the C/D-trans alkaloids of the matrine series.

Thus, in the cis-matrine molecule, together with the steric hindrance characteristic of matrine and other matrine alkaloids and caused by the approach of the C(8) and C(12) atoms and also of the C(17) and O atoms, additional steric hindrance due to the cis configuration of the C/D fragment arises. The cis-matrine molecule is the most strained among the molecules of alkaloids of the matrine series that we have studied. It is not excluded that the instability of the molecule caused by this strain makes the identification of this compound as an individual substance difficult in spite of its presence in plants together with other alkaloids of this class.

The intermolecular contacts in the crystal structure are within permissible limits from the point of view of ideas on intermolecular radii [7].

EXPERIMENTAL

Single crystals of cis-matrine grown from solution in petroleum ether have a prismatic form. The main crystallographic characteristic of the crystal measured and refined on a Syn-

TABLE 2. Coordinates and Parameters of the Anisotropic Thermal Vibrations of the Nonhydrogen Atoms in the Structure of cis-Matrine (all values multiplied by 10^4; the standard deviations are given in parentheses)

Atom	x/a	y/b	z/c	B(11)	B(22)	B(33)	B(12)	B(23)	B(13)
N (1)	8943 (5)	6827 (4)	708 (10)	87 (6)	51 (3)	291 (22)	7 (7)	8 (16)	41 (20)
C (2)	0414 (7)	7047 (5)	1328 (14)	102 (8)	72 (6)	364 (35)	—7 (11)	—3 (24)	—9 (30)
C (3)	0803 (7)	8216 (5)	873 (15)	77 (7)	72 (5)	419 (31)	—18 (9)	—1 (22)	—6 (27)
C (4)	0540 (6)	8491 (5)	8200 (15)	87 (8)	79 (5)	373 (31)	—39 (9)	—10 (23)	95 (29)
C (5)	9067 (5)	8194 (4)	7430 (13)	93 (6)	55 (4)	328 (28)	5 (8)	15 (19)	64 (25)
C (6)	8675 (5)	7036 (4)	8117 (12)	86 (6)	56 (4)	226 (22)	1 (8)	—30 (17)	25 (22)
C (7)	7161 (5)	6773 (4)	7418 (13)	87 (6)	42 (4)	378 (28)	13 (8)	—27 (19)	—1 (24)
C (8)	6301 (6)	5604 (4)	8113 (13)	121 (8)	43 (4)	407 (31)	—22 (8)	—43 (19)	26 (28)
C (9)	7124 (7)	5402 (5)	806 (14)	125 (8)	50 (4)	00 (31)	—29 (9)	—7 (20)	35 (28)
C (10)	8634 (6)	5709 (4)	1366 (13)	123 (8)	50 (4)	335 (29)	14 (9)	35 (19)	—6 (27)
C (11)	6184 (5)	7592 (4)	8593 (11)	88 (6)	43 (3)	238 (22)	—2 (8)	—2 (15)	—14 (25)
C (12)	4628 (7)	7402 (6)	8011 (16)	90 (8)	63 (5)	340 (37)	3 (11)	0 (25)	0 (32)
C (13)	4306 (8)	7581 (6)	5377 (17)	114 (15)	71 (6)	382 (40)	4 (13)	0 (26)	0 (33)
C (14)	4644 (7)	8747 (6)	4724 (20)	116 (9)	62 (6)	521 (42)	4 (12)	0 (30)	0 (42)
C (15)	6084 (8)	9129 (5)	5645 (16)	123 (10)	51 (5)	376 (37)	4 (11)	0 (25)	0 (35)
N (16)	6622 (5)	8645 (4)	7690 (10)	91 (6)	49 (3)	284 (24)	4 (7)	—14 (6)	6 (21)
C (17)	8017 (7)	8968 (5)	8546 (16)	96 (8)	47 (5)	340 (33)	3 (10)	0 (22)	0 (30)
O	6663 (5)	9884 (4)	4660 (12)	139 (9)	64 (3)	416 (24)	—15 (7)	118 (18)	—41 (27)

TABLE 3. Coordinates and Isotropic Temperature Parameters of the Hydrogen Atoms in the Structure of cis-Matrine (the values of the coordinates are multiplied by 10^3)

Atom	x/a	y/b	z/c	B_j	Atom	x/a	y/b	z/c	B_j
H_2 (1)	59	681	325	4,42	H_9 (1)	650	588	198	4,15
H_2 (2)	108	652	18	4,42	H_9 (2)	699	456	117	4,15
H_3 (1)	12	874	200	3,73	H_{10} (1)	882	558	329	4,07
H_3 (2)	188	841	131	3,73	H_{10} (2)	931	517	30	4,07
H_4 (1)	70	935	782	4,00	H_{11}	636	756	57	3,14
H_4 (2)	124	804	702	4,00	H_{12} (1)	437	655	857	4,07
H_5	894	831	549	3,82	H_{12} (2)	405	792	428	4,07
H_6	933	649	712	3,37	H_{13} (1)	493	706	428	4,60
H_7	699	685	545	3,73	H_{13} (2)	321	742	509	4,60
H_8 (1)	555	551	799	3,64	H_{14} (1)	466	880	269	4,72
H_8 (2)	718	505	689	3,64	H_{14} (2)	386	926	542	4,72
					H_{17} (1)	807	894	56	3,63
					H_{17} (2)	827	979	796	3,63

tex $P2_1$ automatic diffractometer are as follows: a = 9.619(2) Å, b = 12.541(3) Å, c = 5.475 (5) Å; γ = 91.2(5)°. Space group $P2_1$, z = 2; ρ_{calc} = 1.25 g/cm³.

The integral intensities of the reflections were measured in the above-mentioned diffractometer by the θ/2θ-scanning method in monochromatic CuK_α radiation. A total of 1055 independent reflections were recorded, of which, after reflections with $I \leqslant 2\sigma$ had been rejected in the first processing (introductions of LP corrections), 805 reflections were used for the subsequent calculations.

The structure was deciphered by the direct multivariant method using the tangent formula by means of the Rentgen-75 group of programs [11]. In the automatic regime, 1024 sets of phases of structural amplitudes were calculated. For the 14 best sets of phases according to statistical estimates E-syntheses were constructed with the simultaneous localization of the peaks and calculation of the R factor for each model. The first in order of the E-syntheses was the best and had an R factor of 0.12. All the first 18 peaks proved to be the 18 nonhydrogen atoms of the structure.

The structure was refined according to a program [12] of the Kristall group by the method of least squares in the full-matrix variant. By using the coordinates of the nonhydrogen atoms refined in the isotropic and anisotropic approximations (R = 0.102), the positions of the hydrogen atoms were calculated. Then the structure was refined by including the hydrogen atoms, for which, in their turn, the positional and isotropic thermal parameters were refined. In this process, as the initial B_j values we took the isotropic thermal parameters of the carbon atoms bearing hydrogen atoms. The final value of the divergence factor of the structure was 0.065. Table 2 gives the coordinates and anisotropic thermal parameters of the nonhydrogen atoms, and Table 3 the coordinates and isotropic thermal parameters of the hydrogen atoms in the structure of cis-matrine.

SUMMARY

In an investigation of the spatial structure of matrine by x-ray structural analysis, a new stereoisomer of matrine has been detected — the first representative of the C/D-cis series — and it has been called cis-matrine. Its crystal and molecular structure has been studied and accurate geometric parameters of the molecule have been established.

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