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MOLECULAR AND CRYSTAL STRUCTURE OF SOPHORIDINE

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UDC 547.837

The three-dimensional structure of the alkaloid sophoridine $C_{15}H_{24}ON_2$ has been studied by x-ray structural analysis; the parameters of the elementary cell are: a = 5.458, b = 10.640, c = 11.989 Å; $\gamma = 99.7°$; z = 2; space group $P2_1$. The experimental set was obtained on a "Sinteks-$P2_1$" diffractometer, the structure being determined by the direct method with refinement by the method of least squares in the anisotropic approximation taking the hydrogen atoms into account to R = 0.059. Ring A has the chair conformation, rings B and C the boat conformation, and ring D the half-chair conformation. The linkages of rings A/B, B/C, and C/D are trans, and of B/C cis. There are no shortened intermolecular contacts in the crystal structure of the compound.

Sophoridine, $C_{15}H_{24}ON_2$, was first isolated by A. P. Orekhov from the plant *Sophore alopecuroides* [1, 2]. The spatial structure of sophoridine has been widely studied. A. I. Begisheva et al., who had considered the chemical transformations of sophoridine, showed that this alkaloid exists either in the C/D-cis form with the chair conformations of all the rings or in the C/D-trans form with ring C in the boat conformation [3]. PMR investigations of the conformation of sophoridine also confirmed the boat shape of ring C with the chair conformations of the other rings [4]. However, the results of later investigations of the conformation of sophoridine in solution performed by F. G. Kamaev et al. by the INDOR method and by PMR spectroscopy at 300 MHz show that ring B has the boat conformation, as well as ring C [5]. The IR spectra of sophoridine in the solid and liquid phases proved not to be identical [6].

Taking into account the lability of the conformation of sophoridine found in a study of chemical reactions in solutions, it could be assumed that the spatial structure of this alkaloid in the crystal is different from that in solutions. In order to elucidate the three-dimensional structure of the sophoridine molecule in crystals and to compare the conformational state of the molecule in the solid and liquid phases, we have made an x-ray structural study of this compound. The main conformational information that we obtained in a study of the structure of the sophoridine molecule by the method of x-ray structural analysis has been given previously [7]. The present paper contains a more detailed discussion of the results obtained.

In a stereoisomer of sophoridine that we have studied previously — matrine — all the six-membered rings have the chair conformation [8]. In sophoridine, rings B and C have the energetically less favorable boat conformation with retention of the chair form and a form close to the half-chair conformation for rings A and D, respectively. The same relationship of forms is observed for another stereoisomer — (+)-isomatrine [9]. Rings B and C of sophoridine are linked to one another diequatorially at the C(6) and C(7) carbon atoms. The linkage of

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 0009-3130/79/1503-0308$07.50

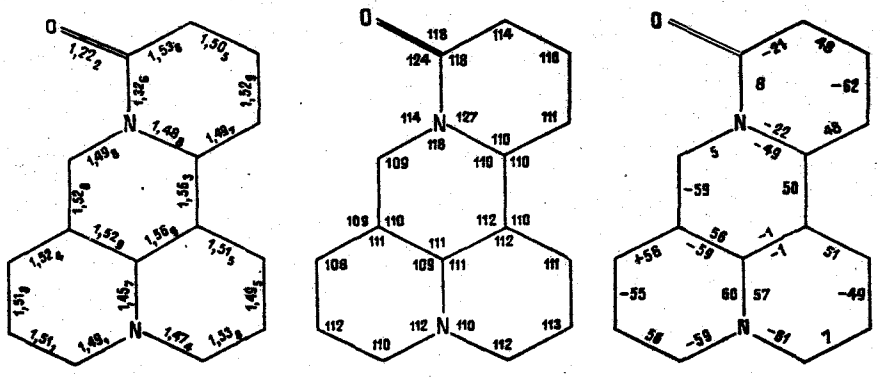
TABLE 1. Coefficients of the Equations of the Planes and the Deviations of the Atoms from them, δ

Plane	Atoms	Coefficients of equations of planes				δ, Å
		A	B	C	D	
I (ring A)	N(1)					−0.0009
	C(2)					0.0009
	C(4)	4.51	−4.56	−5.78	−0.34	−0.0009
	C(5)					0.0009
	C(3)*					0.6931
	C(6)*					−0.6792
II (ring B)	C(6)					−0.0211
	C(7)					0.0182
	C(9)	4.40	−4.80	−5.95	−0.24	−0.0180
	C(10)					0.0211
	N(1)*					−0.6721
	C(8)*					−0.6039
III (ring C)	C(6)					−0.0201
	C(7)					0.0202
	N(16)	4.57	−4.56	−5.55	0.45	−0.0209
	C(17)					0.0210
	C(5)*					−0.6868
	C(11)*					−0.6051
IV (ring D)	C(14)					−0.0111
	C(15)					0.0278
	N(16)	−3.25	4.77	8.66	1.52	−0.0279
	C(11)					0.0131
	C(12)*					0.3750
	C(13)*					−0.3561
V	C(11)					0.0200
	C(15)	−3.26	5.16	8.41	1.66	0.0200
	N(16)					−0.0599
	C(17)					0.0199

*Atoms not included in the calculation of the equations of the planes.

rings A and C also takes place via equatorial bonds. As a result, the conformation of the molecule is determined by A/B, A/C, and C/D-trans and B/C-cis linkages.

Table 1 gives the coefficients of the equations of the planes Ax + By + Cz = D drawn through the individual fragments of the molecule, and also the deviations of the atoms from these planes. In comparison with matrine, in the case of sophoridine the deviations of the C(2) and C(5) atoms from the planes of the remaining atoms of ring A are closer to the deviations in the ideal cyclohexane conformation [10], in which they are ±0.73 Å. Rings B and C are unsymmetrical boats ^{1,8}B and ^{5,11}B with different bends of the angles. The deviations of the atoms from the plane of the "floor" of the boat are smaller than in the ideal cyclohexane structure (these deviations likewise amount to ±0.73 Å, and are very close for rings B and C (Table 3). Ring D has a form close to the half-chair conformation. A detailed consideration of the conformation of this ring has shown that, in contrast to the C(11), N(16), C(15),



a b c

Fig. 1. Geometric parameters of the sophoridine molecule: a) bond lengths; b) valence angles; c) torsion angles.

TABLE 2. Coordinates and Parameters of the Thermal Vibrations of the Nonhydrogen Atoms of the Structure (the standard deviations are given in parentheses; the values of B(ij) have been multiplied by 10^4)

Atom	x/a	y/b	z/c	B(11)	B(22)	B(33)	B(12)	B(23)	B(13)
N(1)	0,2803(16)	0,1552(6)	0,1561(7)	499(43)	85(7)	93(7)	—13(30)	—4(13)	—53(33)
C(2)	0,2569(19)	0,0396(8)	0,2292(9)	633(50)	114(11)	146(12)	—5(40)	9(18)	—49(47)
C(3)	0,3045(20)	0,0779(9)	0,3487(8)	633(53)	109(10)	133(10)	116(42)	92(18)	14(30)
C(4)	0,5539(17)	0,1619(8)	0,3652(8)	475(42)	112(10)	94(8)	32(34)	52(50)	16(32)
C(5)	0,5722(16)	0,2764(7)	0,2864(8)	310(39)	89(8)	69,8)	—7(31)	24(14)	17(29)
C(6)	0,5258(17)	0,2336(8)	0,1652(8)	374(41)	111(10)	76,8)	66(35)	—19(16)	—7(31)
C(7)	0,5593(17)	0,3517(8)	0,0845(8)	416(40)	119(10)	67(7)	71(34)	—22(14)	—10(31)
C(8)	0,3227(20)	0,3515(9)	0,0174(9)	569(53)	157(19)	78(9)	—20(42)	27(19)	—147(43)
C(9)	0,7562(22)	0,7753(12)	0,4603(9)	623(57)	201(16)	111(10)	—27(53)	52(22)	151(42)
C(10)	0,2378(23)	0,1121(10)	0,0407(10)	803(65)	173(14)	124(12)	57(52)	—112(23)	—173(49)
C(11)	0,6276(18)	0,4793(9)	0,1486(8)	502(43)	161(12)	56(7)	233(38)	39(17)	—16(33)
C(12)	0,6871(21)	0,5877(8)	0,0677(8)	667(53)	102(10)	84(8)	56(39)	30(15)	—25(38)
C(13)	0,8053(22)	0,7112(8)	0,1285(7)	924(67)	135(11)	104(11)	124(47)	66(19)	—94(46)
C(14)	0,0400(20)	0,6944(8)	0,1822(9)	637(50)	109(10)	122(11)	42(40)	24(18)	45(42)
C(15)	0,0223(22)	0,5673(10)	0,2491(8)	357(49)	179(14)	72(9)	146(50)	—24(18)	72(38)
N(16)	0,8399(13)	0,4747(6)	0,2251(5)	319(31)	90(8)	65(6)	15(29)	0(12)	—68(26)
C(17)	0,8255(18)	0,3610(8)	0,2985(8)	449(43)	104(9)	76(8)	96(34)	50(14)	12(32)
O	0,1814(13)	0,5594(6)	0,3194(6)	390(30)	151(9)	99(7)	27(28)	—33(13)	—65(28)

TABLE 3. Coordinates and Isotropic Thermal Parameters of the Hydrogen Atoms*

Atom	x/a	y/b	z/c	B, Å²	Atom	x/a	y/b	z/c	B, Å²
$H_2(1)$	0,0731	−0,0165	0,2199	8,18	$H_9(2)$	0,3469	0,2170	−0,1051	5,01
$H_2(2)$	0,4086	−0,0084	0,2093	8,73	$H_{10}(1)$	0,3629	0,0544	0,0167	9,27
$H_3(1)$	0,3026	−0,0086	0,4025	6,20	$H_{10}(2)$	0,0436	0,0532	0,0358	9,21
$H_3(2)$	0,1599	0,1303	0,3746	6,00	H_{11}	0,4678	0,4866	0,2083	9,37
$H_4(1)$	0,6932	0,1110	0,3463	3,15	$H_{12}(1)$	0,8246	0,5726	0,0092	6,39
$H_4(2)$	0,5561	0,1968	0,4519	7,24	$H_{12}(2)$	0,5233	0,5978	0,0209	8,12
H_5	0,4086	0,3103	0,3175	2,85	$H_{13}(1)$	0,8503	0,7906	0,0309	8,82
H_6	0,6365	0,1748	0,1423	8,26	$H_{13}(2)$	0,6883	0,7199	0,2175	3,62
H_7	0,6870	0,3341	0,0244	8,85	$H_{14}(1)$	0,9320	0,7731	0,2379	5,25
$H_8(1)$	0,3205	0,4231	−0,0342	9,95	$H_{14}(2)$	0,0752	0,6933	0,1181	6,12
$H_8(2)$	0,1653	0,3634	0,0634	5,32	$H_{17}(1)$	0,9616	0,3134	0,2735	5,21
$H_9(1)$	0,0783	0,2288	−0,0755	9,69	$H_{17}(2)$	0,7988	0,3896	0,3829	3,68

*The hydrogen atoms have been allocated the numbers of the carbon atoms to which they are attached.

C(14), and C(13) atoms, which are not completely coplanar, the C(11), N(16), C(15), and C(14) lie fairly well in a single plane or, in other words, the inclusion of the C(13) atom in the C(11), N(16), C(15), and C(14) group of atoms worsens their coplanarity.

Previously [7], in a consideration of the plane of the C(11), N(16), C(15), C(14), and C(13) atoms of ring D, the deviation of the C(12) atom from this plane was found to be 0.60 Å. In addition to the deviation of the atoms from this plane, it is desirable to consider the deviation from the C(11), N(16), C(15), C(14) plane. The C(12) and C(13) atoms depart from the plane of the other atoms in opposite directions by 0.35 and 0.37 Å, respectively. In matrine [8], ring D also has a conformation close to the half-chair conformation, but, unlike sophoridine, the C(13) departs from the plane of the other atoms by 0.73 Å.

The planes of rings A, B, and C are almost parallel: the plane of ring A makes an angle of 1.1° with the plane of ring B, and the angle between the planes of rings B and C is 2.7°. The planarity of the "relief" of the molecules as a whole is disturbed because of the deviation of the plane of ring D from the common plane of the other three rings: the angle between them is 21°.

It can be seen from the values of the torsion angles given in Fig. 1c that the conformation of ring A is closer to the ideal chair conformation [11] then the conformations of the corresponding rings of matrine and (+)-isomatrine. On comparing the torsion angles in rings B and D of the sophoridine and (+)-isomatrine molecules, in which these rings have the boat conformation, attention is attracted by the fact that angles equal in the ideal boat to zero are decreased in sophoridine. This may indicate some greater eclipsing strain in sophoridine.

The coordination of the N(1) atom is pyramidal, and that of the N(16) is plane-trigonal, because of conjungation in the lactam fragment of the molecule. The valence angles at N(16) in sophoridine and (+)-isomatrine are equal, while in matrine the C(15), N(16), C(17), and the C(11), N(16), and C(17) angles are inverted, while the endocyclic C(11), N(16), and C(15) angle remains unchanged. This difference is apparently due to the different conformations of ring C in sophoridine and matrine: in the first compound it has the boat conformation and in the second the chair conformation. In the molecules of the compounds the distribution of the valence angles at the C(15) atom and the C(15)–O bond length, which is 1.22 Å, remain constant.

The lengths of the C(15)–N(16) bonds in (+)-isomatrine, matrine, and sophoridine are 1.37, 1.35, and 1.33 Å, respectively (Fig. 1a). The values of the N(1)–C bond lengths are close to the lengths of the bonds found in other alkaloids, their mean value in sophoridine being 1.47 Å. The N(1)–C(6) bond is somewhat shorter than the other two bonds, but the effect is slight. The mean value of the C–C bond lengths is 1.53 Å. The C(6)–C(7) and C(7)–C(8) interatomic distances are 1.57 and 1.51 Å, respectively, while these distances in matrine are 1.53 and 1.56 Å. Such a redistribution of bond lengths may be connected with the more highly strained conformation on passing from the chair conformation to the boat conformation in rings B and C.

The C–C–C valence angles (Fig. 1b) are close to tetrahedral. Both in sophoridine and in matrine, the angle at C(14) is increased to 113-114°C. As can be seen from the results given, the forms of rings A, B, and C established in the present work confirm previous results [5]

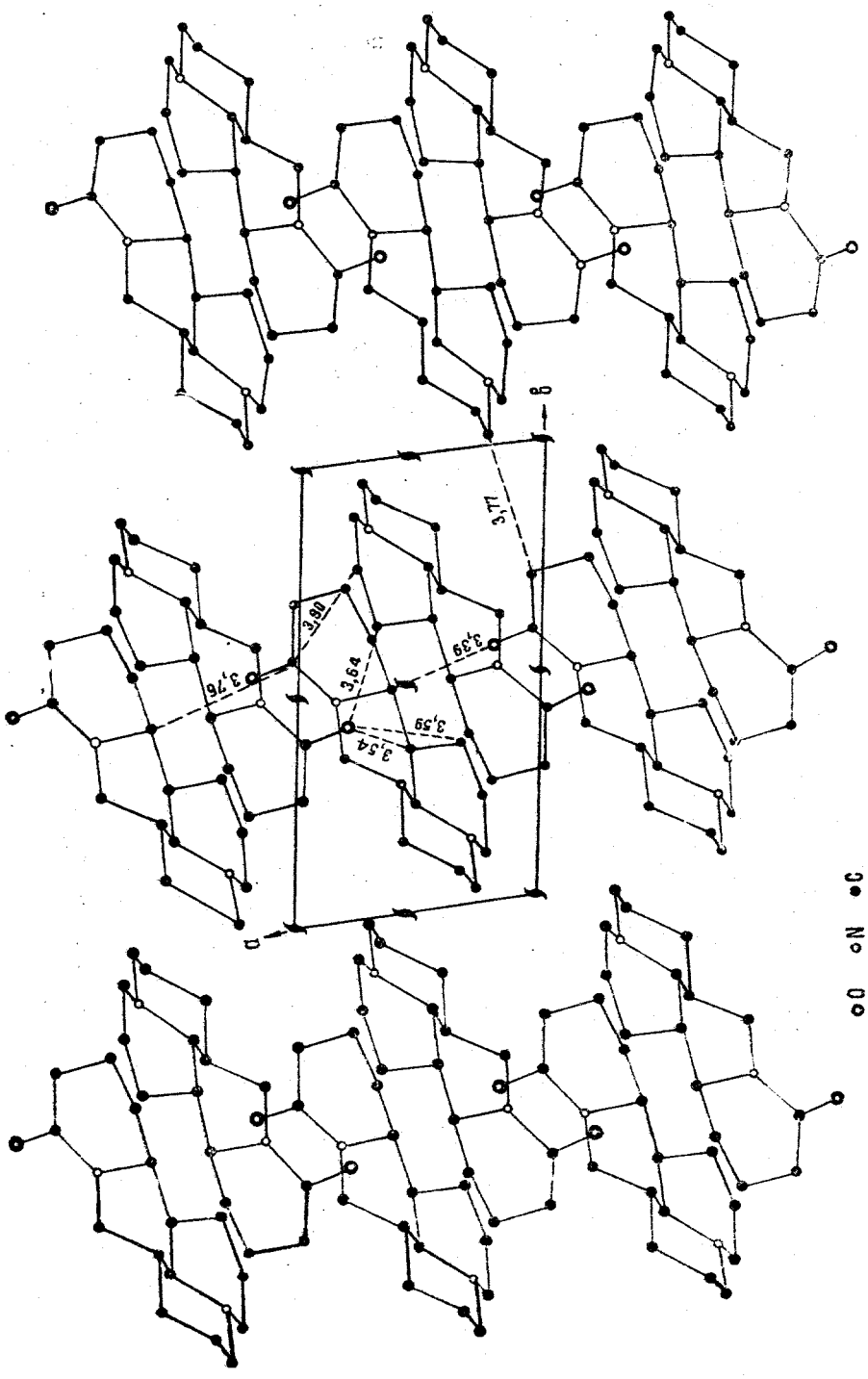


Fig. 2. Arrangement of the molecules in the crystal structure of sophoridine.

TABLE 4. Ellipsoids of the Thermal Vibrations of the Nonhydrogen Atoms and Their Orientations Relative to the Crystallographic Axes

Atom	Semi-axis, Å of ETV	Angles, deg			Atom	Semi-axis, Å of ETV	Angles, deg		
		a, j	*b, j*	*c, j*			*a, j*	*c, j*	*b, j*
N(1)	0,460	160	69	73	C(10)	0,565	123	114	48
	0,391	75	101	17		0,527	40	138	81
	0,312	76	24	85		0,342	71	58	43
C(2)	0 506	125	74	37	C(11)	0,474	57	42	88
	0,459	41	112	53		0,397	140	53	65
	0,374	772	28	90		0,285	70	108	25
C(3)	0,513	101	60	31	C(12)	0,508	174	78	85
	0,445	11	92	82		0,374	84	56	36
	0,317	88	1150	61		0,335	89	144	54
C(4)	0,442	108	60	31	C(13)	0,546	156	76	66
	0,403	22	92	82		0,474	71	47	55
	0,332	101	150	61		0,351	75	134	45
C(5)	0,379	125	51	52	C(14)	0,528	22	101	68
	0,326	50	106	42		0,428	108	56	37
	0,293	120	137	75		0,354	103	143	62
C(6)	0,393	80	48	58	C(15)	0,462	97	163	85
	0,362	10	90	94		0,402	40	100	50
	0,334	92	58	32		0,284	129	76	40
C(7)	0,416	65	156	73	N(16)	0,384	135	69	48
	0,382	26	74	92		0,353	92	159	72
	0,316	96	73	17		0,291	45	86	47
C(8)	0,516	142	60	62	C(17)	0,426	133	48	62
	0,424	103	149	70		0,391	43	72	58
	0 319	56	86	36		0,300	95	132	45
C(9)	0,567	117	18	86	O	0,453	83	156	66
	0 493	48	80	47		0,422	119	68	35
	0,337	126	105	43		0,339	30	82	66

relating to the forms of these rings. A discrepancy is that we have found the half-chair conformation for ring D, while the chair conformation was found previously [5].

Figure 2 shows the packing of the molecules in the crystal structure of sophoridine (projection ab); no special features can be observed in this.

EXPERIMENTAL

Colorless transparent crystals of sophoridine obtained by crystallization from petroleum ether have an acicular habit and belong to the monoclinic system. The parameters of the primitive elementary cell were determined from precission x-ray diagrams and were refined by the method of least squares with respect to 15 reflections on a "Sinteks-$P2_1$" automatic four-circle diffractometer:

a=5,458(1) Å	$C_{15}H_{24}O_2N_2$
b=10,640(2)Å	M=258
c=11,989(2)Å	d_{calc}=1,19 g/cm^3
γ=99,7(3) deg	Z=2
V=686,2Å^3	Space group $O2_1$

A three-dimensional set of intensities was obtained on this diffractometer using copper radiation monochromatized by reflection from a graphite crystal, with scanning by the $\theta/2\theta$ method to $\theta \leqslant 52°$. In the primary treatment of the group of results, weak reflections with $I \leqslant 2\sigma$ were discarded. The final group of structural amplitudes amounted to 802 independent nonzero reflections. No correction was made for absorption.

The model of the structure was found by using the "Rentgen-75" automated system of programs [12]. From the 1024 sets of phases calculated, the 15 best according to S-estimates were selected and these were then used to construct the E-syntheses. The correct variant was the 10th according to the size of the estimates and had R = 0.26. The E-synthesis constructed from the phases of this variant contained 21 peaks: 17 peaks corresponded to the atoms of the structure and four were false (only the C(13) atom was absent). However, a F-synthesis from the subsequent series of syntheses revealed the missing carbon atom.

Refinement of the structure by the method of least squares in the full-matrix variant was carried out by the programs of the "Kristall" complex [13]. After a series of refinements of the nonhydrogen atoms, first in the isotropic approximation (R = 0.12) and then in the anisotropic approximation (R = 0.99), the positioning of the hydrogen atoms was carried out using geometric considerations. The subsequent refinement of the coordinates of the nonhydrogen atoms taking into account the anisotropy of their thermal vibrations, and also the coordinates and isotropic thermal parameters of the hydrogen atoms, led to R = 0.059. As the initial temperature factors of the hydrogen atoms we used the B(ij) values of the carbon atoms to which they were attached.

The coordinates and the anisotropic thermal parameters of the nonhydrogen atoms of the structure are shown in Table 2, and the coordinates and isotropic thermal parameters of the hydrogen atoms in Table 3.

From the values of the anisotropic thermal parameters B(ij) for the nonhydrogen atoms we calculated the semiaxes of the ellipsoids of thermal vibrations and their orientations relative to the crystallogrphic axes. It follows from Table 4 that the thermal vibrations of the atoms become greater with increasing distance from the center of gravity of the molecule and with a decrease in the number of bonds to nonhydrogen atoms, particularly to atoms belonging to several rings.

SUMMARY

The conformation of the molecule of the alkaloid sophoridine in the crystal has been determined by x-ray structural analysis: the ring-linkages are A/B-, A/C-, and C/D-trans and B/C-cis with the chair conformation of ring A, the boat conformation of rings B and C, and the half-chair conformation of ring D.

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