CRYSTAL AND MOLECULAR STRUCTURE OF THE MACROCYCLIC PYRROLIZIDINE ALKALOID INCANINE

B. Tashkhodzhaev, M. V. Telezhenetskaya, and S. Yu. Yunusov

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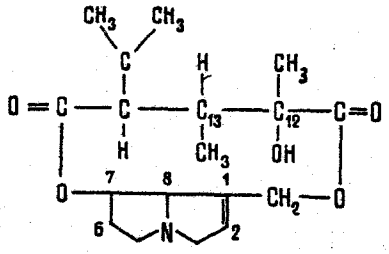
An x-ray structural investigation (diffractometer, Cu, 1001 reflections, direct method, MLS in the anisotropic approximation to R = 0.066), of the alkaloid incanine has been performed. The crystals are rhombic, a = 10.07, b = 16.20, c = 14.04 Å, space group $P2_12_12_1$, z = 4. The conformation of the backbone of the macrocycle in incanine practically coincides with those in fulvine and axillarine.

The macrocyclic pyrrolizidine alkaloid incanine has been isolated from the Central Asian plant *Trichodesma incanum*, which belongs to the family Boraginaceae [1]. It has been established previously [1, 2] that incanine has the structure



However, no stereochemical investigations of the alkaloid have been performed. There have been some attempts to predict the conformation of the side chains of the macrocycle: the relative positions of the substituents at C(12) and C(13) have been suggested on the basis of mass spectrometric results. Here it was assumed that the methyl groups at C(12) and C(13) have the transoid conformation [3]. Later, on the basis of the results of an x-ray structural

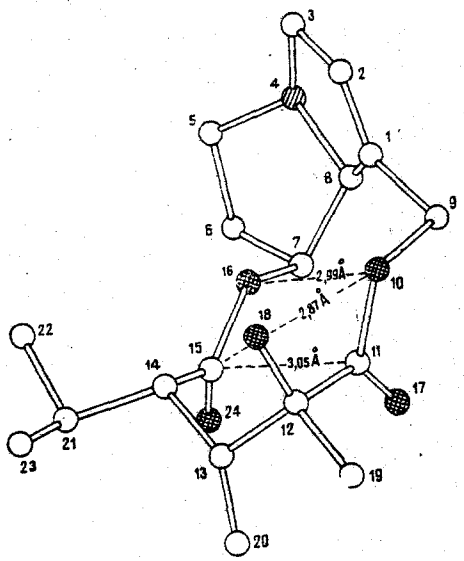


Fig. 1. Geometry of the incanine molecule.

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TABLE 1. Bond Lengths (r, Å) and Valence Angles (ω, degrees)

Bond	r	Angle	ω	Angle	ω
C(1) —C(2)	1,301(11)	C(2) C(1) C(9)	126,8(7)	O(18) C(12) C(13)	105,3(6)
C(1) —C(8)	1,532(10)	C(8) C(1) C(2)	107,3(6)	O(18) C(12) C(19)	110.3(6)
C(1) —C(9)	1,499(11)	C(8) C(1) C(9)	122 3(7)	C(11) C(12) C(19)	106.0(6)
C(2) — C(3)	1,498(11)	C(1) C(2) C(3)	113.6(7)	C(13) C(12) C(19)	109,6(7)
C(3) —N(4)	1,497(10)	C(2) C(3) N(4)	103,0(7)	C(12) C(13) C(20)	116,7(8)
N(4) —C(5)	1,457(11)	C(3) N(4) C(5)	109,6(6)	C(12) C(13) C(14)	112 2(6)
N(4) —C(8)	1,497(10)	C(3) N(4) C(8)	114,8(7)	C(20) C(13) C(14)	112,2(7)
C(5) —C(6)	1,498(12)	C(5) N(4) C(8)	107,2(6)	C(13) C(14) C(15)	110,4(6)
C(6) — C(7)	1,518(11)	N(4) C(5) C(6)	104,0(7)	C(13) C(14) C(21)	115.8(7)
C(7) —C(8)	1,518(11)	C(5) C(6) C(7)	102,8(7)	C(15) C(14) C(21)	108,1(7)
C(7) —O(16)	1,465(9)	C(6) C(7) C(8)	101,6(7)	C(14) C(15) O(16)	111,3(6)
C(9) —O(10)	1,474(6)	C(16) C(7) C(8)	107,3(6)	C(14) C(15) O(24)	124,7(8)
O(10)—C(11)	1,332(9)	C(16) C(7) C(6)	110 0(6)	O(16) C(15) O(24)	124,0(7)
C(11) — O(17)	1,214(10)	N(4) C(8) C(7)	106,3(6)	C(15) O(16) C(7)	115,2(6)
C(11) — C(12)	1,496(10)	N(4) C(8) C(1)	102,9(6)	C(14) C(21) C(22)	108,4(8)
C(12) — O(18)	1,416(9)	C(7) C(8) C(1)	118,6(6)	C(14) C(21) C(23)	111,8(8)
C(12) — C(19)	1,554(12)	C(1) C(9) O(10)	109,2(6)	C(23) C(21) C(22)	110,2(8)
C(12) — C(13)	1,539(10)	C(9) O(10) C(11)	118,9(6)	C(25) C(26) C(27)	117.7(1,0)
C(13) — C(20)	1,546(12)	O(10) C(11) O(17)	123,4(7)	C(26) C(27) C(28)	118,7(1,0)
C(13) — C(14)	1,555(11)	O(10) C(11) C(12)	111,8(7)	C(27) C(28) C(29)	121,6(1,2)
C(14) — C(21)	1,555(11)	O(17) C(11) C(12)	124,8(8)	C(28) C(29) C(30)	123,2(1,1)
C(14) — C(15)	1,544(11)	C(11) C(12) C(13)	112,5(6)	C(29) C(30) C(25)	118,2(1,0)
C(15) — O(24)	1,187(10)	O(18) C(12) C(11)	113,1(7)	C(30) C(25) C(26)	120,6(1,0)
C(15) — O(16)	1,332(9)				
C(21) — C(22)	1,577(15)				
C(21) — C(23)	1,543(14)				
C(25) — C(26)	1,420(15)				
C(26) — C(27)	1,432(17)				
C(27) — C(28)	1,360(17)				
C(28) — C(29)	1,336(16)				
C(29) — C(30)	1,390(15)				
C(30) — C(25)	1,358(15)				

analysis of the alkaloids fulvine [4] and axillarine [5], which are related to incanine, the authors concerned [3] recognized the necessity for a careful check of their hypothesis [6].

In order to establish the spatial structure of incanine unambiguously, we have performed an x-ray structural investigation.

The geometry of the incanine molecule that has been found is shown in projection on the (001) plane in Fig. 1. The valence angles and bond lengths (Table 1), both in the pyrrolizidine ring and in the macrocycle itself differ little from those found in the related pyrrolizidine alkaloids fulvine [4], axillarine [5], and retusamine [7], and also in the 12-membered bases of this series jacobine [8] and yamataimine [9].

The pyrrolizidine nucleus in incanine has a conformation similar to that in the alkaloids mentioned above. The dihedral angle between the two linked five-membered rings is 125.4° (without taking the C(6) atom into account). The saturated five-membered ring [the N(4), C(5), C(6), C(7), and C(8) atoms] has the "envelope" conformation; the angle between the C(5)C(6)C(7) and C(5)N(4)C(8) planes is 45.3° (or the C(6) atom departs from the plane of the other four by 0.61 Å). The other five-membered ring is planar.

The polar carbonyl groups C(11)=O(17) and C(15)=O(24) are syn-parallel. The lactone groups [the C(9), O(10), C(11), O(17), and C(12), and the C(14), C(15), O(24), O(16), and C(7) atoms] are planar with an accuracy of 0.04 Å and have the trans conformation, and the angle between them is 20.3°. The distance between the lactone groups of 3.0 Å shows the possibility of a transannular interaction of the π-electron systems [4].

On considering the configurations of the C(12) and C(13) asymmetric centers, it may be noted that the substituents at these centers, the methyl and hydroxy groups, have an almost transoid conformation since the angle between the C(12)C(13)O(18) and C(12)C(13)C(20) planes is 168°. The methyl groups are approximately gauche-oriented (dihedral angle 49.4°). These facts are not in harmony with the hypothesis put forward previously [3].

It is striking that the conformation of the backbone of the 11-membered macrocycle of incanine is similar to that of the macrocycle in fulvine. The torsion angles of the macrocycle are given after Fig. 2 at the top of the next page.

The elementary cell of the substance under investigation contains, in addition to an incanine molecule, a molecule of benzene of crystallization. The bond lengths and valence angles

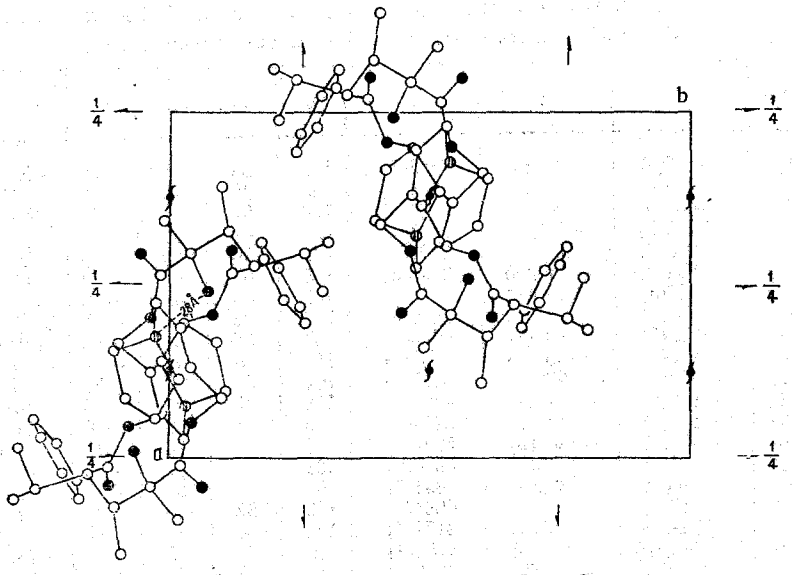

Fig. 2. Packing of the molecules.

Fragment	φ, degrees
8 — 1— 9—10	—100,6
1 — 9—10—11	105,2
9 —10—11—12	175,5
10—11—12—13	127,8
11—12—13—14	— 63,1
12—13—14—15	81,4
13—14—15—16	—103,4
14—15—16— 7	—175 2
15—16— 7— 8	—167,2

in the ring of the benzene of crystallization agree with those given in the literature within the limits of experimental error. The lengths of the C–H bonds average 1.06±0.08 Å.

Packing of the Molecules. The arrangement of the molecule in the crystal cell as projected on the plane of the crystallographic axes is shown in Fig. 2. Analysis of intermolecular contacts shows the possibility of an intermolecular hydrogen bond: the O(18)...N(4) distance is 2.8 Å (Fig. 2). No other anomalously short intermolecular contacts are observed. There is one molecule of benzene or crystallization to one molecule of incanine in the elementary cell.

EXPERIMENTAL

The incanine crystals, which were grown from benzene solution by slow cooling, had the form of elongated prisms.

The space group and the parameters of the elementary cell were determined from rotation of Weissenberg x-ray diagrams. Then the cell parameters were refined on a Hilger–Watts diffractometer using CuK_α radiation: a = 10.068(1), b = 16.199(2), c = 14.038(1) Å; d_{calc} = 1.211 g/cm^3, space group $P\,2_12_12_1$, z = 4.

The intensities of all the reflections with $\theta \leqslant 57.5°$ were measured in the diffractometer mentioned. About 1100 independent nonzero reflections were obtained. The 1001 structural factors exceeding 3σ were used in the calculations.

The structure of incanine was deciphered by the direct method according to the "Rentgen-75" program [10] using 206 values of $E \geqslant 1.20$ composed of 2,03 ternary derivatives. The basis group consisted of eight reflections. A E-series was constructed from the best variant of the signs (R factor 0.37) and in this all the nonhydrogen atoms of the incanine molecule and of the molecule of benzene of crystallization were found. For a more accurate localization of the atoms we calculated a ρ(xyz) synthesis, and then the structure was refined by several successive approximations of the electron density and by the method of least squares (MLS) in the isotropic approximation to R = 0.15. In the following stage, the position parameters of all the atoms were refined in the full-matrix anisotropic approximation to R = 0.08. In the last stage of the MLS the difference syntheses of the electron density were

TABLE 2. Coordinates and Anisotropic Thermal Parameters ($\times 10^4$) of the N, O, and C atoms of the Incanine Molecule

Atom	x	y	z	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C(1)	2633(8)	438(4)	6523(5)	111	35	41	−18	−22	− 7
C(2)	3793(8)	156(5)	6277(5)	125	40	48	−27	− 4	− 7
C(3)	4482(9)	− 311(6)	7055(5)	110	61	57	35	46	25
N(4)	3510(7)	− 269(4)	7861(5)	125	41	52	12	15	6
C(5)	3048(9)	−1067(6)	8206(6)	136	50	69	5	−20	10
C(6)	1654(9)	− 904(6)	8526(6)	155	61	47	0	14	15
C(7)	1120(8)	− 343(5)	7749(5)	107	48	42	−15	25	10
C(8)	2309(8)	208(5)	7556(5)	113	36	47	11	−14	0
C(9)	1709(9)	941(5)	5920(6)	144	36	56	−55	−35	2
O(10)	980(6)	389(3)	5268(3)	111	45	46	−14	− 6	− 4
C(11)	− 289(8)	220(5)	5451(6)	104	39	57	39	− 15	3
C(12)	− 842(8)	− 399(4)	4766(5)	105	37	49	−10	−16	− 9
C(13)	−1512(8)	−1131(5)	5273(6)	90	35	69	−28	18	−15
C(14)	− 514(8)	−1637(5)	5884(6)	94	40	60	−19	26	−17
C(15)	− 291(8)	−1214(5)	6856(6)	103	39	57	−16	41	18
O(16)	870(5)	− 820(3)	6881(3)	92	42	51	− 2	28	− 3
O(17)	− 917(7)	549(4)	6084(4)	120	58	100	31	37	−66
O(18)	138(6)	− 755(3)	4171(4)	125	40	52	12	12	−20
C(19)	1886(10)	71(6)	4158(7)	109	60	79	0	−23	27
C(20)	−2814(9)	− 945(8)	5816(7)	68	108	95	23	−42	23
C(21)	− 897(11)	−2553(6)	6070(7)	154	43	91	−10	92	−17
C(22)	286(12)	−2983(6)	6614(10)	190	35	148	−10	−63	55
C(23)	−1200(13)	−3018(6)	5136(8)	254	47	120	−23	−29	−58
O(24)	−1038(6)	−1250(4)	7509(4)	122	85	68	−50	89	− 2
C(25)	− 532(12)	−2113(6)	439(7)	202	50	78	−52	15	1
C(26)	661(11)	−2554(7)	622(9)	147	63	121	−62	−49	27
C(27)	1113(10)	−2597(6)	1588(9)	121	43	137	−41	62	−11
C(28)	382(13)	−2221(7)	2279(9)	221	66	110	−42	4	8
C(29)	− 702(12)	−1815(7)	2072(8)	20	58	90	−63	−27	17
C(30)	−1213(11)	−1750(6)	1161(8)	147	56	106	−13	6	− 4

TABLE 3. Coordinates ($\times 10^3$) of the H Atoms of the Incanine Molecule

Atoms	x	y	z	Atoms	x	y	z
H(2)	423	18	550	H(13)	−178	−160	476
H(5)	370	−133	878	H(13)′	45	−167	548
H(5)′	299	− 152	770	H(19)	−128	26	371
H(6)	184	− 72	920	H(20)	−341	− 80	551
H(6)′	127	−154	806	H(22)	− 1	−367	667
H(7)	− 11	− 16	798	H(25)	− 63	−211	971
H(8)	227	72	799	H(29)	−125	−150	1,267
H(9)	193	147	555	H(9)′	95	123	646

calculated in order to find the coordinates of the H atoms, 16 out of the 33 hydrogen atoms being located. The final value of the R factor taking the H coordinates into account was 0.066. The coordinates of the atoms and the anisotropic temperature factors are given in Table 2, and the coordinates of the hydrogen atoms found from the difference synthesis of the electron density are given in Table 3.

SUMMARY

1. The three-dimensional structure of the macrocyclic pyrrolizidine alkaloid incanine has been established unambiguously on the basis of a complete x-ray structural investigation.

2. It has been shown that the methyl groups at C(12) and C(13) have the gauche orientation, and the methyl and hydroxy groups have the trans arrangement with respect to one another.

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CRYSTAL AND MOLECULAR STRUCTURE OF THE MACROCYCLIC PYRROLIZIDINE ALKALOID TRICHODESMINE

B. Tashkhodzhaev, M. R. Yagudaev, and S. Yu. Yunusov

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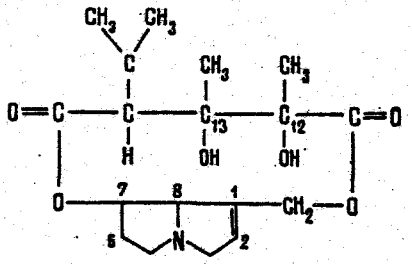
An x-ray structural investigation (diffractometer, λCu, 1286 reflections, direct method, MLS in the anisotropic approximation to R = 0.085) of the alkaloid trichodesmine has been performed. The crystals are monoclinic, a = 23.30, b = 15.11, c = 8.79 Å, γ = 144.3°, space group B2, z = 4. The conformation of the trichodesmine macrocycle differs substantially from that of the other alkaloids of this series that have been studied.

The alkaloid trichodesmine was isolated from the Central Asian plant *Trichodesma incanum* as early as 1935 [1]. The following structure has been established for it [2].



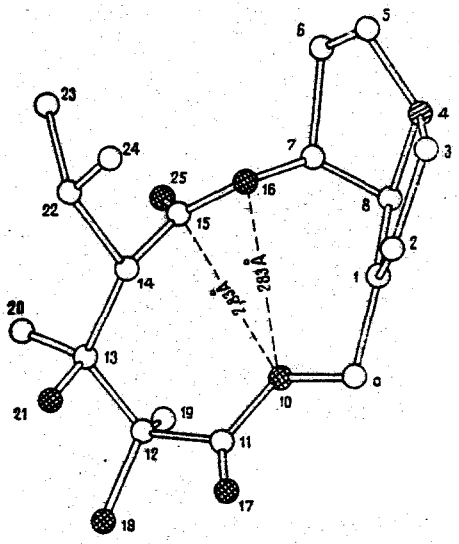


Fig. 1. Geometry of the trichodesmine molecule.

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