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CRYSTAL AND MOLECULAR STRUCTURE OF THE MACROCYCLIC PYRROLIZIDINE

ALKALOID TRICHODESMINE

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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, $\gamma = 144.3^\circ$, 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].

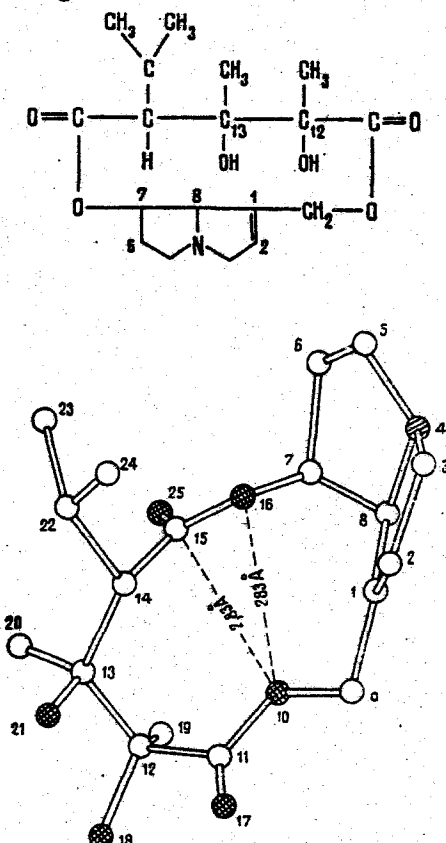


Fig. 1. Geometry of the trichodesmine molecule.

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

Bond	r	Angle	ω	Angle	ω
C(1) - C(2)	1.334(14)	C(2) C(1) C(8)	109.8(6)	O(18) C(12) C(13)	107.4(7)
C(1) - C(8)	1.490(12)	C(2) C(1) C(9)	124.2(9)	O(18) C(12) C(11)	106.3(6)
C(1) - C(9)	1.502(9)	C(8) C(1) C(9)	125.8(9)	C(19) C(12) C(13)	115.9(7)
C(2) - C(3)	1.467(9)	C(1) C(2) C(3)	113.0(9)	C(19) C(12) C(11)	109.5(7)
C(3) - N(4)	1.478(16)	C(2) C(3) N(4)	105.3(9)	C(11) C(12) C(13)	110.5(8)
N(4) - C(5)	1.483(7)	C(3) N(4) C(5)	114.7(9)	O(21) C(13) C(14)	103.9(8)
N(4) - C(8)	1.523(0)	C(3) N(4) C(8)	107.0(6)	O(21) C(13) C(20)	109.7(6)
C(5) - C(6)	1.528(15)	C(8) N(4) C(5)	107.5(5)	O(21) C(13) C(12)	104.7(6)
C(6) - C(7)	1.520(9)	N(4) C(5) C(6)	105.8(7)	C(14) C(13) C(20)	113.2(5)
C(7) - C(8)	1.530(6)	C(5) C(6) C(7)	102.4(7)	C(14) C(13) C(12)	113.1(4)
C(7) - O(16)	1.454(10)	C(6) C(7) C(8)	104.6(4)	C(20) C(13) C(12)	111.6(8)
C(9) - O(10)	1.467(6)	C(6) C(7) O(16)	109.9(7)	C(13) C(14) C(15)	115.1(8)
O(10) - C(11)	1.353(10)	C(8) C(7) O(16)	106.4(7)	C(13) C(14) C(22)	114.5(5)
C(11) - O(17)	1.174(14)	N(4) C(8) C(7)	105.2(5)	C(15) C(14) C(22)	110.3(6)
C(11) - C(12)	1.562(7)	N(4) C(8) C(1)	104.7(7)	C(14) C(15) O(16)	110.4(8)
C(12) - O(18)	1.424(8)	C(7) C(8) C(1)	116.4(5)	C(14) C(15) O(25)	125.8(5)
C(12) - C(19)	1.53(21)	C(1) C(9) C(10)	109.4(5)	O(16) C(15) O(25)	123.8(8)
C(12) - C(13)	1.568(11)	C(9) C(10) C(11)	115.3(7)	C(15) O(16) C(7)	116.8(7)
C(13) - C(20)	1.53(9)	O(10) C(11) C(12)	111.0(8)	C(14) C(22) C(23)	113.6(1.2)
C(13) - O(21)	1.421(13)	O(10) C(11) O(17)	125.1(5)	C(14) C(22) C(24)	109.5(6)
C(13) - C(14)	1.552(7)	O(17) C(11) C(12)	123.9(7)	C(23) C(22) C(24)	110.1(9)
C(14) - C(22)	1.562(12)	O(18) C(12) C(19)	105.3(9)		
C(14) - C(15)	1.519(13)				
C(15) - O(25)	1.208(12)				
C(15) - O(16)	1.329(5)				
C(22) - C(23)	1.533(18)				
C(22) - C(24)	1.525(18)				

TABLE 2. Torsion Angles of the Macrocycles of Trichodesmine (ψ_I) and Incanine (ψ_{II})

Fragment	ψ_I	ψ_{II}
8-1-9-10	-56.1	-100.6
1-9-10-11	-129.6	100.5
9-10-11-12	180.0	175.5
10-11-12-13	-90.7	127.8
11-12-13-14	38.2	-83.1
12-13-14-15	57.2	81.4
13-14-15-16	-142.7	-103.4
14-15-16-7	159.3	-175.2
15-10-7-8	-137.5	-167.2

The cisoid orientation of the OH groups at the C(12) and C(13) asymmetric centers in the trichodesmine macrocycle have been established previously [2-4]. However, Adams and Gianturco [5] consider that the OH groups in these centers have the transoid orientation with respect to one another. The configurations with respect to the other asymmetric centers and the conformation of the backbone of the macrocycle as a whole have not so far been determined.

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

The trichodesmine molecule is shown in projection on the (010) plane in Fig. 1. The lengths of the valence angles and the magnitudes of the angles (Table 1) do not differ from those found for incanine [6] and agree well with the values observed for other related alkaloids [7, 8], as well. The average length of the C-H bonds is 1.01 ± 0.11 Å.

The conformation of the pyrrolizidine nucleus as a whole coincides with the conformation observed for incanine [6], fulvine [7], and axillarine [8]. The angle between the two linked five-membered rings (123.7°) is comparable with the angles found in incanine (125.4°) and axillarine (126°), but is somewhat larger than in fulvine (115°). One five-membered ring [the N(4), C(1), C(2), C(3), and C(8) atoms] is planar and the other five-membered ring [the N(4), C(5), C(6), C(7), and C(8) atoms] has the "envelope" conformation. The angle between the N(4), C(5), C(6) and the C(6), C(7), C(8), N(4) planes (36.7°) is considerably smaller than the corresponding angles in incanine (45.4°), fulvine (46°), and axillarine (42°).

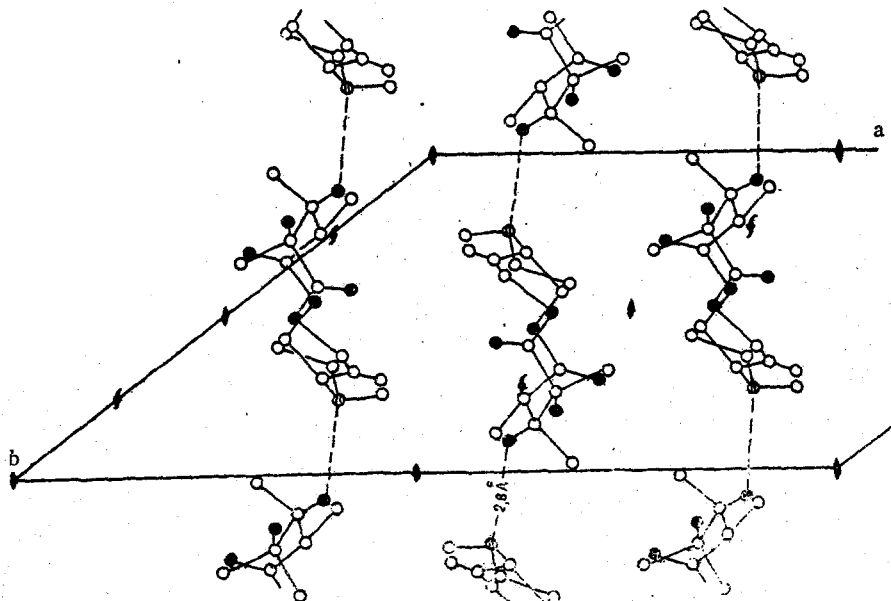


Fig. 2. Packing of the molecules.

The polar C=O bonds of the lactone groups in trichodesmine have the opposite orientation (155.5°). This is somewhat unusual for the 11-membered macrocyclic alkaloids, since in other, related, alkaloids — incanine, fulvine, and axillarine — the carbonyl bonds are arranged in parallel. The angle between the planes of the lactone groups (24.6°) is comparable with that found in incanine (20.3°). The lactone group formed by the C(7), O(16), C(15), O(25), and C(14) atoms of the skeleton is twisted (torsion angle 159.3°) (Table 4), which shows the presence of strain in the macrocycle.

Intramolecular contacts shortened in comparison with the sum of the Van der Waals radii (Fig. 1) show the possibility of the transannular interaction of the π -electron systems in the lactone groups [7].

Dwelling on the configuration of the C(12) and C(13) asymmetric centers, it may be mentioned that the methyl groups [or the C(12)–C(19) and C(13)–C(20) bonds], and also the hydroxy groups [or the C(12)–O(18) and C(13)–O(21) bonds] are approximately gauche oriented (dihedral angles 41.4°). Such an orientation of the OH groups favors the formation of intramolecular hydrogen bonds, as can be seen from the O(18)...O(21) contacts (2.58 \AA). The formation of a hydrogen bond is also possible between O(18) and O(17), while the C(11)=O(17) and C(12)–O(18) bonds have the cisoid conformation (26.9°), and the O(17)...C(18) distance is equal to 2.75 \AA . We confirmed the presence of an intramolecular hydrogen bond by IR spectroscopy, since when trichodesmine was diluted more than 20-fold in solution in absolute chloroform, no shift of the frequency of the maximum at 3510 cm^{-1} corresponding to O–H...O was observed. Likewise, there was no change in the $\nu_{\text{C=O}}$ frequency of 1730 cm^{-1} under the same conditions.

The conformation of the backbone of the macrocycle is characterized by the torsion angles given in Table 2. For comparison, Table 2 also gives the values of the torsion angles found for incanine. In spite of the inconsiderable difference in the compositions of these two alkaloids — trichodesmine differs from incanine only by the presence of an OH group at C(13) [2] — the conformation of the backbone of the trichodesmine molecule differs substantially from that of incanine. Thus, it can be stated that when H is replaced by an OH group at C(13) a substantial change of the conformation of the backbone of the macrocycle takes place in the molecule.

Packing of the Molecule. The arrangement of the molecules in the crystal cell as projected on a plane of crystallographic axes is shown in Fig. 2. Analysis of the intermolecular contacts shows the possibility of an intermolecular hydrogen bond — the distance between O(21) and N(4) is 2.8 \AA (Fig. 2). No other anomalously short intermolecular contacts are observed.

TABLE 3. Coordinates and Isotropic Temperature Parameters ($\times 10$) of the N, O, and C Atoms of the Trichodesmine Molecule

Atoms	x	y	z	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C(1)	7463(4)	6786(6)	4090(7)	46	94	49	93	-5	-12
C(2)	8159(4)	7098(6)	3625(8)	43	128	71	107	-5	-2
C(3)	8431(5)	7532(8)	2925(8)	70	214	92	211	61	119
N(4)	7836(3)	7577(5)	1496(6)	44	103	65	101	39	70
C(5)	7195(5)	6532(7)	172(8)	65	147	43	144	11	3
C(6)	6218(4)	5822(7)	501(8)	61	121	68	115	23	75
C(7)	6123(4)	5598(5)	2213(7)	43	84	59	91	14	47
C(8)	7173(4)	7017(5)	2813(7)	39	91	69	92	16	22
C(9)	7093(5)	6330(7)	5698(8)	57	140	46	116	22	23
O(10)	4257(3)	2783(4)	2911(6)	50	125	150	121	12	87
C(11)	5748(4)	3885(6)	6685(7)	64	134	52	150	-1	-8
C(12)	4500(4)	2416(6)	6594(7)	62	141	48	147	52	77
C(13)	4160(4)	1286(6)	5351(7)	48	90	62	103	26	61
C(14)	4825(3)	2096(5)	3959(6)	44	88	31	99	16	41
C(15)	4913(4)	3077(5)	3107(7)	39	85	77	86	19	60
O(16)	5821(2)	4321(3)	2578(5)	40	77	75	84	23	35
O(17)	6120(4)	4023(6)	7487(7)	98	181	127	217	-95	-76
O(18)	4167(4)	1704(7)	8045(6)	114	217	81	246	140	170
C(19)	4090(6)	2840(9)	6383(12)	77	200	202	213	51	9
C(20)	3059(4)	5(7)	5914(10)	46	134	155	115	23	88
C(21)	4329(3)	569(4)	6102(6)	51	115	104	119	6	70
C(22)	4599(5)	1043(6)	2825(9)	69	100	83	128	-3	-11
C(23)	3990(9)	668(11)	1443(15)	142	204	201	259	-131	-141
C(24)	5560(7)	1824(10)	2305(13)	97	178	238	200	126	18
O(25)	4257(3)	2783(4)	2911(5)	50	125	150	121	2	87

TABLE 4. Coordinates ($\times 10^3$) of the H Atoms of the Trichodesmine Molecule

Atoms	x	y	z	Atoms	x	y	z
H(2)	163	314	435	H(3)	174	312	168
H(3)'	107	178	195	H(5)	271	391	989
H(5)'	258	271	905	H(6)	361	319	31
H(6)'	67	492	479	H(7)	425	458	288
H(9)	274	393	626	H(9)'	278	295	609
H(14)	50	276	949	H(8)	267	216	293
H(19)	429	338	529	H(19)'	345	205	666
H(20)	214	10	95	H(20)'	197	58	928
H(22)	419	2	347	H(23)	115	15	640
H(23)'	344	19	197	H(24)	50	141	656
H(24)'	125	311	657				

EXPERIMENTAL

The trichodesmine crystals were obtained from methanol solution. They were colorless and transparent and had the form of elongated prisms. The space group and the parameters of the elementary cell were determined from rotation and Weissenberg x-ray diagrams and were defined on a Hilger-Watts diffractometer using $\text{CuK}\alpha$ radiation: $a = 23.305(18)$, $b = 15.108(10)$, $c = 8.792(2)$ Å, $\gamma = 144.33(1)^\circ$, $d_{\text{calc}} = 1.305$ g/cm³, space group B_2 , $z = 4$.

A three-dimensional set of intensities was obtained on the above-mentioned diffractometer with $\theta \leq 57.5^\circ$. About 1500 independent nonzero reflections were measured, and by excluding reflections with $|F| \leq 3\sigma$ a final group of 1286 structural amplitudes was formed.

The structure was determined by the direct method using the "Rentgen-75" program [9]. After the standardization of the structural amplitudes to determine phases, 243 amplitudes with $E \geq 1.30$ were selected by the program. An attempt to interpret the structure in the automatic regime, i.e., by scanning through 1024 variants and investigating the 15 E-synthesis with the best s-estimates, was unsuccessful. Calculation was then performed under the manual regime. After several selections of coordinates and basis reflections success was achieved. The basis group consisted of the following reflections:

Coordinate	$\frac{h}{20}$	k	l	E
	13	0	2.75	
Basis	$\frac{7}{4}$	2	5	2,30
	11	2	2,90	
	$\frac{5}{1}$	5	1	2,34
	7	1	1,88	
	7	0	3	2,32

With this basis group we calculated 256 variants. From the best variant of the signs we constructed a E-series in which all the nonhydrogen atoms of the molecule apart from the C(23) atom were found. For a more accurate localization of the atoms and to find the position of the C(23) atom we calculated several $\rho(xyz)$ synthesis. Then the structure was refined by the method of least squares (MLS) in the isotropic approximation to $R = 0.20$. In the following stage the position parameters of all the atoms were defined in the block-diagonal anisotropic approximation to $R = 0.085$. In the following stage of MLS we calculated the difference syntheses of the electron density in order to find the coordinates of the H atoms, 21 out of the 27 H atoms being fixed. We did not succeed in localizing one H atom in each of the methyl groups and the hydrogens in the hydroxy groups. The coordinates of the atoms and the anisotropic temperature factors are given in Table 3, which also gives the coordinates of the hydrogen atoms found from the difference synthesis of the electron density (Table 4).

The IR spectra were taken on a UR-20 instrument in the prism region.

SUMMARY

1. The three-dimensional structure of the macrocyclic pyrrolizidine alkaloid trichodesmine has been established reliably by x-ray structural analysis.
2. The conformation of the macrocycle of trichodesmine differs substantially from that for the other alkaloids of this series studied.
3. The existence of an intramolecular O-H...O hydrogen in trichodesmine has been found by the methods of x-ray structural analysis.

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