CRYSTAL AND MOLECULAR STRUCTURES OF THE ALKALOID VERDINE

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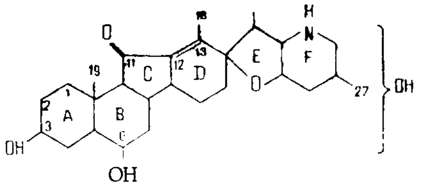
An x-ray structural analysis has been made with the object of reliably determining the structure of the alkaloid verdine. The position of the hydroxy group, not determined by other methods has been found and it has been established that the alkaloid verdine has the structure and configuration of 1β,3α,6α-trihydroxy-5β-jervanin-12-en-11-one.

On the basis of the results of mass, PMR, and IR spectra, and also of chemical transformations, the following structure, close to that of the known jervine [2], has been proposed for the alkaloid verdine isolated from the epigeal part of *Veratrum lobelianum* [1]:



However, the position of the last hydroxy group and the configuration of the asymmetric centers was not determined. To prove the structure and configuration of the molecule unambiguously, we have performed an x-ray structural analysis and its results are given in the present paper.

The structure of the verdine (I) molecule as a projection on the (001) plane is shown in Fig. 1. The conformations of the rings of the molecule of (I) can be judged unambiguously from Table 1, which gives the main planes of the fragments of the molecule and the deviations of the atoms from them. The cyclohexane rings A and B have the chair conformation: the deviations of the opposite atoms in the rings are −0.62 and 0.69 Å (A), and 0.66 and −0.74 Å (B), with accuracies of ±0.04 and ±0.02 Å, respectively (see Table 1). The six-membered heterocycle F also has the chair conformation with an accuracy of ±0.05 Å, the deviations of the atoms being −0.69 and 0.66 Å. All these magnitudes of the deviations of the atoms from the planes of the other four are somewhat less than the ideal value for the chair conformation, which is 0.73 Å [3], and this indicates some flattening of the ideal chain conformation. The five-membered ring C has the form of a C(8) β-envelope (±0.04 Å). Ring D, containing the C(12) = C(13) double bond, has the half chair conformation (±0.02 Å): The deviations of the two neighboring atoms C(15) and C(16) from the other four are 0.66 and −0.74 Å, respectively. The five-membered heterocycle E also has the half-chair conformations, of which it is possible to convince oneself by drawing the planes through the atoms C(17)O(5)C(23)C(20) E_I and C(17)O(5)C(20)C(22) (E_{II}), when the deviations of the C(22) and C(23) atoms amount to 0.55 and −0.55 Å, respectively (see Table 1).

The bonds from the ring to the substituents have the following orientations: C(1)—O(1), β-axial; C(3)—O(2), α-equatorial; C(10)—C(19), β-equatorial to ring A; C(6)—O(3), α-equatorial to ring B; C(20)—C(21), α-equatorial to ring E; C(25)—C(27), β-equatorial to ring F; and C(17)—O(5), running from the spiro center, β-oriented to ring D. The linkage of rings A/B is cis, of B/C trans, and of E/F trans.

Thus, on the basis of what has been said above it may be concluded that the hydroxy group not determined by other methods is present in position 1, and verdine has the structure and configuration of 1β,3α,6α-trihydroxy-5β-jervanin-12-en-11-one.

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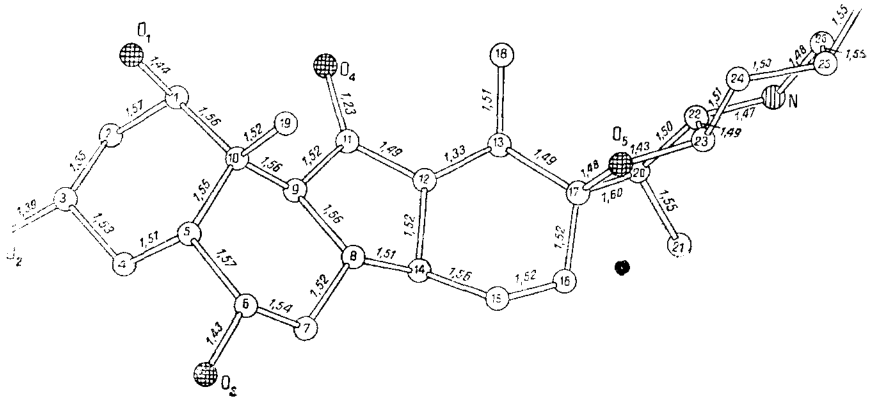

Fig. 1. Structure of the molecule of (I).

TABLE 1. Main Planes of the Fragments of the Molecule (I) and the Deviations of the Atoms from these Planes, δ, Å

Plane	Atom	δ	Plane	Atom	δ
Ring A	C (2)	0,037	Ring C	C (9)	0,029
	C (3)	—0,038		C (11)	—0,047
	C (5)	0,038		C (12)	0,047
	C (10)	—0,037		C (14)	—0,029
	C (1)*	—0,620		C (8)*	0,560
	C (4)*	0,692	Ring E_I	C (17)	0,075
Ring B	C (10)	—0,018		O (5)	—0,083
	C (5)	0,018		C (23)	0,053
	C (7)	—0,018		C (20)	—0,046
	C (8)	0,018		C (22)*	—0,551
	C (9)*	0,662	Ring E_{II}	C (22)	—0,049
	C (6)*	—0,740		C (20)	0,070
Ring D	C (14)	0,004		C (17)	—0,071
	C (12)	—0,009		O (5)	0,050
	C (13)	0,009		C (23)*	0,553
	C (17)	—0,004	Ring F	C (22)	—0,048
	C (15)*	0,488		C (23)	0,048
	C (16)*	—0,304		C (26)	0,047
				C (25)	—0,046
				C (24)*	—0,693
				N*	0,655

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

The bond lengths (Fig. 1) and valence angles (Table 2) in the molecule (I) are the usual ones and are close to the corresponding standard values [4] within the 3σ limits. The mean square deviations (SDs) of the determination of the bond lengths do not exceed 0.13 Å, with the exception of the C(25)—C(27) bond, where the SD reaches 0.017 Å because of the large thermal factor of the C(27) atom. On the whole, the values of the valence bonds and angles in (I) agree with those observed in other alkaloids containing similar fragments of the molecule (see, for example, [5, 6]).

The packing of the molecules of (I) as projected on the plane of the crystallographic axes *a*, c is shown in Fig. 2. An analysis of the intermolecular contacts in the packing shows the possibility of the existence of hydrogen bonds of the OH...O and OH...N types. The molecules, linked by 2_1 screw axes passing through the points 1/2, 0, 0, and 1/2, 1/2, 0, are contiguously the O(3)...O(5) atoms (2.95 Å) and the N...O(2) atoms (2.95 Å). In addition, the distance from the O(1) atom of the initial molecule to O(3) of a molecule translated along the b axis, amounting to 3.00 Å, shows the possible formation of a weak H-bond between these OH groups.

EXPERIMENTAL

Crystals of the alkaloid (I) were grown from methanol solution. The space group and the parameters of the elementary cell were determined from precession photographs and were refined

TABLE 2. Values of the Valence Angles (ω, deg) in the Molecule (I)

Angle	ω	Angle	ω	Angle	ω
C (10) C (1) O (1)	108,4 (6)	C (10) C (9) C (11)	121,0 (7)	C (15) C (16) C (17	110,0 (7)
C (2) C (1) C (10)	113,1 (7)	C (1) C (10) C (5)	110,5 (6)	C (13) C (17) O (5)	104,6 (7)
O (1) C (1) C (2)	104,8 (6)	C (1) C (10) C (9)	110,6 (6)	C (13) C (17) C (16)	113,5 (7)
C (1) C (2) C (3)	111,2 (7)	C (1) C (10) C (19)	107,1 (7)	C (13) C (17) C (20)	113,1 (7)
C (2) C (3) C (4)	107,1 (7)	C (5) C (10) C (9)	107,5 (7)	O (5) C (17) C (16)	108,0 (6)
C (2) C (3) O (2)	111.2 (7)	C (5) C (10) C (19)	111,1 (7)	O (5) C (17) C (20)	103,0 (6)
O (2) C (3) C (4)	114,0 (8)	C (9) C (10) C (19)	110,1 (7)	C (16) C (17) C (20)	113,6 (8)
C (3) C (4) C (5)	112,2 (7)	C (9) C (11) O (4)	125,3 (7)	C (17) O (5) C (29)	105,5 (6)
C (4) C (5) C (6)	111,0 (7)	C (9) C (11) C (12)	108,4 (7)	C (17) C (20) C (21)	114,5 (8)
C (4) C (5) C (10)	113,2 (7)	O (4) C (11) C (12)	126,4 (8)	C (17) C (20) C (22)	103,0 (7)
C (6) C (5) C (10)	111,0 (6)	C (11) C (12) C (13)	128,8 (9)	C (21) C (20) C (22)	110,7 (7)
C (5) C (6) C (7)	113,8 (7)	C (11) C (12) C (14)	106,2 (7)	C (20) C (22) C (23)	103,9 (8)
C (5) C (6) O (3)	110,7 (7)	C (13) C (12) C (14)	124,0 (8)	C (20) C (22) N	119,[illegible] (8)
O (3) C (6) C (7)	109.4 ( )	C (12) C (13) C (17)	122,5 (9)	NC (22) C (23)	111,5 (6)
C (6) C (7) C (8)	107,8 (7)	C (12) C (13) C (18)	119 7 (8)	C (22) C (23) C (24)	109,4 (8)
C (7) C (8) C (9)	109,7 (7)	C (18) C (13) C (17)	117,5 (7)	C (22) C (23) O (5)	103,9 (6)
C (7) C (8) C (14)	122,4 (8)	C (8) C (14) C (12)	104,5 (7)	C (24) C (23) O (5)	114,0 (7)
C (9) C (8) C (14)	102,9 (7)	C (8) C (14) C (15)	114,5 (7)	C (23) C (24) C (25)	108,3 (7)
C (8) C (9) C (10)	110,9 (7)	C (12) C (14) C (15)	109,6 (7)	C (24) C (25) C (26)	110 8 (7)
C (8) C (9) C (11)	103,6 (6)	C (14) C (15) C (16)	109,1 (7)	C (24) C (25) C (27)	110,7 (8)
C (22) NC (26)	109,1 (7)	NC (26) C (25)	114,0 (8)	C (26) C (25) C (27)	109,4 (9)

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

Atom	x/a	y/b	z/c	Bj, Å²
O (1)	8167 (4)	10688 (10)	1592 (6)	2,72
O (2)	9529 (4)	6644 (11)	3694 (6)	2,52
O (3)	7117 (4)	3894 (9)	469 (6)	2,00
O (4)	5986 (4)	10777 (10)	3748 (6)	2,63
O (5)	2641 (4)	9241 (9)	2107 (5)	0,02
N	930 (4)	10795 (11)	3879 (6)	1,42
C (1)	7652 (5)	9950 (13)	2481 (7)	1.18
C (2)	8380 (5)	9005 (14)	3441 (8)	2,16
C (3)	8841 (5)	7401 (13)	2868 (8)	1,50
C (4)	8087 (6)	6075 (13)	2376 (8)	1,90
C (5)	7400 (5)	6905 (10)	1394 (8)	1.37
C (6)	6678 (6)	5470 (13)	839 (8)	1.31
C (7)	5999 (6)	4921 (12)	1698 (7)	2,11
C (8)	5535 (6)	6629 (13)	2054 (8)	1,70
C (9)	6265 (5)	7963 (12)	2707 (7)	0.53
C (10)	6928 (5)	8609 (12)	1825 (7)	1.17
C (11)	5706 (5)	9310 (13)	3316 (8)	1,62
C (12)	4779 (5)	8535 (12)	3322 (8)	0,93
C (13)	4010 (5)	9381 (14)	3471 (7)	1,17
C (14)	4820 (5)	6602 (13)	2885 (8)	0,67
C (15)	3853 (5)	5993 (13)	2265 (9)	1,25
C (16)	3161 (6)	6436 (12)	3100 (8)	2.36
C (17)	3101 (5)	8469 (13)	3260 (7)	0,86
C (18)	4026 (5)	11381 (11)	3734 (8)	2,01
C (19)	6401 (6)	9615 (12)	757 (9)	1,79
C (20)	2446 (6)	9066 (14)	4219 (8	1,35
C (21)	1889 (6)	7499 (16)	4674 (9)	2,86
C (22)	1824 (5)	10423 (14)	3520 (8)	1,56
C (23)	1736 (5)	9775 (12)	2244 (3)	1,02
C (24)	1353 (5)	11274 (13)	1395 (7)	1,69
C (25)	413 (6)	11797 (15)	1705 (9)	2,94
C (26)	467 (6)	12213 (13)	3078 (8)	2.49
C (27)	30 (7)	13466 (20)	958 (12)	5.57

on a Syntex $P2_1$ diffractometer (Institute of Bioorganic Chemistry, Academy of Sciences of the Uzbek SSR) using Cu K_α radiation: $a = 14.828(5)$, $b = 7.397(3)$, $c = 11.136(4)$ Å, $\beta = 98.53(8)°$, $d_{calc} = 1.269$ g/cm^3; space group $P2_1$; $z = 2$. The complete set of experimental results was obtained on the diffractometer mentioned. The calculations were performed with 1385 independent reflections having intensities exceeding 2σ.

The search for a model of the structure was performed by the direct method using the "Rentgen-75" programs [7]. The calculation was begun in the automatic regime, but the structure could not be interpreted, and after this the search was performed in the manual regime.

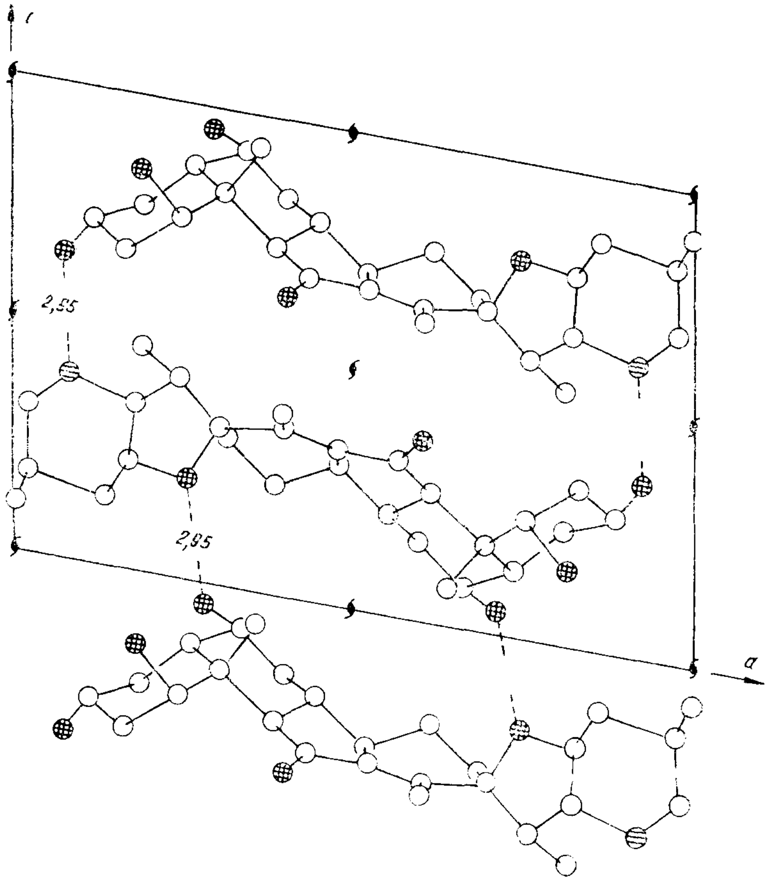

Fig. 2. Packing of (I) molecules.

After the selection of 11 ($3k + 8a_i$) reference reflections, 1024 phase variants were calculated from the same set of TPRs with R = 0.96 and σ = 0.75. This operation was repeated nine times with different reference reflections, but without success. It was decided to decrease the number of standardized amplitudes, and 252 $E_{hkl} \geqslant 1.25$ participated in the TPRs, but this did not lead to the solution of the problem either. Then a "Sigma-1" operation was performed and it was established that the reflection with the indices 12 0 4 had the phase φ = 180 with w = 0.708 and it was included in a new initial set as known. From seven ($3k + 4a_i$) reference projections taking the known one into account, we calculated 256 phase variants, whereupon the variant E_I with an R estimate of 0.942 and an R(E) factor of 0.184 stood out sharply. Analysis of the E-synthesis revealed 31 nonhydrogen atoms out of 33. In the following electron density (ED) synthesis, plotted over the whole group of reflections, the missing basis atoms were found. The structure was refined initially by successive approximations of the ED (R = 0.17) and by the method of least squares (MLS) in the isotropic approximation (R = 0.16) and then in the full-matrix MLS method taking the anisotropy of the thermal vibrations of the nonhydrogen atoms into account to R = 0.111. At this stage the ED difference synthesis was made and the positions of 27 H atoms were found. The final value of the discrepancy index after three iterations of the MLS procedure taking the H atoms into account was 0.094. The coordinates of the basis atoms are given in Table 3.

SUMMARY

The spatial structure of the alkaloid verdine has been determined as the result of an x-ray structural analysis. It has been found the verdine has the structure and configuration of 1β,3α,6α-trihydroxy-5β-jervanin-12-en-11-one.

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