CRYSTAL AND MOLECULAR STRUCTURE OF THE ALKALOID DICTYSINE

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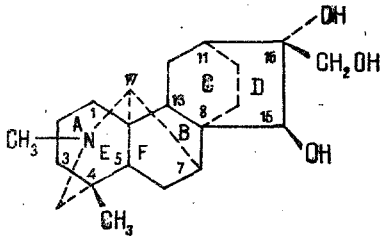
In order to determine the spatial structure of the diterpene alkaloid dictysine unambiguously, x-ray structural analysis has been performed: diffractometer, CuK_α radiation, 1028 reflections, direct method, R factor 0.118. It has been established that dictysine has not a songorine but a denudatine skeleton. All the hydroxy groups participate in inter- and intramolecular hydrogen bonds.

Results of a previous preliminary x-ray structural analysis show that the diterpene alkaloid dictysine (I), isolated from the epigeal part of the plant *Delphinium dictyocarpum* DC [1] has not a songorine [2] but a denudatine [3] skeleton. Thus, a structure has been found with the linkage of rings C and D in positions 8 and 11 and the following orientations of the constituents at C(15) and C(16):



In the present paper we give the results of a complete x-ray structural analysis of the diterpene alkaloid dictysine. The structure of the molecule of (1) is represented in Fig. 1 in the form of a projection on the (100) plane. The model has a fairly rigid bridge structure consisting of six rings. The shapes and conformations of the rings can be judged from the figures of Table 1, which gives the coefficients of the equations of the main planes and the deviations of the atoms from them. The cyclohexane ring A [the C(1)C(2)C(3)C(4)C(5)C(14) atoms] has an almost ideal $^1C_4$ chair conformation, while the other cyclohexane rings B C(5)C(6)C(7)C(8)C(13)C(14) atoms], C [the C(8)C(9)C(10)C(11)C(12)C(13) atoms] and D [the C(8)C(9)C(10)C(11)C(15)C(16) atoms] have distorted boat conformations (twist forms): $T_{14,7}$, $^{8,11}T$ and $^{8,11}T$, respectively. The piperidine ring E [the C(4)C(5)C(14)C(17)N(22)C(18) atoms] is present in the $^{14}C_{18}$ chair form (to an accuracy of 0.04 Å). The five-membered ring [the C(5)C(6)C(7)C(17)C(14) atoms] have the ^{17}E envelope conformation (also to an accuracy of 0.04 Å). Both the conformations and the linkages of the rings are the same as in the related alkaloid denudatine [4, 5]: A/B — trans; A/F — cis; B/C — cis; B/E — cis. Rings B and F form a bicyclo[2.2.1]heptane (norbornane) structure and rings C and D, in their turn, a bicyclo-[2.2.2]octane structure. The hydroxy group at C(16) and the CH_2OH group at C(15) are β-oriented, and the OH at C(15) α-oriented.

The bond lengths and valence angles are given in Table 2. In spite of the fact that the lengths of the ordinary C_{sp^3}—C_{sp^3} bonds vary in the range of 1.51-1.59 Å they can be harmonized with the standard value of 1.54 Å [6] within a 3σ range. The N—C heterobonds average 1.47 Å. The appreciable scatter in the lengths of the C—OH bonds from 1.40 to 1.54 Å) can be explained by the large thermal parameters of the O(23) and O(25) atoms (see Table 3). The values of the valence angles (Table 2) were determined with an error not exceeding 1.4°. A considerable variation of the angles (from 97 to 124°C) at the tetrahedral carbon atoms is connected with the stresses present in the bridge fragments of the molecule.

The mutual arrangement of the hydroxy groups favors the formation of intramolecular hydrogen bonds, as can be seen from the distances between the O atoms: O(25)...O(24) 2.64 Å, and O(23)...O(24) 2.84 Å.

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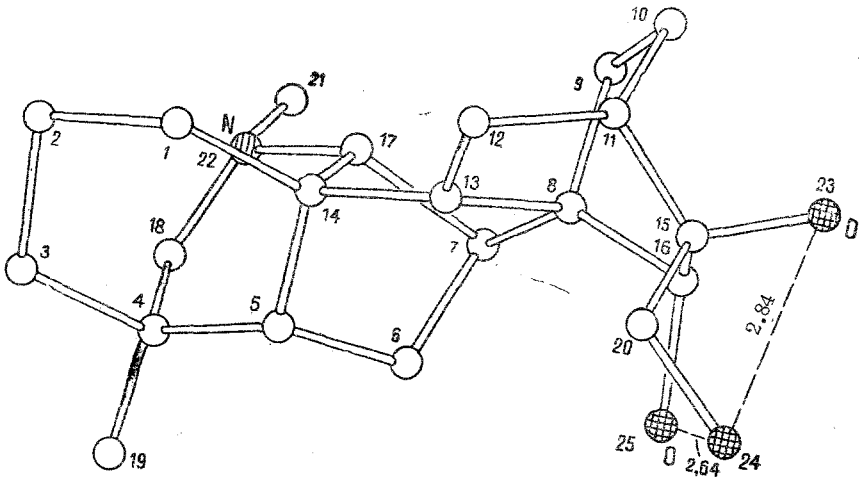

Fig. 1. Structure of the dictysine molecule.

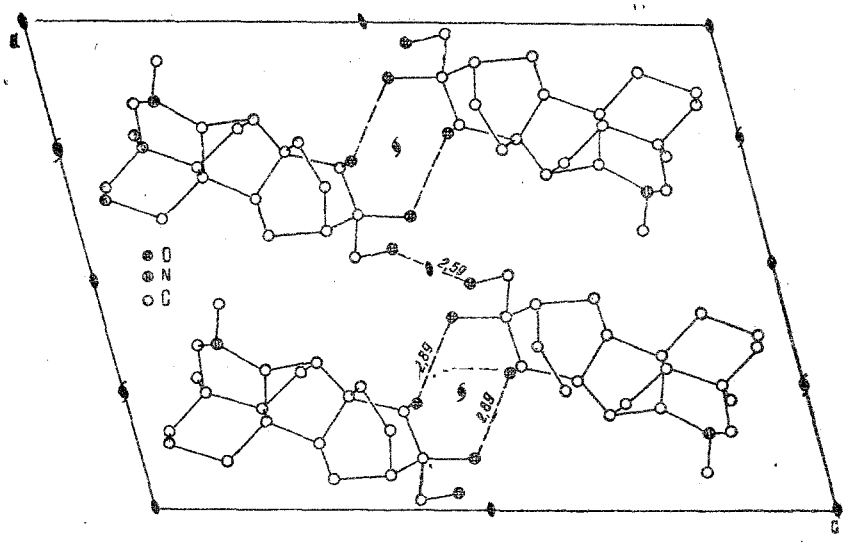

Fig. 2. Packing of the molecules of (I).

The packing of the molecules of (I) in the projection on the plane of the a and c axes is shown in Fig. 2. All the hydroxy groups participate in intermolecular hydrogen bonds of the O-H...O type. The molecules, transformed by second-order axes, are connected by intermolecular H-bonds and form infinite chains directed along the crystallographic a axis.

EXPERIMENTAL

Crystals of dictysine from methanolic solution were first studied by the photomethod: the space group and parameters of the elementary cell were found from rotation and Weissenberg x-ray patterns. These parameters were then refined on a Syntex $P2_1$ diffractometer using CuK_α radiation: a = 14.387(7); b = 7.315(3); c = 18.116(11); β = 105.35(4)°; d_{calc} = 1.26 g/cm^3; space group C2; z = 4. A three-dimensional set of intensities was obtained on the diffractometer mentioned with $\theta \leqslant 57.5°$. About 1500 independent nonzero reflections were measured, and 1028 structural factors exceeding 3σ were used in the calculations. The structure was determined by the direct method using the Rentgen-75 program [7]. After the standardization of the structural amplitudes, 249 amplitudes with $E \geqslant 1.16$ were selected for determined the phases. An attempt to interpret the structure in the automatic regime was unsuccessful. After several selections of the coordinate and reference reflections, we found a solution in which the reference group consisted of the following reflections:

TABLE 1. Coefficients of the Equations Ax + By + Cz = D of the Main Planes of the Fragments of the Molecules of (I) and the Deviations of the Atoms (δ) from the Planes

Plane	Atom	δ, Å	A	B	C	D
A	C(2)	−0,005	13,96	1,73	−3,83	2,78
	C(3)	0,005				
	C(5)	−0,005				
	C(14)	0,005				
	C(1)*	0,654				
	C(4)*	−0,734				
B	C(5)	−0,10	8,23	4,88	−11,08	1,44
	C(6)	0,09				
	C(8)	−0,10				
	C(13)	0,10				
	C(7)*	0,77				
	C(14)*	−0,91				
C	C(13)	−0,12	3,89	−4,28	14,66	0,51
	C(12)	0,12				
	C(9)	0,13				
	C(10)	−0,13				
	C(8)*	−0,57				
	C(11*)	−0,80				
D	C(16)	−0,09	3,24	1,83	15,36	8,00
	C(15)	0,09				
	C(9)	0,09				
	C(10)	−0,09				
	C(8)*	0,84				
	C(11)*	0,64				
F	C(14)	−0,03	−11,48	−1,12	14,02	0,02
	C(5)	0,04				
	C(6)	−0,04				
	C(7)	0,03				
	C(17)	0,89				
E	C(5)	−0,04	9,09	−3,38	7,82	1,90
	C(4)	0,04				
	C(17)	0,04				
	N(22)	−0,04				
	C(18)	−0,50				
	C(14)	0,91				

TABLE 2. Interatomic Distances (r, Å) and Valence Angles (ω, deg)

Distance	r	Angle	ω	Angle	ω
C(1)—C(2)	1,55(2)	C(2) C(1) C(14)	111	C(12) C(13) C(14)	120
C(2)—C(3)	1,59(3)	C(3) C(2) C(1)	107	C(12) C(13) C(8)	109
C(3)—C(4)	1,51(2)	C(4) C(3) C(2)	112	C(8) C(13) C(14)	106
C(4)—C(5)	1,54(2)	C(5) C(4) C(3)	108	C(13) C(14) C(1)	114
C(4)—C(19)	1,51(2)	C(5) C(4) C(18)	111	C(13) C(14) C(5)	103
C(4)—C(18)	1,54(2)	C(5) C(4) C(18)	110	C(13) C(14) C(17)	103
C(5)—C(6)	1,56(1)	C(3) C(4) C(18)	112	C(1) C(14) C(5)	113
C(5)—C(14)	1,59(2)	C(3) C(4) C(19)	107	C(1) C(14) C(17)	124
C(6)—C(7)	1,58(2)	C(18) C(4) C(19)	109	C(5) C(14) C(17)	98
C(7)—C(8)	1,54(2)	C(4) C(5) C(6)	110	C(11) C(15) C(16)	111
C(7)—C(17)	1,51(1)	C(4) C(5) C(14)	108	C(11) C(15) C(20)	107
C(8)—C(9)	1,59(2)	C(6) C(5) C(14)	101	C(11) C(15) O(23)	109
C(8)—C(13)	1,53(2)	C(5) C(6) C(7)	104	C(16) C(15) O(23)	107
C(8)—C(16)	1,54(1)	C(6) C(7) C(8)	113	C(16) C(15) C(20)	117
C(9)—C(10)	1,51(2)	C(6) C(7) C(17)	100	C(20) C(15) O(23)	105
C(10)—C(11)	1,54(2)	C(8) C(7) C(17)	101	C(8) C(16) C(15)	106
C(11)—C(12)	1,53(2)	C(7) C(8) C(9)	111	C(8) C(16) O(25)	116
C(11)—C(15)	1,52(2)	C(7) C(8) C(13)	99	C(15) C(16) O(25)	111
C(12)—C(13)	1,58(2)	C(7) C(8) C(16)	124	C(7) C(17) C(14)	96
C(13)—C(14)	1,56(2)	C(9) C(8) C(13)	114	C(7) C(17) N(22)	123
C(14)—C(17)	1,53(2)	C(9) C(8) C(16)	103	C(14) C(17) N(22)	111
C(17)—N(22)	1,48(1)	C(13) C(8) C(16)	107	C(4) C(18) N(22)	112
N(22)—C(21)	1,42(1)	C(8) C(9) C(10)	111	C(15) C(20) O(24)	110
N(22)—C(18)	1,50(2)	C(9) C(10) C(11)	109	C(17) N(22) C(18)	118
C(15)—O(23)	1,49(1)	C(10) C(11) C(12)	107	C(17) N(22) C(21)	111
C(15)—C(20)	1,53(2)	C(10) C(11) C(15)	109	C(18) N(22) C(21)	109
C(20)—O(24)	1,54(2)	C(12) C(11) C(15)	111	C(11) C(12) C(13)	106
C(16)—O(25)	1,40(2)				

TABLE 3. Coordinates and Anisotropic Thermal Parameters ($\times 10^4$) of the C, O, and N Atoms

Atom	x/a	y/b	z/c	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C (1)	1013 (7)	6908 (22)	1255 (6)	57	279	34	20	32	56
C (2)	1340 (9)	6458 (25)	534 (6)	60	435	29	61	51	76
C (3)	1604 (10)	4313 (25)	555 (7)	99	413	34	—50	56	—45
C (4)	2589 (9)	3853 (23)	1263 (6)	82	339	23	—27	44	52
C (5)	2013 (9)	4221 (17)	1966 (6)	77	134	36	—61	44	—63
C (6)	2851 (8)	4087 (19)	2712 (6)	69	193	26	23	23	57
C (7)	3054 (7)	6147 (16)	2982 (5)	55	226	26	139	27	94
C (8)	2293 (8)	6902 (16)	3356 (6)	65	135	33	—67	15	20
C (9)	2475 (10)	9024 (19)	3551 (7)	93	176	36	—79	16	49
C (10)	1618 (12)	9884 (26)	3752 (8)	129	167	49	85	47	47
C (11)	778 (9)	8511 (17)	3583 (7)	99	158	31	—14	55	—17
C (12)	593 (10)	7970 (20)	2742 (7)	85	279	32	108	—20	—29
C (13)	1392 (6)	6528 (17)	2704 (5)	31	184	32	—1	16	4
C (14)	1745 (8)	6333 (19)	1967 (5)	50	277	20	—70	1	—32
C (5)	1069 (10)	6872 (20)	4107 (6)	120	186	24	11	11	—44
C (16)	2099 (8)	6132 (16)	4095 (5)	84	231	26	91	36	38
C (17)	2772 (7)	7103 (17)	2216 (5)	66	214	37	34	37	41
C (18)	3329 (9)	4918 (20)	1320 (7)	87	286	54	—1	87	9
C (19)	2587 (10)	1843 (19)	1214 (7)	136	189	77	115	64	5
C (20)	228 (8)	5518 (20)	3911 (7)	74	326	49	—82	47	—51
C (21)	4231 (6)	7561 (19)	1843 (8)	100	383	84	—21	4	—30
N (22)	3283 (6)	6825 (15)	1614 (5)	59	303	42	—7	43	44
O (23)	1136 (7)	7449 (13)	4908 (5)	135	329	40	81	62	—3
O (24)	444 (6)	3871 (16)	4464 (5)	106	397	64	—34	82	2
O (21)	2145 (6)	4226 (11)	4180 (4)	110	186	36	—7	50	17

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

Atom	x/a	y/b	z/c
H (1)	26	612	117
H (1)′	114	860	112
H (2)	411	194	6
H (2)′	201	636	54
H (6)	297	300	312
H (7)	379	657	348
H (9)	312	942	415
H (10)	149	104	330
H (12)	495	229	235
H (13)	102	500	276
H (16)	256	602	467
H (20)	8	548	328
H (21)′	494	659	232
H (21)″	392	866	167
H (21)‴	476	850	204

	h	k	l	|E|
Coordinate	1	1	1	1.86
Reference	$\bar{4}$	0	9	3.15
	1	1	8	2.29
	2	4	0	2.36
	$\bar{5}$	5	6	2.13
	$\bar{7}$	3	14	2.06

With this reference group we calculated 250 variants. From the best variants of the signs we constructed an E series in which we found all the nonhydrogen atoms of the molecule except the C(19) atom. For a more accurate localization of the atoms and to find the position of the C(19) atom we calculated a number of $\rho(xyz)$ syntheses. Then the structure was refined by the method of least squares in the isotropic approximation to R = 0.185. In the following stage the positional parameters of all the atoms were refined in the full-matrix anisotropic approximation to R = 0.118. In the final stage electron-density difference syntheses were calculated by the method of least squares to ascertain the coordinates of the H atoms. Out of the 33 H atoms, the positions of 15 were determined. The coordinates of the

atoms and the anisotropic temperature factors are given in Table 3. The coordinates of the H atoms found from the electron-density difference synthesis are given in Table 4.

CONCLUSION

The spatial structure of the diterpene alkaloid dictysine has been determined by x-ray structural analysis. Dictysine has a denudatine skeleton.

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ANALOGS OF D(+)-PANTOTHENIC ACID.

VI. SYNTHESIS OF D-, L-, AND DL-4'-AMINO-4'-DEOXYPANTOTHENIC ACID

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UDC 547.164.14.074

A new analog of pantothenic acid, DL-4-amino-2-hydroxy-3,3-dimethylbutanoic acid, has been synthesized and it has been separated into stereoisomer. D-, L-, and DL-N-(4-Amino-2-hydroxy-3,3-dimethylbutyryl)-β-alanines — amino analogs of pantothenic acid — have been synthesized by the condensation of the N-hydroxysuccinimide esters of N-BOC-D-, -L-, and -DL-4-amino-2-hydroxy-3,3-dimethylbutanoic acids with β-alanine, followed by the elimination of the protective groups.

The importance of D-pantothenic acid as a component of coenzyme A and acyl carriers protein has led to the synthesis of a considerable number of its analogs and derivatives. However, the structure of the natural vitamin has proved to be so unusual that even slight modifications of its molecule have resulted in a decrease or in the complete loss of its specific biological activity and, in a number of cases, to the formation of antagonists [1]. At the same time, the study of synthetic analogs of pantothenic acid is giving valuable information on the role of its various groupings in the manifestation of biological activity, which is determined by the conversion of pantothenic acid into coenzyme A. Since the first stage of this process is the phosphorylation of the 4'-hydroxy group of pantothenic acid under the action of pantothenate kinase [2], analogs in which the primary hydroxyl have been modified may be of great interest for studying the specificity of pantothenate kinase. Continuing investigations on the synthesis of pantothenic acid derivatives and their biological activity [2], we have obtained an analog containing an amino group in place of the hydroxy group in position 4' of the pantothenic acid, 4'-amino-4'-deoxypantothenic acid.

The conversion of a hydroxy group into an amino group usually requires several stages [4]. To introduce an amino group into position 4' of pantothenic acid we alkylated potassium phthalimide with D-pantolactone, as a result of which the optically inactive 2-hydroxy-3,3-dimethyl-4-phthaloylaminobutanoic acid (I) was formed. We obtained the stereoisomers of aminopantothenic acid by resolving (I) through its conversion into a salt with L(+)-threo-2-

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