

Structure of Octa-*O*-acetyl-tris(*N*-ethoxycarbonyl)destomycin AShigeomi HORITO, Yuji OHASHI, Nobert GASSNER, Juji YOSHIMURA,*
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The molecular and crystal structure of octa-*O*-acetyl-tris(*N*-ethoxycarbonyl)destomycin A tetrahydrate, $C_{45}H_{65}N_3O_{27} \cdot 4H_2O$, has been determined by X-ray analysis. The space group is $P2_1$ with $a=14.738(4)$, $b=17.391(4)$, $c=12.171(4)$ Å, $\beta=105.58(4)^\circ$, and $Z=2$. The structure was solved by the direct method, and the least-squares refinement using 4008 reflections led to the final R value of 0.12. The configuration of the ortho ester carbon atom is (*R*). The D-talose moiety has the boat conformation whereas the other rings are in the chair form.

A group of antibiotics such as everninomicins, flambamycin, curamycin, avilamycins, destomycins, hygromycin B, the antibiotics A-396-I and SS-56C was recently named as the orthosomycin family,¹⁾ because they commonly include a very unique ortho ester linkage of a glyconic acid lactone to an α -diol function of an aldose in their molecules. This interlinkage provides two possible stereoisomers depending on the (*R*) or (*S*) configuration at the ortho ester carbon atom; however, no absolute configuration has been determined except for one of the two orthoester linkages in everninomicin D.²⁾ The difficulties in the elucidation of the configuration is attributed to that only X-ray analysis is applicable for this purpose at the present stage and that these sugar derivatives are not easily crystallizable.

In this paper, we intended to confirm the proposed structure and to determine the absolute configuration of the ortho ester linkage of destomycin A (Fig. 1),³⁾ which is the main aminoglycoside antibiotic produced by a strain of *Streptomyces rimofaciens*. By the examination of several derivatives, octa-*O*-acetyl-tris(*N*-ethoxycarbonyl)destomycin A (**1**) was obtained as crystals, and its X-ray analysis disclosed the structure to be 4,6-di-*O*-acetyl-3-ethoxycarbonylamino-1-[*N*-(ethoxycarbonyl)methylamino]-5-*O*-[4,6-di-*O*-acetyl-2,3-*O*-(2,3,7-tri-*O*-acetyl-6-deoxy-6-ethoxycarbonylamino-L-glycero-D-galacto-)-(*R*)-heptopyranosylidene]- β -D-talopyranosyl]-1D-1,2,3-trideoxy-*myo*-inositol.

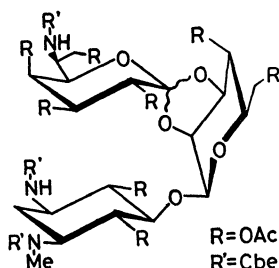


Fig. 1. The chemical structure.

Experimental and Structural Determination

Preparation of Octa-*O*-acetyl-tris(*N*-ethoxycarbonyl)destomycin A (1**).** To an ice-chilled aqueous solution of destomycin A (0.53 g, 1.0 mmol) and sodium carbonate (0.42 g, 4.0 mmol) was added ethoxycarbonyl chloride (0.35 g, 3.2 mmol) with stirring, and the resulting mixture was stirred

overnight at room temperature, neutralized with dilute hydrochloric acid, and evaporated. The residue was fractionated on a silica gel column (1-butanol-methanol-water 3:2:1), and evaporation of the fractions showing one spot on TLC gave pure tri-*N*-ethoxycarbonyl derivative as a light yellow, hygroscopic hard syrup. Yield, 0.53 g (70.9%); $[\alpha]_D -17.0^\circ$ (c 0.4, ethanol).

A solution of the above tri-*N*-ethoxycarbonyl derivative (0.74 g, 1 mmol) and acetic anhydride (1 ml, 10.6 mmol) in chloroform (10 ml) and pyridine (1 ml) was allowed to stand overnight at room temperature, diluted with water, and the organic layer was washed with aqueous sodium hydrogencarbonate and three times with water. The organic layer was evaporated, and the residual sirup was purified on a silica gel column with ethyl acetate as an eluent to give crystalline (**1**) which was recrystallized twice from ethanol-water (1:1). Single crystals suitable for X-ray studies were obtained as well-formed parallelepipeds. Yield, 0.75 g (69.8%), mp 143–145 °C, $[\alpha]_D +20.4^\circ$, (c 1.07, pyridine); NMR (δ): ca. 1.22 (3×C-CH₃, t), 1.98, 2.30, 2.08, 2.10, 2.12, 2.14 (8×Ac, each s), 2.74 (N-CH₃, s). Found: C, 50.01; H, 6.14; N, 4.01%. Calcd for $C_{45}H_{65}N_3O_{27}$: C, 50.04; H, 6.07; N, 3.89%.

X-Ray Analysis. Preliminary unit-cell dimensions and space group were obtained from photographs. The space group was determined as $P2_1$ from the systematic absences of reflections for $0k0$ with odd k . A crystal with dimensions of $0.5 \times 0.4 \times 0.2$ mm³ was used for data collection on a Rigaku automated four-circle diffractometer with Ni-filtered Cu $K\alpha$ radiation ($\lambda=1.54184$ Å). Accurate cell dimensions were determined by least-squares calculation with 2θ values of 16 high-angle reflections measured on the diffractometer. Crystal data are summarized in Table 1. Intensity data

TABLE 1. CRYSTAL DATA

$C_{45}H_{65}N_3O_{27} \cdot 4H_2O$	
$M.W. = 1152.1$	
Monoclinic	
$P2_1$	
$a = 14.738(4)$ Å	$a = 14.65(1)$ Å ^{a)}
$b = 17.391(4)$ Å	$b = 17.41(1)$ Å
$c = 12.171(4)$ Å	$c = 12.16(1)$ Å
$\beta = 105.58(4)^\circ$	$\beta = 105.5(1)^\circ$
$V = 3005(2)$ Å ³	$V = 2989(4)$ Å ³
$Z = 2$	
$D_x = 1.273$ g cm ⁻³	
$D_m = 1.275$ g cm ⁻³	
$\mu(\text{Cu } K\alpha) = 10.6$ cm ⁻¹	

a) The values after the data collection.

TABLE 2. FINAL ATOMIC COORDINATES WITH THEIR ESTIMATED STANDARD DEVIATIONS, MULTIPLIED BY 10^4 FOR NON-HYDROGEN AND 10^3 FOR HYDROGEN ATOMS

Atom	<i>x</i>	<i>y</i>	<i>z</i>	B_{eq}^a or $B/\text{\AA}^2$	Atom	<i>x</i>	<i>y</i>	<i>z</i>	B_{eq}^a or $B/\text{\AA}^2$
C(1)	3430 (8)	6308 (7)	9888 (9)	65 (4)	C(2''1)	1258 (8)	4806 (8)	2891 (20)	151 (9)
C(2)	2428 (9)	6333 (7)	10034(10)	76 (5)	O(2''2)	1425 (9)	4835 (8)	1860(13)	197 (7)
C(3)	1773 (7)	6836 (7)	9123(10)	65 (4)	C(2''3)	423(14)	4866(14)	3385(39)	317(25)
C(4)	1833 (8)	6584 (6)	7914 (9)	67 (4)	O(3'')	2747 (5)	3219 (4)	3672 (6)	62 (2)
C(5)	2803 (7)	6477 (5)	7798 (8)	55 (3)	C(3''1)	2632(10)	2624 (9)	4312(13)	115 (6)
C(6)	3475 (9)	6005 (6)	8702 (9)	72 (4)	O(3''2)	2953(14)	2586(10)	5194(12)	157 (8)
O(1')	2713 (6)	6148 (4)	6699 (6)	69 (3)	C(3''3)	2103(10)	1994 (7)	3461(15)	119 (7)
O(0')	2027 (5)	6599 (4)	4930 (5)	63 (2)	O(4'')	4336 (5)	3640 (4)	3017 (6)	59 (2)
C(1')	2866 (8)	6563 (6)	5832 (8)	64 (4)	C(4'1)	4614(10)	3001 (7)	2738(11)	86 (5)
C(2')	3643 (7)	6246 (5)	5378 (8)	48 (3)	O(4'2)	4886(10)	2455 (6)	3421 (9)	151 (6)
C(3')	3617 (7)	6549 (5)	4206 (7)	46 (3)	C(4'3)	4656(12)	2999 (9)	1504(12)	118 (7)
C(4')	3044 (8)	7267 (5)	3934 (8)	56 (4)	O(7'')	7370 (5)	5137 (4)	5389 (7)	82 (3)
C(5')	2024 (8)	7167 (6)	4120 (9)	69 (4)	C(7''1)	8028(11)	4668 (8)	6116(14)	110 (6)
C(6')	1363 (7)	6894 (8)	2997(11)	81 (5)	O(7''2)	7696 (7)	4302 (9)	6835 (8)	145 (5)
O(2')	3478 (5)	5427 (4)	5216 (5)	59 (2)	C(7''3)	8967 (9)	4761 (10)	5929(18)	137 (8)
O(3')	3195 (4)	5923 (4)	3465 (5)	52 (2)	N(6'')	6014 (6)	4496 (5)	3554 (7)	62 (3)
O(0'')	4442 (5)	5130 (4)	4064 (5)	53 (2)	C(6'1)	6679(10)	4102 (7)	3188(12)	93 (5)
C(1'')	3511 (7)	5276 (6)	4112 (7)	52 (3)	O(6'2)	7138 (8)	3576 (5)	3779 (8)	115 (4)
C(2'')	2910 (8)	4585 (6)	3692(11)	71 (4)	O(6'3)	6718 (7)	4302 (7)	2194 (6)	110 (4)
C(3'')	3285 (7)	3866 (6)	4277 (8)	54 (3)	C(6'4)	7493(15)	3993(11)	1748(13)	149 (9)
C(4'')	4331 (8)	3769 (6)	4247 (8)	63 (4)	C(6'5)	7864(21)	4559(18)	1130(24)	242(17)
C(5'')	4887 (7)	4455 (6)	4696 (8)	55 (3)	O(W1)	325(15)	5251(11)	9506(22)	200(12)
C(6'')	5907 (7)	4485 (6)	4677 (8)	55 (3)	O(W2)	1251(18)	4257(21)	8044(23)	335(16)
C(7'')	6429 (7)	5109 (8)	5441(10)	76 (4)	O(W3)	9037(22)	4279(24)	8812(26)	130(14)
N(1)	4093 (7)	5894 (6)	10822 (7)	80 (4)	O(W4)	2167(27)	4428(21)	6510(22)	94(14)
C(11)	3920(12)	5084 (8)	10966(11)	112 (7)	H(1)	350 (7)	708 (6)	1018 (8)	90(28)
C(12)	4875(12)	6222 (9)	11432(12)	112 (7)	H(151)	683 (5)	705 (5)	1201 (6)	59(21)
O(13)	5438 (7)	5897 (7)	12258 (9)	133 (5)	H(152)	580 (4)	727 (4)	1248 (5)	32(15)
O(14)	4993 (7)	6970 (6)	11291 (7)	104 (4)	H(21)	238 (6)	652 (5)	1103 (7)	67(22)
C(15)	5883(14)	7447(21)	11946(14)	215(14)	H(22)	202 (6)	606 (6)	982 (7)	75(24)
C(16)	6026(30)	8178(26)	11560(30)	362(29)	H(3)	209 (5)	734 (5)	933 (6)	54(20)
N(3)	832 (8)	6889 (7)	9241(10)	97 (5)	H(N3)	58 (7)	679 (7)	899 (9)	114(33)
C(31)	368(10)	7514 (7)	9459(11)	87 (5)	H(341)	-111 (6)	820 (5)	896 (7)	68(23)
O(32)	814 (7)	8122 (6)	9554(11)	125 (5)	H(342)	-66 (4)	821 (4)	1008 (5)	30(15)
O(33)	-502 (6)	7410 (7)	9379(10)	124 (5)	H(4)	144 (4)	618 (4)	788 (5)	32(16)
C(34)	-971(15)	8007(20)	9678(20)	227(16)	H(5)	328 (4)	702 (4)	792 (5)	35(16)
C(35)	-1941(11)	7773(21)	9616(18)	223(15)	H(6)	322 (5)	552 (5)	843 (6)	57(20)
O(4)	1334 (5)	7176 (4)	7139 (6)	72 (3)	H(1')	320 (5)	703 (4)	604 (6)	45(18)
C(41)	472 (8)	7088 (8)	6447(11)	88 (5)	H(2')	418 (5)	634 (4)	600 (6)	47(19)
O(42)	112 (6)	6479 (6)	6301 (8)	105 (4)	H(3')	422 (4)	674 (4)	421 (5)	22(14)
C(43)	111 (11)	7794 (9)	5758(14)	113 (7)	H(4')	347 (4)	787 (4)	435 (5)	28(15)
O(6)	4377 (6)	6086 (4)	8578 (6)	78 (3)	H(5')	168 (6)	774 (6)	448 (7)	75(24)
C(61)	4906(13)	5512 (8)	8559(12)	114 (7)	H(6'1)	212 (5)	659 (4)	292 (6)	48(19)
O(62)	4550 (9)	4860 (6)	8460(11)	154 (6)	H(6'2)	125 (7)	732 (7)	212 (9)	108(32)
C(63)	5914(10)	5724 (9)	8424(14)	110 (7)	H(2'')	280 (5)	448 (5)	318 (6)	51(19)
O(4')	2905 (5)	7520 (4)	2784 (5)	62 (2)	H(3'')	350 (5)	396 (4)	517 (6)	48(19)
O(4'1)	3579 (5)	8044 (6)	2624 (9)	73 (4)	H(4'')	469 (4)	343 (4)	463 (5)	37(17)
O(4'2)	4239 (5)	8264 (5)	3376 (6)	75 (3)	H(5'')	488 (5)	432 (5)	567 (6)	53(20)
C(4'3)	3316 (9)	8334 (7)	1375 (8)	76 (4)	H(6'')	638 (5)	410 (4)	508 (5)	38(17)
O(6')	438 (6)	6775 (8)	3261 (8)	132 (5)	H(N6'')	551 (8)	496 (8)	325(10)	134(39)
C(6'1)	315(14)	2028(12)	7210(17)	148 (9)	H(641)	694 (5)	358 (5)	75 (7)	64(22)
O(6'2)	21 (9)	2832 (8)	7200(11)	157 (6)	H(642)	761 (6)	380 (6)	219 (8)	84(26)
C(6'3)	1134(10)	1751(11)	6914(14)	120 (7)	H(7'1)	612 (5)	507 (4)	593 (5)	42(17)
O(2'')	1995 (5)	4683 (4)	3792(10)	107 (4)	H(7'2)	625 (5)	545 (4)	496 (6)	48(19)

a) $B_{eq} = \frac{4}{3} \sum_i \sum_j \beta_{ij} \mathbf{a}_i \cdot \mathbf{a}_j$, where $\mathbf{a}_i$ and $\mathbf{a}_j$ are the base vectors in real space, and β_{ij} 's are anisotropic thermal parameters.

within the range of $3^\circ \leq 2\theta \leq 125^\circ$ were collected in the ω - 2θ scan mode at a scanning rate of $8^\circ (2\theta) \text{ min}^{-1}$. Stationary background counts were accumulated for 5 s before and after each scan. The periodic check of the intensity values of three standard reflections revealed a slight change. The intensities decreased by 5–6% during the data collection. The cell dimensions also changed appreciably; the values after the data collection are also listed in Table 1. This is probably due to the dehydration of the crystal. As this change did not seem to be serious, it was ignored in the structure determination. A total of 4957 independent reflections was obtained, of which 4008 [$|F_o| \geq 3\sigma(|F_o|)$] were used for the structure determination. Any correction for absorption or extinction was not applied.

Structure Determination. The structure was solved by direct methods with the MULTAN 78 program.⁴⁾ At the first stage, only 40 chemically significant peaks were found on the *E*-map. The other non-hydrogen atoms were obtained by the subsequent Karle recycling procedure. The structure was refined by the block-diagonal least-squares method with the modified HBLS program. The difference synthesis revealed that several substituents were disordered. This is probably due to the rearrangement of the substituents after the dehydration. Since the volume of the disordered portion, however, was probably less than 20%, the disordered model was not taken into account. All the hydrogen atoms except for those of the methyl groups and water molecules were located geometrically. Refinement using the anisotropic and isotropic temperature factors for the non-hydrogen and hydrogen atoms, respectively, gave the final *R* value of 0.12 for 4008 reflections. The weighting scheme used in the final stage was $w = [(|F_o|)^2 + (0.015|F_o|)^2]^{-1}$. Atomic scattering factors were taken from "International Table for X-Ray Crystallography."⁵⁾ The final positional and thermal parameters are given in Table 2.[†]

The stereoscopic drawing of the molecular structure is shown in Fig. 2. The numbering of the atoms and the bond distances and angles are illustrated in Fig. 3.

Results and Discussion

The structure of destomycin A was previously elucidated as 5-*O*-[2,3-(6-amino-6-deoxy-*L*-glycero-*D*-galactohexopyranosylidene)- β -*D*-talopyranosyl]-1*D*-3-amino-1-methylamino-1,2,3-trideoxy-*myo*-inositol by chemical and spectroscopic studies⁶⁾ as shown in Fig. 1. The structure of aminocyclitol⁷⁾ and 6-aminoheptonic acid⁸⁾ (destomic acid) moieties were also proved by syntheses. The analyzed structure confirmed the above-mentioned spectroscopic and chemical elucidations. From the spatial interrelation of the destomic acid and *D*-talose moieties, the absolute configuration of the orthoester carbon atom was determined to be (*R*). The torsional angles around several bonds are listed in Table 3.

Surprisingly, the *D*-talopyranose moiety has $B_{1,4}$ conformation. In the case of everninomicin D in which a pentono-1,5-lactone makes a spiro cyclic ortho ester with the *trans*-diequatorial 3,4-diol function of *L*-lyxopyranose moiety,²⁾ the pyranose ring exists in 1C_4 conformation, because $B_{1,4}$ conformation causes an additional distortion to the five-membered ortho ester

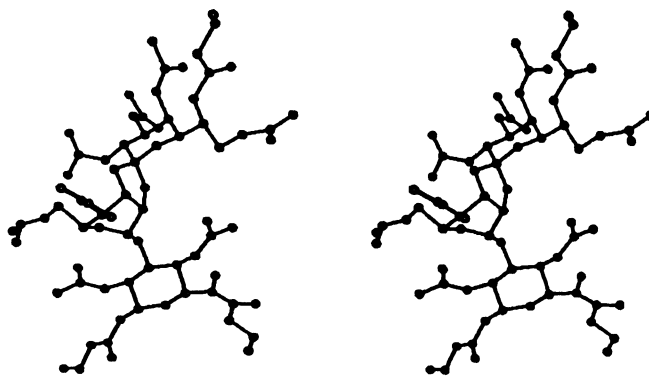


Fig. 2. A stereoscopic drawing of the molecule. This was drawn by TSD:XTAL, which is a computer-graphics interactive modeling program for NOVA 3 computer.¹²⁾

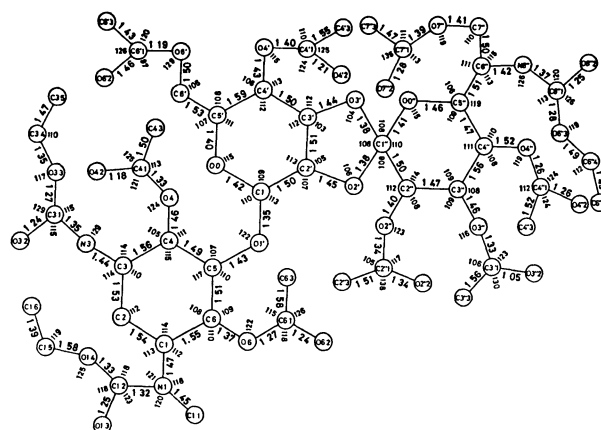


Fig. 3. Bond distances ($\text{\AA}$) and angles ($^\circ$). Their standard deviations are 0.02–0.04 $\text{\AA}$ and 1–2 $^\circ$, respectively. Bond angles of $\text{O}(2')\text{--C}(1')\text{--O}(0'')$ and $\text{O}(3')\text{--C}(1')\text{--C}(2'')$ are 111 $^\circ$ and 112 $^\circ$, respectively.

TABLE 3. TORSIONAL ANGLES ($^\circ$)

C(4)–C(5)–O(1')–C(1')	128
C(6)–C(5)–O(1')–C(1')	–106
C(5)–O(1')–C(1')–O(0')	–118
C(5)–O(1')–C(1')–C(2')	120
O(1')–C(1')–C(2')–O(2')	47
O(0')–C(1')–C(2')–O(2')	–75
O(1')–C(1')–C(2')–C(3')	40
O(0')–C(1')–C(2')–C(3')	162
O(2')–C(2')–C(3')–O(3')	15
C(1')–C(2')–C(3')–C(4')	19
O(3')–C(3')–C(4')–O(4')	–58
C(2')–C(3')–C(4')–C(5')	–52
C(2')–C(3')–O(3')–C(1'')	–33
C(4')–C(3')–O(3')–C(1'')	–153
C(1')–C(2')–O(2')–C(1'')	129
C(3')–C(2')–O(2')–C(1'')	9
C(2')–O(2')–C(1'')–O(3'')	–31
C(2')–O(2')–C(1'')–O(0'')	87
C(2')–O(2')–C(1'')–C(2'')	–153
C(3')–O(3')–C(1'')–O(2'')	41
C(3')–O(3')–C(1'')–O(0'')	–79
C(3')–O(3')–C(1'')–C(2'')	160
O(2'')–C(2'')–C(1'')–O(2'')	55
O(2'')–C(2'')–C(1'')–O(3'')	–64
O(2'')–C(2'')–C(1'')–O(0'')	174

[†] The table of the observed and calculated structure factors and the list of the anisotropic temperature factors are kept as Document No. 8140 at the office of the Chemical Society of Japan.

TABLE 4. LEAST-SQUARES PLANES AND DEVIATIONS (*l*/Å)
FOR FOUR ATOMS OF THE FIVE-MEMBERED
ORTHO ESTER RING

X, *Y*, and *Z* in Å referred to $\bar{a}$, $\bar{b}$, and $\bar{c}$ ^{a)} respectively.
 $-0.9615X + 0.0951Y - 0.2580Z + 4.0005 = 0$

C 2'	-0.05 ^{a)}
C 3'	0.03 ^{a)}
O 2'	0.05 ^{a)}
C 1''	-0.03 ^{a)}
O 3'	0.51

a) Atoms included in the least-squares calculation.

ring.⁹⁾ Besides, in the case of (1) in which the 6-aminoheptono-1,5-lactone links to the *cis*-2,3-diol function of D-talopyranose moiety, B_{1,4} conformation assists the formation of five-membered ortho ester ring, and erases the non-bonded interactions caused by C4'-hydroxyl group previously in axial orientation. In fact, the dihedral angle of C(2')-O(2') and C(3')-O(3') is 15°. These facts must also be true in the natural destomycin A itself.

From the synthetic studies,¹⁰⁾ it was suggested that the five-membered ring has a twist or envelope conformation to avoid the non-bonded interactions. The determined structure proved that the ring takes an envelope conformation in which the O(3') atom of D-talopyranose moiety deviated significantly from the average plane of other four atoms. The equation of the plane and the deviation of each atom from the plane in the five-membered ring are shown in Table 4.

It is characteristic that the both C-O bonds in the five-membered ring concerned with ortho ester carbon is slightly short as was observed in the anomeric C-O bond in the usual aldopyranosides.¹¹⁾ Other bond distances and angles show the values common in carbohydrate derivatives.

The crystal structure viewed along the *b* axis is shown in Fig. 4. The hydrogen bonds, listed in Table 5, make a three-dimensional network through the water molecules.

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TABLE 5. HYDROGEN BOND LENGTHS (*l*/Å)

O(13)···N(6'') ^{III}	2.90 (2)
O(W1)···N(3) ^I	2.99 (3)
O(W1)···O(W2) ^I	3.05 (5)
O(W1)···O(2'') ^{III}	2.98 (3)
O(W1)···O(W3) ^{II}	2.51 (5)
O(W2)···O(W4) ^I	2.60 (6)
O(W2)···O(6'2) ^I	3.08 (4)
O(W2)···O(7'2) ^I	2.67 (5)

I. (0.0+*x*, 0.0+*y*, 0.0+*z*)

II. (-1.0+*x*, 0.0+*y*, 0.0+*z*)

III. (1.0+*x*, 0.0+*y*, 1.0+*z*)

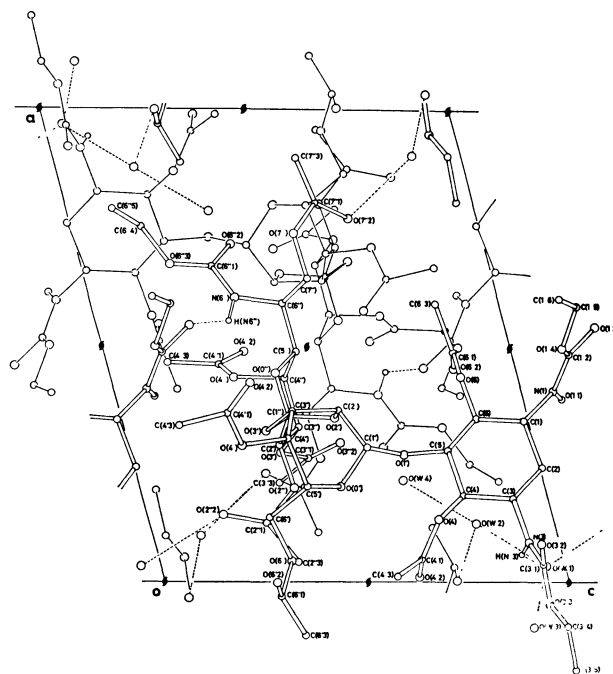


Fig. 4. Projection of the crystal structure along the *b* axis. The dotted lines indicate the hydrogen bonds.

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