Carbohydrate Research, 162 (1987) 171–179
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

CRYSTAL AND MOLECULAR STRUCTURES OF SUBSTITUTED α-D-GLUCOPYRANOSIDES

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(Received August 13th, 1986; accepted for publication, November 3rd, 1986)

ABSTRACT

The crystal and molecular structures of methyl 2,4,6-tri-*O*-pivaloyl-α-D-glucopyranoside (**1**), methyl 4,6-*O*-(*R*)-benzylidene-2-*O*-pivaloyl-α-D-glucopyranoside (**2**), and methyl 4,6-*O*-(*R*)-benzylidene-2,3-di-*O*-pivaloyl-α-D-glucopyranoside (**3**) were determined by X-ray analysis. Crystals of **1** are orthorhombic, space group $P2_12_12_1$ with the unit cell $a = 13.026(2)$, $b = 16.832$, $c = 11.929(2)$ Å, $Z = 4$. Crystals of **2** are monoclinic, space group $P2_1$. The unit-cell parameters are $a = 6.519(1)$, $b = 14.664(4)$, $c = 10.635(4)$ Å, $\beta = 93.18(1)°$, $Z = 2$. Crystals of **3** are orthorhombic, space group $P2_12_12_1$ with $a = 10.006(3)$, $b = 13.874(3)$, $c = 18.527(5)$ Å, $Z = 4$. The structures were solved by MULTAN and refined by a full-matrix procedure to final values of $R = 0.084$ (**1**), 0.048 (**2**), and 0.069 (**3**). The pyranose ring in each compound adopts the $^4C_1$ conformation. The 1,3-dioxane rings in **2** and **3** show a chair conformation. The molecular packing in **1** is through the hydrogen bonds involving HO-3 and the 6-*O*-pivaloyl carbonyl group [HO-3 · · · O-9, 2.855(8) Å], which connect the molecules into a chain along $\vec{b}$. The endocyclic oxygen atom is involved in an intermolecular hydrogen-bond with HO-3 [2.848(4) Å], joining molecules of **2** into the chains along $\vec{a}$. There are no free hydroxyl groups in **3** and molecular packing reflects van der Waals interactions only.

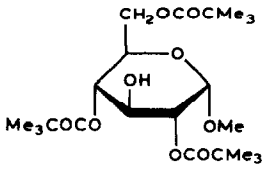
INTRODUCTION

Protection of carbohydrates has been often achieved by esterification; the pivaloyl group is an excellent ester protecting group, and pivaloylation may be used for the partial or total protection of sugars[1,2]. The high selectivity of the esterification process, ease in identification of products, and the stability of the derivatives in solution make pivaloyl the group of choice in solving various problems in preparative carbohydrate chemistry.

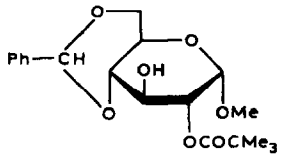
0008-6215/87/$ 03.50

Esters can be used as clinically useful prodrugs, and the pharmacological potential of selectively pivaloylated derivatives has been demonstrated[3].

We have reported[4] on the X-ray analysis of some pivaloylated D-gluco-furanurono-6,3-lactone derivatives, and now describe the crystal and molecular structures of three representatives (**1–3**) of a series of substituted α-D-gluco-pyranosides.



1



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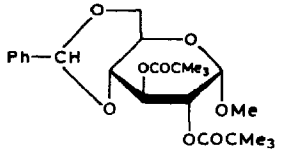

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EXPERIMENTAL

Preliminary cell dimensions and the space groups were determined from oscillation and Weissenberg photographs recorded with Cu$K\alpha$ radiation. Final cell parameters were refined from diffractometer measurements of 45 reflections (in the range $9 < \theta < 13°$) for **1**, 75 reflections ($10 < \theta < 15°$) for **2**, and 13 reflections ($10 < \theta < 15°$) for **3**.

Crystal data: **1** ($C_{22}H_{38}O_9$), $M_r = 446.54$, orthorhombic, space group $P2_12_12_1$, $a = 13.026(2)$, $b = 16.832(5)$, $c = 11.929(2)$ Å, $V = 2615.48$ Å^3, $Z = 4$, $D_c = 1.134$ Mg.m^{-3}, μ(Mo$K\alpha$) = 0.81 cm^{-1}, $F(000)$ = 968 electrons; **2** ($C_{19}H_{26}O_7$), M_r = 366.42, monoclinic, space group $P2_1$, $a = 6.519(1)$, $b = 14.664(4)$, $c = 10.635(1)$ Å, $\beta = 93.18(1)°$, $V = 1015.08$ Å^3, $Z = 2$, $D_c = 1.199$ Mg.m^{-3}, μ(Mo$K\alpha$) = 0.85 cm^{-1}, $F(000)$ = 392 electrons; **3** ($C_{24}H_{34}O_8$), M_r = 450.53, orthorhombic, space group $P2_12_12_1$, $a = 10.006(3)$, $b = 13.874(3)$, $c = 18.527(5)$ Å, $V = 2571.98$ Å^3, Z = 4, $D_c = 1.164$ Mg.m^{-3}, μ(Cu$K\alpha$) = 6.82 cm^{-1}, $F(000)$ = 968 electrons.

Intensities for **1** and **2** were collected on an Enraf-Nonius CAD-4F diffractometer in the $\omega/2\theta$ mode with a graphite monochromator and Mo$K\alpha$ radiation in the $1.5 < \theta < 25°$ range. Intensities for **3** were recorded on a Philips PW 1100 computer-controlled four-circle diffractometer in the $\omega/2\theta$ mode with a graphite monochromator and Cu$K\alpha$ radiation in the $3 < \theta < 69°$ range. Dimensions of the crystals used in data collection were 0.10 × 0.15 × 0.40 mm (**1**), 0.20 × 0.30 × 0.50 mm (**2**), and 0.18 × 0.20 × 0.45 mm (**3**), and 1865 independent reflections of **1**, 2607 of **2**, and 1250 of **3** were measured. Of these, 1664 (**1**), 1715 (**2**) [$I \geq 2\sigma(I)$], and 1230 [$I \geq 3\sigma(I)$] were treated as observed reflections and used in the calculations.

The structures were solved by direct methods using the MULTAN-80 programme[5]. The values $|E| \geq 1.5$ for **1** (281 reflections), **2** (254 reflections), and $|E| \geq 1.2$ for **3** (252 reflections) were used. Difference Fourier syntheses were used

to locate 5 atoms of **1**, 7 atoms of **2**, and 12 atoms of **3**. Hydrogen atoms attached to the pyranose ring and those bonded to the methoxyl group at C-1 were located from difference Fourier maps for **1**, **2**, and **3**. The hydrogen atoms at C-11 of pivaloyl in **2** were also located from the map. However, other hydrogen atoms of pivaloyl groups were not visible in the difference Fourier maps, probably due to considerable temperature movements* of these terminal groups. The hydrogen atoms of phenyl rings in **2** and **3** were introduced at their calculated positions on stereochemical grounds. The structures were refined by a full-matrix least-squares procedure, minimizing $\Sigma w.\Delta F^2$, $w = 1$. Scale factors, atomic co-ordinates of the non-hydrogen atoms and those hydrogen atoms bonded to the ring skeleton in **2** only, and the anisotropic thermal parameters of all non-hydrogen atoms were refined. Those hydrogen atoms which were not refined were included in the structure factor calculations only. For the hydrogen atoms, the isotropic thermal parameters were those of the bonded atoms enlarged for one unit (in Å^2).

The final R values of 0.084 (**1**), 0.048 (**2**) for observed reflections having $I \geq 2\sigma(I)$, and 0.069 (**3**) [$I > 3\sigma(I)$] were obtained [S = 0.86 (**1**), 0.96 (**2**), 3.3 (**3**) (18 H atoms were not located: maximum value $\Delta/\sigma = 0.529$ (C-13 of **1**), 1.38 (C-4 of **2**), and 0.401 (C-6 of **3**)]. High thermal movements* of the terminal parts of the pivaloyl groups were more pronounced in **1** and **3**. The values of the thermal parameters of the ring atoms are of the same order of magnitude*.

The difference Fourier maps did not reveal any significant residual density ($-0.02 < \Delta\rho < 0.02$ eÅ^{-3}).

Scattering factors given by Cromer and Mann[6] and (for H) by Stewart *et al.*[7] were used. The calculations were performed on a Univac 1110 computer at the University Computing Centre in Zagreb with the XRAY system[8].

The final atomic co-ordinates and isotropic thermal parameters for the non-hydrogen atoms of **1–3**, together with the final temperature parameters, final atomic co-ordinates for the hydrogen atoms, and complete lists of bond angles and lengths, have been deposited*

DISCUSSION

The structural formulae with the atom numbering are given for **1–3** in Fig. 1. Bond lengths and angles are listed in Tables I (for **1**) and II (for **2** and **3**). Because D compounds were used as the starting materials, the D enantiomers were selected with corresponding signs of torsion angles [Tables III (for **1**) and IV (for **2** and **3**)]. The Bijvoet pairs were not measured. The absolute configuration at the new chiral centre C-7 of the benzylidene derivatives **2** and **3** was determined by using the α-D-carbohydrate moiety as the internal standard.

*These data have been deposited with, and may be obtained from Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/358/*Carbohydr. Res.*, 162 (1987) 171–179.

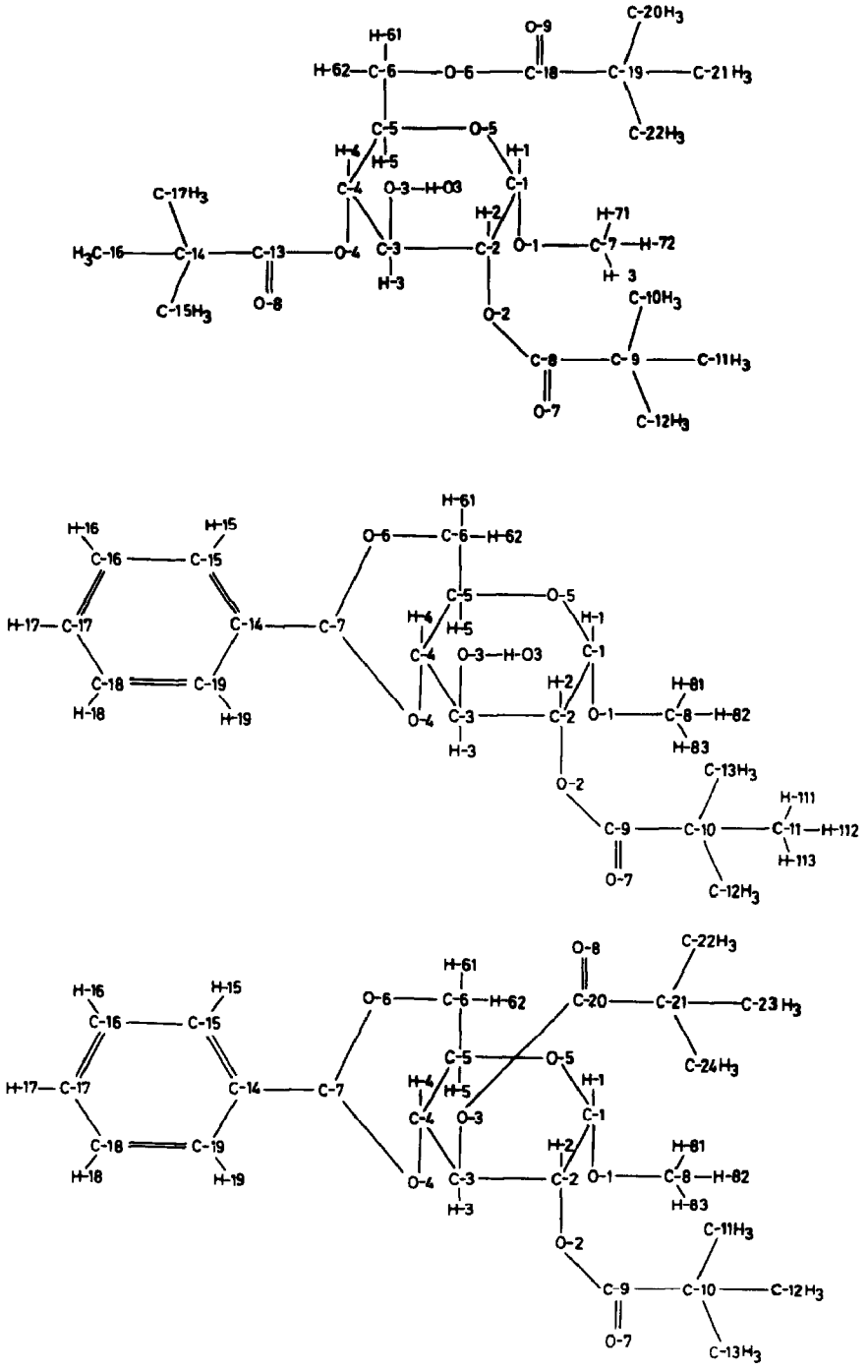

Fig. 1. Atom numbering of **1–3**.

TABLE I

BOND LENGTHS (Å) AND ANGLES (°) FOR 1

O-5–C-1	1.415(8)	C-5–C-6	1.52(1)
O-5–C-5	1.435(9)	C-6–O-6	1.436(9)
C-1–C-2	1.51(1)	C-7–O-1	1.40(1)
C-1–O-1	1.424(9)	C-8–O-2	1.31(1)
C-2–C-3	1.54(1)	C-8–O-7	1.18(1)
C-2–O-2	1.442(8)	C-13–O-4	1.356(9)
C-3–C-4	1.51(1)	C-13–O-8	1.19(1)
C-3–O-3	1.415(9)	C-18–O-6	1.308(9)
C-4–C-5	1.53(1)	C-18–O-9	1.21(1)
C-4–O-4	1.452(8)	C-18–C-19	1.50(1)
O-5–C-1–O-1	112.8(6)	O-6–C-6–C-5	110.6(6)
O-5–C-1–C-2	109.4(5)	O-2–C-8–O-7	120.5(9)
O-1–C-1–C-2	107.2(6)	O-2–C-8–C-9	113.3(7)
O-2–C-2–C-1	110.8(6)	O-7–C-8–C-9	126.1(9)
O-2–C-2–C-3	106.4(5)	O-4–C-13–O-8	123.1(7)
C-1–C-2–C-3	112.0(6)	O-4–C-13–C-14	110.1(7)
O-3–C-3–C-2	109.9(6)	O-8–C-13–C-14	126.7(8)
O-3–C-3–C-4	110.8(6)	O-6–C-18–O-9	121.2(7)
C-2–C-3–C-4	107.3(5)	O-6–C-18–C-19	115.1(7)
O-4–C-4–C-3	107.9(5)	O-9–C-18–C-19	123.7(7)
O-4–C-4–C-5	106.3(5)	C-1–O-1–C-7	113.6(6)
C-3–C-4–C-5	110.4(6)	C-2–O-2–C-8	120.4(6)
O-5–C-5–C-4	107.6(5)	C-4–O-4–C-13	117.7(5)
O-5–C-5–C-6	108.5(6)	C-1–O-5–C-5	113.1(5)
C-4–C-5–C-6	114.6(6)	C-6–O-6–C-18	116.3(5)

The anomeric effect (shortening of the C-1–O-1 bond) in **2** and **3**, in spite of the axial position of the ligands, is pronounced (Tables I and II). Otherwise C–O exocyclic bonds (contiguous to the ring C atoms) are not significantly different to endocyclic ones; the differences are within 3σ. The valence angles at O-5 are in the range from 111.1(7) to 113.1(5)°; the values of valence angles at O-4 and O-6 in the dioxane rings are closer to the tetrahedral value. The unusual values of the C–C bonds involving groups of C-19 of **1** and C-21 of **3** can be explained by the high thermal movement of these bulky substituents.

α-D-Glucopyranose rings adopt the $^4C_1$ conformation with the range of torsion angles from 53.9(7) to 63.8(7)°, **1**; 51.0(5)–64.4(4)°, **2**; and 50(1)–63.3(9)°, **3**. The puckering parameters according to the Cremer and Pople[9] criteria for the atom sequence C-1, C-2, C-3, C-4, C-5, O-5 are $\varphi = 51°$, $Q = 0.591$ Å, $\theta = 176.1°$, **1**; $\varphi = 54°$, $Q = 0.589$ Å, $\theta = 173.1°$, **2**; and $\varphi = 66°$, $Q = 0.565$ Å, $\theta = 173.6°$, **3**. The specified sequence of atoms has been used in order to be in accordance with nomenclature defined for carbohydrates[10,11].

The 4,6-*O*-benzylidene-α-D-glucopyranosides have *trans*-fused [4.4.0] ring systems[10]. The 1,3-dioxane ring of **2** and **3** adopts a chair conformation (Table IV). The phenyl ring in **2** and **3** is attached equatorially, the absolute configuration being *R*.

TABLE II

BOND LENGTHS (Å) AND ANGLES (°) FOR **2** AND **3**

	2	**3**		**2**	**3**
O-5–C-1	1.423(2)	1.42(1)	C-1–O-5–C-5	112.1(3)	111.1(7)
O-5–C-5	1.440(5)	1.44(1)	O-5–C-1–C-2	110.0(3)	110.8(8)
C-1–C-2	1.525(6)	1.53(1)	O-5–C-1–O-1	111.6(3)	112.7(8)
C-1–O-1	1.380(6)	1.37(1)	C-2–C-1–O-1	108.6(3)	109.2(8)
C-2–C-3	1.518(6)	1.52(1)	C-1–C-2–C-3	113.6(4)	113.2(8)
C-2–O-2	1.444(6)	1.44(1)	C-1–C-2–O-2	110.4(3)	109.3(8)
C-3–C-4	1.514(6)	1.50(1)	C-3–C-2–O-2	105.6(3)	107.3(8)
C-3–O-3	1.414(5)	1.43(1)	C-2–C-3–C-4	107.4(3)	108.7(8)
C-4–C-5	1.517(6)	1.51(1)	C-2–C-3–O-3	107.6(4)	106.4(7)
C-4–O-4	1.430(5)	1.43(1)	C-4–C-3–O-3	111.9(4)	109.8(7)
C-5–C-6	1.518(7)	1.50(1)	C-3–C-4–C-5	110.7(4)	110.8(8)
C-6–O-6	1.427(6)	1.42(1)	C-3–C-4–O-4	109.0(3)	109.5(7)
C-7–O-4	1.424(6)	1.41(1)	C-5–C-4–O-4	109.2(3)	108.9(7)
C-7–O-6	1.408(6)	1.39(1)	O-5–C-5–C-4	108.0(4)	110.2(7)
C-7–C-14	1.502(6)	1.54(1)	O-5–C-5–C-6	110.7(3)	110.5(8)
C-8–O-1	1.421(7)	1.44(2)	C-4–C-5–C-6	109.1(4)	108.0(8)
C-9–C-10	1.523(8)	1.52(1)	C-5–C-6–O-6	106.7(4)	109.8(8)
C-9–O-2	1.347(6)	1.29(1)	C-4–O-4–C-7	109.9(3)	109.5(7)
C-9–O-7	1.180(6)	1.16(2)	C-6–O-6–C-7	112.2(4)	110.9(7)
C-20–C-21		1.51(2)	O-4–C-7–O-6	110.3(4)	113.1(8)
C-20–O-3		1.32(1)	O-4–C-7–C-14	107.1(3)	107.3(8)
C-20–O-8		1.20(2)	O-6–C-7–C-14	108.8(4)	107.6(8)
			C-1–O-1–C-8	113.7(4)	113.0(8)
			C-2–O-2–C-9	117.3(3)	118.5(8)
			O-2–C-9–O-7	122.5(5)	122(1)
			O-2–C-9–C-10	111.0(4)	114(1)
			O-7–C-9–C-10	126.5(5)	124(1)
			C-3–O-3–C-20		119.6(8)
			O-3–C-20–O-8		122(1)
			O-3–C-20–C-21		111(1)
			O-8–C-20–C-21		128(1)

TABLE III

TORSION ANGLES (°) FOR **1**

O-5–C-1–C-2–C-3	55.9(7)	O-2–C-8–C-9–C-10	30(1)
C-1–C-2–C-3–C-4	−53.9(7)	C-1–C-2–C-3–O-3	−174.4(5)
C-2–C-3–C-4–C-5	56.1(7)	C-2–C-3–C-4–O-4	171.9(5)
C-3–C-4–C-5–O-5	−60.9(7)	C-3–C-4–O-4–C-13	110.4(7)
C-4–C-5–O-5–C-1	63.8(7)	C-4–O-4–C-13–O-8	2(1)
C-5–O-5–C-1–C-2	−61.6(7)	C-4–O-4–C-13–C-14	−175.2(7)
O-1–C-1–C-2–C-3	−66.7(7)	C-3–C-4–C-5–C-6	178.3(6)
C-2–C-1–O-1–C-7	−172.5(6)	C-4–C-5–C-6–O-6	47.1(8)
O-5–C-1–C-2–O-2	174.5(5)	C-5–C-6–O-6–C-18	−161.9(6)
C-1–C-2–O-2–C-8	101.2(8)	C-6–O-6–C-18–O-9	0(1)
C-2–O-2–C-8–O-7	−1(1)	C-6–O-6–C-18–C-19	175.9(6)
C-2–O-2–C-8–C-9	176.1(6)		

TABLE IV

TORSION ANGELS (°) FOR **2** AND **3**

	2	**3**		**2**	**3**
O-5–C-1–C-2–C-3	53.0(5)	52(1)	C-6–C-5–C-4–O-4	57.0(4)	57.5(9)
C-1–C-2–C-3–C-4	−51.0(5)	−50(1)	O-1–C-1–C-2–C-3	−69.5(4)	−72(1)
C-2–C-3–C-4–C-5	55.6(4)	53(1)	C-8–O-1–C-1–C-2	−165.7(5)	−166.6(9)
C-3–C-4–C-5–O-5	−62.7(4)	−61(1)	O-5–C-1–C-2–O-2	171.3(3)	171.9(7)
C-4–C-5–O-5–C-1	64.4(4)	63.3(9)	C-1–C-2–O-2–C-9	76.1(5)	96(1)
C-5–O-5–C-1–C-2	−59.2(4)	−58(1)	C-2–O-2–C-9–O-7	−1.5(7)	−1(2)
C-2–C-3–C-4–O-4	175.7(3)	173.7(7)	C-2–O-2–C-9–C-10	178.9(4)	179.6(8)
C-3–C-4–C-5–C-6	177.0(4)	178.1(8)	C-1–C-2–C-3–O-3	−171.6(4)	−167.8(7)
C-5–C-4–O-4–C-7	−58.8(3)	−59.6(7)	C-4–O-4–C-7–C-14	180.0(3)	179.9(5)
C-4–O-4–C-7–O-6	61.8(4)	61(1)	O-4–C-7–C-14–C-15	−64.7(5)	−164.5(9)
O-4–C-7–O-6–C-6	−64.0(4)	−60.(1)	C-2–C-3–O-3–C-20		−119.1(9)
C-7–O-6–C-6–C-5	60.5(5)	57(1)	C-3–O-3–C-20–O-8		−2(2)
O-6–C-6–C-5–C-4	−56.3(5)	−56(1)	C-3–O-3–C-20–C-21		−179.8(6)

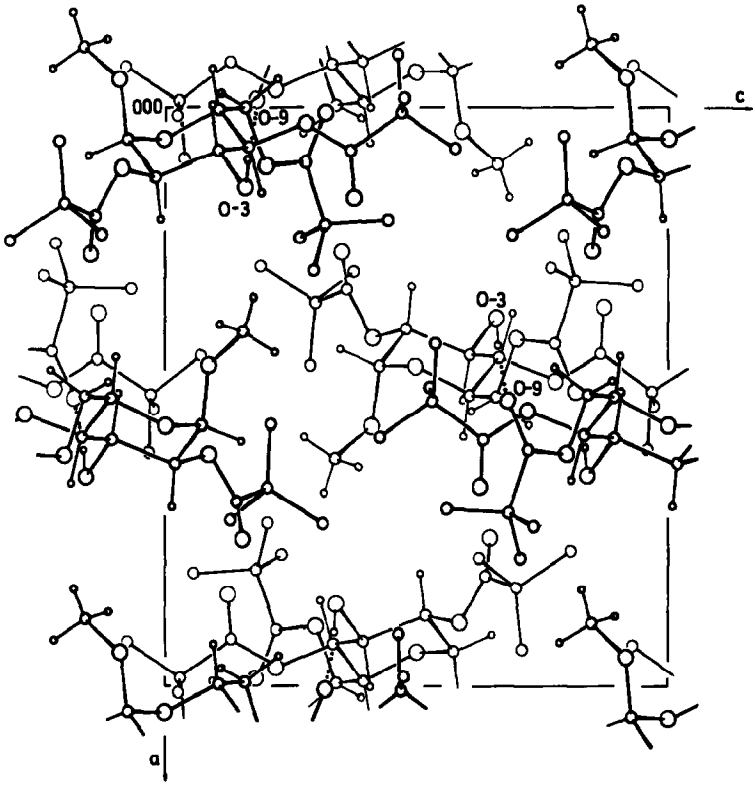

Fig. 2. A view of the crystal structure of **1** down $\vec{b}$. Hydrogen bonds (· · ·) connect the molecules into a chain along $\vec{b}$.

The molecular packing in **1** and **2** is realised through intermolecular hydrogen-bonds (Figs. 2 and 3). In both crystal structures, HO-3 acts as the donor. In **1**, the carbonyl oxygen of the 6-*O*-pivaloyl group accepts HO-3 [HO-3 · · · O-9, 2.855(8) Å, H · · · O-9, 1.85 Å, ∠ O-3–H–O-9, 155°] and connects molecules into the chains along $\vec{b}$. In the crystal structure of **2**, the endocyclic oxygen O-5 is involved in intermolecular hydrogen-bonds [HO-3 · · · O-5, 2.848(4) Å; H · · · O-5, 2.04(5) Å; ∠ O-3–H–O-5, 169(3)°] which join molecules into the chains along $\vec{a}$. In **3**, all hydroxyl groups are esterified and hydrogen bonds are not possible; the molecular packing reflects the van der Waals interactions only (Fig. 4).

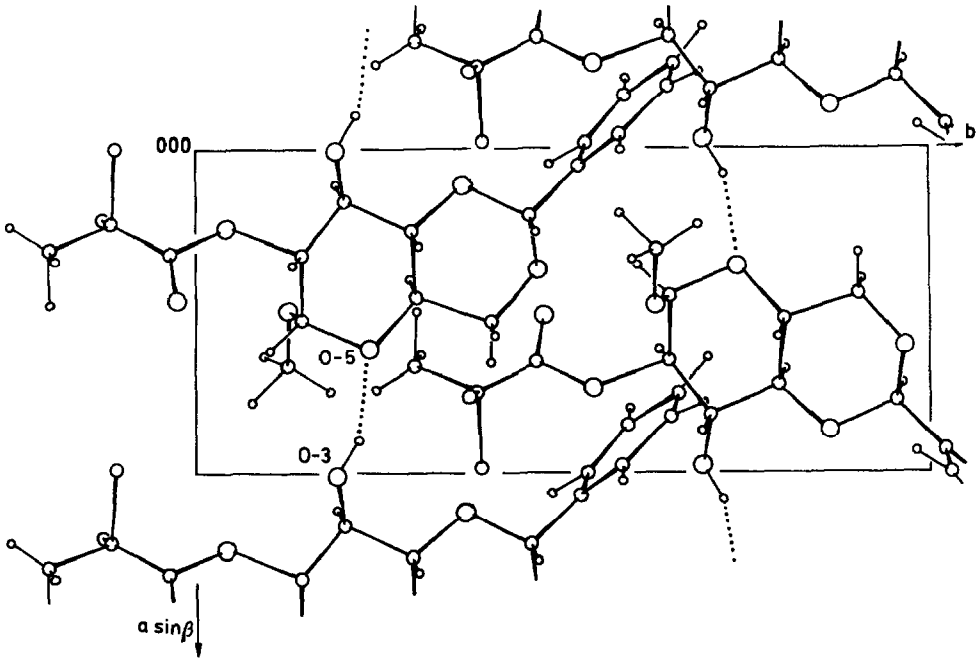

Fig. 3. A view of the crystal structure of **2** down $\vec{c}$. Intermolecular hydrogen-bonds involving the endocyclic oxygen O-5 join molecules into chains along $\vec{a}$.

ACKNOWLEDGMENT

This work was partly financed by the Self-Managing Authority for Scientific Research of the SR Croatia, Yugoslavia.

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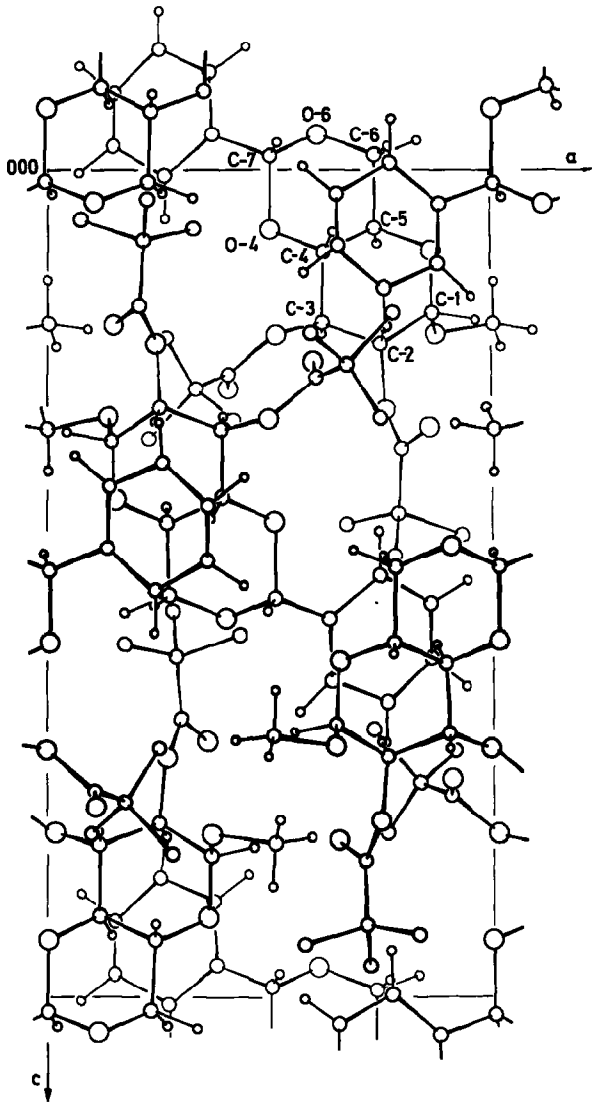

Fig. 4. A view of the crystal structure of **3** down $\vec{b}$. Molecular packing is solely through the van der Waals interactions.

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