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Note

Methyl *O*-pivaloyl-α-D-glucopyranosides

SRDANKA TOMIĆ-KULENOVIĆ AND DINA KEGLEVIĆ
Tracer Laboratory, Department of Organic Chemistry and Biochemistry, "Ruđer Bošković" Institute, 41001 Zagreb (Yugoslavia)

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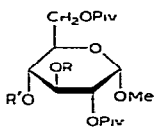
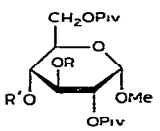
During work on glycosyl esters[1], the need arose for an *O*-acyl protecting group that would not migrate readily and would be easily detectable by p.m.r. spectroscopy. These features have been reported for the pivaloyl group in selective acylations of nucleosides[2–4] and partially protected D-mannitol[5], and in isomerisation studies[6] of 2- and 3-*O*-acyluridines. Hough *et al.*[7] have shown the high selectivity of pivaloyl chloride in the esterification of sucrose and prepared a variety of derivatives thereof. We now report on the pivaloylation of methyl α-D-glucopyranoside and its 4,6-*O*-benzylidene derivative.

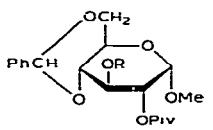
Treatment of methyl α-D-glucopyranoside in ether with 4.8 mol each of pivaloyl chloride and pyridine for 1 h at 4° and then for 24 h at 22° gave an ~1.2:1:1.5 mixture of methyl 2,3,6- (**2**), 2,4,6-tri- (**3**), and 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranoside (**4**), which accounted for more than 80% of the starting material; each product was isolated by chromatography. Reaction for 1 h at 4° gave almost exclusively the 2,6-dipivaloate **1** (89%), whereas after 36 h at room temperature, the tetrapivaloate **4** (82%) was obtained. When the ether in the first experiment above was replaced by pyridine, the tripivaloates **2** and **3** were obtained in yields of 35 and 54%, respectively. Thus, the relative reactivities of HO-3 and HO-4 are greatly influenced by the reaction solvent.



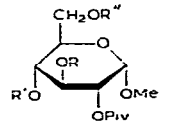
1 R = R′ = H
2 R = Piv, R′ = H
3 R = H, R′ = Piv
4 R = R′ = Piv



5 R = R′ = Ac
6 R = Piv, R′ = Ac
7 R = Ac, R′ = Piv



8 R = H
9 R = Piv
10 R = Ac



11 R = R′ = R″ = H
12 R = Piv, R′ = R″ = H
13 R = R′ = R″ = Ac
14 R = Piv, R′ = R″ = Ac

Piv = Me_3C—CO—

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TABLE I

ANALYTICAL DATA FOR COMPOUNDS **1–14**

Compound	*M.p. (degrees)*	$[\alpha]_D^{22}$ [a] *(degrees)*	*Formula*	*Anal.*			
				Calc.		*Found*	
				C	*H*	*C*	*H*
1	82–84	+57	$C_{17}H_{30}O_8$	56.34	8.34	56.17	8.22
2	75–77	+87	$C_{22}H_{38}O_9$	59.17	8.58	59.45	8.60
3	129–131	+95				59.05	8.38
4	83–85	+102	$C_{27}H_{46}O_{10}$	61.11	8.74	61.00	8.56
5	99–101	+118	$C_{21}H_{34}O_{10}$	56.49	7.68	56.67	7.57
6	91–92	+112	$C_{24}H_{40}O_{10}$	59.00	8.25	59.24	8.23
7	glass	+88				58.83	8.08
8	149–151	+98	$C_{19}H_{26}O_7$	62.28	7.15	62.10	7.25
9	144–146	+57	$C_{24}H_{34}O_8$	63.98	7.61	64.21	7.77
10	88–90	+79	$C_{21}H_{28}O_8$	61.75	6.91	61.82	6.87
11	120–123	+93	$C_{12}H_{22}O_7$	51.79	7.97	51.88	7.70
12	96–98	n.d.[b]	$C_{17}H_{30}O_8$	56.34	8.34	56.35	8.14
13	glass	n.d.[b]	$C_{18}H_{28}O_{10}$	53.46	7.00	53.55	7.15
14	58–60	+116	$C_{21}H_{34}O_{10}$	56.49	7.68	56.20	7.45

[a]In chloroform (*c* 1). [b]Not determined.

An attempt to obtain the monopivaloate derivative(s) by reaction (4°, 1 h) of methyl α-D-glucopyranoside in ether with slightly more than 1 equiv. each of pivaloyl chloride and pyridine resulted in similar rates of acylation of HO-2 and HO-6. T.l.c. of the reaction mixture revealed the simultaneous formation of the two monopivaloates, the amounts of which decreased as the 2,6-dipivaloate **1** was formed. After 24 h, there was still much unchanged starting-material.

When methyl 4,6-*O*-benzylidene-α-D-glucopyranoside in ether was treated with 2.2 equiv. each of pivaloyl chloride and pyridine for 16 h at 22°, 77% of the 2-pivaloate derivative **8** was obtained and, after 48 h, 27% of the 2,3-dipivaloate **9** was isolated. Treatment of **8** and **9** with hot acetic acid removed the benzylidene groups and afforded the 2- (**11**) and 2,3-di-pivaloate (**12**), respectively.

All of the foregoing pivaloates were obtained crystalline and their structures were established on the basis of analytical and p.m.r. data of the compounds and their acetates (**5–7**, **13**, and **14**) (Tables I and II). The positions of the pivaloyl groups were assigned on the basis of the chemical shifts of the *tert*-butyl singlets, which occurred in a region not obscured by other signals.

For solutions in $CDCl_3$ the pivaloate singlet at lowest field was assigned to the group at position 6. The second lowest-field signal in the spectra of **2**, **4**, and **5–7** was assigned to the 2-pivaloyl group; in the spectra of **1** and **3**, this signal coincided with that of the 6-pivaloyl group. The signal assigned to the 3-pivaloyl group (**2**, **4**, **6**, **12**, and **14**) was at the highest field, whereas that for the 4-pivaloyl group (**3**, **4**,

TABLE II

^{1}H-N.M.R. DATA ($CDCl_3$, 100 MHz) FOR METHYL *O*-ACETYL-*O*-PIVALOYL-α-D-GLUCOPYRANOSIDE DERIVATIVES

Compound	*Chemical shifts, δ (p.p.m.)*[a]								
	Me_3C-CO_2				*AcO*			*Others*	
	2	*3*	*4*	*6*	*3*	*4*	*6*	*MeO*	*AcO-2*
1	1.23			1.23				3.37	
2	1.20	1.18		1.23				3.38	
3	1.23		1.22	1.23				3.39	
4	1.17	1.12	1.16	1.23				3.39	
5	1.17			1.23	1.99	2.03		3.40	
6	1.17	1.13		1.23		2.01		3.40	
7	1.17		1.16	1.23	1.96			3.40	
11[b]	1.22							3.35	
12[c]	1.20	1.18						3.39	
13	1.18				2.00	2.03	2.11	3.40	
14	1.17	1.13				2.01	2.11	3.40	
15[d]					2.01	2.03	2.09	3.43	2.07

[a]All signals are singlets. [b]Derived from **8**. [c]Derived from **9**. [d]Methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside.

and **7**) was in the region between those for the 2- (at lower field) and the 3-pivaloyl group (at the highest field). The location of the acetyl groups in **5**–**7**, **13**, and **14**, as compared to those in the spectrum of methyl α-D-glucopyranoside tetra-acetate (**15**), is fully consistent with the above assignments. There is a general shift of the pivaloyl singlets (except for that at C-6) to higher fields in the spectra of acetylated derivatives. However, the signal sequence of the pivaloyl groups does not change and it is the same as that established[8] for the acetoxyl signals in the spectrum of **15**.

Saponification of the pivaloyl groups with methanolic sodium methoxide proceeded readily, but slower than that of the acetyl groups in **15**. The pivaloyl group was resistant towards acid. For example, **4** was not affected by treatment with trifluoroacetic acid in acetic acid (1 : 1), or 1 % hydrogen chloride in methanol, for 48 h at room temperature.

The foregoing results indicate the utility of the pivaloyl group for the synthesis of partially protected methyl α-D-glucopyranosides.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were determined for 1 % solutions in chloroform. Column chromatography was performed on silica gel (Merck) and t.l.c. on Kieselgel G (Merck) with benzene–ethyl acetate (*A*) in the proportions given in the text. Detection after t.l.c. was effected by charring with

sulphuric acid. P.m.r. spectra (100 MHz, internal Me_4Si) were recorded with a Jeol JNM FX-100 Fourier-transform NMR spectrometer.

Selective acylation of methyl α-D-*glucopyranoside.* — (*a*) To a stirred suspension of methyl α-D-glucopyranoside (485 mg, 2.5 mmol) in dry ether (15 ml) at 4° was added pyridine (1 ml, 12 mmol) followed by pivaloyl chloride (1.445 g, 12 mmol). The mixture was stirred at 4° for 1 h and then at ambient temperature for 24 h. T.l.c. (solvent *A*, 5:1) then revealed three major (R_F 0.45, 0.56, 0.80) and one minor (R_F 0.08) components together with traces of the starting compound (R_F 0.00). The mixture was poured onto ice and extracted with chloroform (3 ×), and the combined extracts were washed with saturated, aqueous sodium hydrogencarbonate, 10% aqueous citric acid, and water, dried (Na_2SO_4), and concentrated. The residual syrup was eluted from silica gel (solvent *A*, 10:1) to give chromatographically homogeneous methyl 2,3,6-tri-*O*-pivaloyl-α-D-glucopyranoside (**2**, 186 mg), methyl 2,4,6-tri-*O*-pivaloyl-α-D-glucopyranoside (**3**, 151 mg), and methyl 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranoside (**4**; 374 mg, 28%) (R_F 0.15, 0.21, and 0.80, respectively). Re-chromatography of the residue (150 mg) from fractions containing a mixture of **2** and **3** raised the total yields of pure **2** and **3** to 23 and 18.6%, respectively. The physical constants and elemental analyses for all of the pivaloates described herein are recorded in Table I.

To a solution of **4** (100 mg, 0.19 mmol) in dry methanol (5 ml) was added 0.1M methanolic sodium methoxide (0.5 ml), and the mixture was kept overnight at room temperature. T.l.c. (1-butanol–pyridine–water, 6:4:3) then revealed only one product, and methyl α-D-glucopyranoside (32.6 mg, 89%) was isolated: m.p. 165–166°, $[\alpha]_D$ +157° (water); lit.[9] m.p. 166°, $[\alpha]_D$ +158° (water).

(*b*) When the reaction in (*a*) was conducted for 1 h at 4°, chromatography (solvent *A*, 1:1) of the product afforded methyl 2,6-di-*O*-pivaloyl-α-D-glucopyranoside (**1**; 803 mg, 88.8%).

(*c*) When the reaction in (*a*) was conducted at room temperature for 36 h, chromatography (solvent *A*, 10:1) of the product gave **4** (1.09 g, 82%).

(*d*) A mixture of methyl α-D-glucopyranoside (485 mg) and pyridine (15 ml) was stirred with pivaloyl chloride (1.445 g, 12 mmol) for 2 h at 4° and then at room temperature for 24 h. Chromatography (solvent *A*, 10:1) of the product gave **2** (390 mg, 34.9%) and **3** (600 mg, 53.8%).

Conventional treatment of **1**–**3** with acetic anhydride–pyridine (1:1) for 16 h afforded, after chromatography (solvent *A*, 10:1), the acetates **5**–**7** in yields of 81, 93, and 90%, respectively.

*Selective acylation of methyl 4,6-O-benzylidene-*α-D-*glucopyranoside.* — (*a*) A suspension of the title compound (1 g, 3.54 mmol) in dry ether (30 ml) was treated with pyridine (0.63 ml, 7.79 mmol) and pivaloyl chloride (0.94 g, 7.79 mmol) at 4°, and the mixture was then stirred for 16 h at room temperature. Chromatography (solvent *A*, 5:1) of the product gave methyl 4,6-*O*-benzylidene-2-*O*-pivaloyl-α-D-glucopyranoside (**8**; 1 g, 76.9%), which was purified by crystallisation from light

petroleum, P.m.r. data: δ 7.45–7.33 (m, Ph), 5.55 (s, PhC*H*), 3.38 (s, OMe), and 1.24 (s, Me_3C, PivO-2).

Acetylation of **8** (50 mg) and chromatography (solvent *A*, 5:1) of the product gave the 3-acetate **10** (89%). P.m.r. data: δ 3.40 (s, OMe), 2.03 (s, OAc), and 1.19 (s, Me_3C, PivO-2).

(*b*) Treatment of the title compound (300 mg) as in (*a*), but for 48 h at ambient temperature, and chromatography of the product gave **8** (210 mg, 54%) and methyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-α-D-glucopyranoside (**9**; 129 mg, 27%). P.m.r. data for **9**: δ 3.39 (s, OMe), 1.19 (s, Me_3C, PivO-2), and 1.16 (*s*, PivO-3).

Methyl 2-O-pivaloyl-α-D-glucopyranoside (**11**). — To a stirred suspension of **8** (700 mg) in acetic acid (16 ml) at 100° was added water (4 ml), the mixture was kept at this temperature for 1 h and then concentrated, and the residue was subjected to chromatography (solvent *A*, 1:10), to give **11** (346 mg, 65%).

Acetylation of **11** (100 mg) and chromatography (solvent *A*, 5:1) of the product gave methyl 3,4,6-tri-*O*-acetyl-2-*O*-pivaloyl-α-D-glucopyranoside (**13**) as a chromatographically homogeneous glass (110 mg, 76%).

Methyl 2,3-di-O-pivaloyl-α-D-glucopyranoside (**12**). — Treatment of **9** (100 mg), as described for **11**, afforded **12** (66 mg, 82.5%).

Acetylation of **12** (30 mg) and chromatography (solvent *A*, 5:1) of the product gave methyl 4,6-di-*O*-acetyl-2,3-di-*O*-pivaloyl-α-D-glucopyranoside (**14**, 78%).

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REFERENCES

1 Dj. Ljevaković and D. Keglević, *Carbohydr. Res.*, 86 (1980) 43–57.
2 G. Weimann and H. G. Khorana, *J. Am. Chem. Soc.*, 84 (1962) 4329–4341.
3 B. E. Griffin, C. B. Reese, G. F. Stephenson, and D. R. Trentham, *Tetrahedron Lett.*, (1966) 4349–4354.
4 B. E. Griffin and C. B. Reese, *Tetrahedron Lett.*, (1964) 2925–2931.
5 S. J. Angyal and M. E. Evans, *Aust. J. Chem.*, 25 (1972) 1495–1512.
6 J. Baker, M. Jarman, and J. A. Stock, *J. Chem. Soc., Perkin Trans. 1*, (1973) 665–669.
7 L. Hough, M. S. Chowdhary, and A. C. Richardson, *Chem. Commun.*, (1978) 664–665.
8 D. Horton and J. H. Lauterbach, *J. Org. Chem.*, 34 (1969) 86–92.
9 E. Pacsu, *Methods Carbohydr. Chem.*, 2 (1963) 356.