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The Synthesis of Methyl 2,4,6-Tri-*O*-benzyl-α-D-glucopyranoside

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In synthetic carbohydrate chemistry, the partially benzylated derivative of sugar is, in general, used as an important intermediate.[1] This paper will deal with a facile method of preparing a new, partially-benzylated derivative of D-glucopyranose, methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (I), directly from methyl α-D-glucopyranoside by means of a controlled benzylation.[2] Methyl α-D-glucopyranoside was very carefully heated below 110°C in benzyl chloride in the presence of sodium hydride (3.3 molar equiv.) to give a mixture of partially- as well as fully-substituted products. After chromatographic separation, the main product, I, was obtained as a distillable oily product with a high reproducible yield; it was fully characterized as crystalline *p*-nitrobenzoate and *p*-phenylazobenzoate. The results of the elemental analysis and the $\varepsilon_{258.5}^{\text{ethanol}}$ value[2] of I indicated the existence of three benzyl groups. The position with a free hydroxyl group was determined by the methylation; *i.e.*, I was converted into the known methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside[3] and 1,2,4,6-tetra-*O*-benzoyl-3-*O*-methyl-β-D-glucopyranose[4] respectively. Thus, the 3-OH of I was unsubstituted.

The high reactivity of the 6-OH and 2-OH of α-D-glucopyranoside compared with that of others is frequently observed[5] and has led to successful preparations of the 2,6-di-*O*-substituted derivative. By the way, the difference between the reactivity of 3-OH and that of 4-OH is usually small, and their order is rather variable according to circumstances. In certain cases, however, a significantly lower reactivity of 3-OH has been reported;[6] the present result may be another example of this.

After the hydrolysis of I, 2,4,6-tri-*O*-benzyl-1,3-di-*O*-

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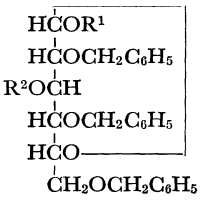
Table 1. Physical data of compounds

Cpd. No.	R^1	R^2	Yield %	Mp °C (recryst. solv.)	Bp °C (mmHg)	n_D^{20}	$[\alpha]_D$ (conc.)	$\varepsilon_{258.5}^{EtOH}$	Formula	Elemental analyses Found: % Calcd: % C	H	N
I	CH_3	H	62	——	253—255 (0.002)	1.5582	67.1 (2.9)	598	$C_{28}H_{32}O_6$	72.20 72.39	7.10 6.94	— —
II	CH_3	Ac	88	——	247—249 (0.003)	1.5466	56.8 (1.7)	552	$C_{30}H_{34}O_7$	70.73 71.13	6.81 6.76	— —
III	CH_3	Pnb	>50	133—134 (PE; needles)	——	——	6.1 (2.1)	——	$C_{36}H_{35}NO_9$	68.13 68.50	5.65 5.75	2.22 2.28
IV	CH_3	Az	20	109.5—111 (NH; needles)	——	——	−32.0 (4.5)	——	$C_{41}H_{41}N_2O_7$	72.88 73.20	6.07 5.99	3.88 4.16
V	CH_3	CH_3	78	——	226—229 (0.002)	1.5482	60.4 (1.4)	533	$C_{29}H_{34}O_6$	72.42 72.78	7.16 7.16	— —
VI	Pnb	Pnb	35	247—148.5 (IPA; needles)	——	——	96.0 (1.1)	——	$C_{41}H_{36}N_2O_{12}$	65.61 65.79	4.82 4.85	3.70 3.74



Ac=acetyl PE=petroleum ether
Az=*p*-phenylazobenzoyl NH=*n*-hexane
Pnb=*p*-nitrobenzoyl IPA=isopropyl alcohol

p-nitrobenzoyl-α-D-glucopyranose (VI) was obtained as fine crystals.

Experimental

Tlc was carried out by the use of Silica Gel G (Merck). The silica gel used for the column chromatography was the product of the Kanto Chemical Co. The PMR spectra were measured with Varian S-60T in $CDCl_3$, with TMS as the internal standard. The melting points were determined by means of a Yanagimoto micro-melting-point apparatus; uncorrected values are given. The specific rotation was measured in a 1-dm tube by means of an Atago Polux apparatus in $CHCl_3$ at 25±3°C.

Methyl 2,4,6-Tri-O-benzyl-α-D-glucopyranoside (I). A suspension of methyl α-D-glucopyranoside (5.0 g; 26 mmol) and sodium hydride (*ca.* 50% dispersion; 2.7 g; 2.2 molar equiv.) in freshly-distilled benzyl chloride (26 g; 8 molar equiv.) was cautiously heated at 104—105°C (the oil bath was maintained below 110°C) with very efficient stirring (magnetic) under anhydrous condition. When, after 1.5—2.5 hr, a sharp rising of the reaction temperature and a violent evolution of hydrogen gas began, the oil bath was removed at once and the reaction vessel was immersed in a cold-water bath. After the evolution of the gas had ceased, the vessel was carefully heated at 104—105°C for 2 hr. During the reaction, the mixture became a porous mass, and then it turned into a thin slurry. After cooling to room temperature, another portion of sodium hydride (1.5 g; 1.1 molar equiv.) was added to the mixture; the reaction was then continued at the same temperature overnight. The cooled mixture was filtered through a bed of Hyflo Super-Cel. The filtrate and the washings were combined and evaporated on a boiling-water bath under reduced pressure. A yellow sirup (17 g) was chromatographed on a column of SiO_2 (350 g), eluting it with a mixed solvent of benzene and 2-butanone (20: 1). The order of elution was as follows: a mixture of the dispersion oil, the remaining benzyl chloride and other non-carbohydrate by-products, the tetrasubstituted product, and the main product, I (7.4 g; 62%). I was used directly for the further reactions.

When the original benzylation reaction was continued with additional benzyl chloride (5 g) and sodium hydride (2 g) at 125°C, the perbenzylated glucoside[2] was formed quantitatively.

Methy 2,4,6-Tri-O-benzyl-3-O-methyl-α-D-glucopyranoside (V). I (2.0 g) was heated with methyl iodide (1.1 ml) in DMF (3.3 ml) in the presence of BaO (1.5 g) at 70—80°C for 3 hr.[7] A brief chromatography gave thin, colorless oil of V.

Methyl 4,6-O-Benzylidene-3-O-methyl-α-D-glucopyranoside. V was hydrogenated quantitatively by the use of palladium on carbon (5%) in methanol and then treated with benzaldehyde in the presence of $ZnCl_2$. Tlc showed the complete exhaustion of the hydrogenated material. Long needles (from diisopropyl ether; 84%). Mp 152—153°C, $[\alpha]_D^{24}$ 118.4° (*c* 2.5, $CHCl_2CHCl_2$). [Lit,[3] mp 150—151°C; $[\alpha]_D^{14}$ 119.5° (*c* 1.6, $C_2H_2Cl_4$)]. The PMR spectrum showed the benzylidene tertiary proton as a singlet at δ 5.56. (Found: C, 61.23; H, 6.91%.)

1,2,4,6-Tetra-O-benzoyl-3-O-methyl-β-D-glucopyranose. The above-mentioned hydrogenolyzed product was hydrolyzed with hot dilute hydrochloric acid and then subjected to neutralization, evaporation, and ordinary benzoylation. Colorless crystals (from methanol; 85%). Mp 203—204°C, $[\alpha]_D^{25}$ 2.5° (*c* 3.9, $CHCl_3$). The authentic sample had a mp of 200—202°C and $[\alpha]_D^{27}$ value of −2.3° (*c* 4.2, $CHCl_3$). [Lit,[4] mp 198—199°C; $[\alpha]_D$ 3.6° (*c* 4.94, $CHCl_3$)]. The mixed mp was 200.5—203.5°C. The IR (KBr) and PMR spectra of the two compound were superimposable. (Found: C, 68.25; H, 4.94%).

2,4,6-Tri-O-benzyl-1,3-di-O-p-nitrobenzoyl-α-D-glucopyranose (VI). I (1.03 g) was heated with aqueous mixed acid prepared from glacial acetic acid (11 ml) and sulfuric acid (2N, 2.9 ml) for 80 min on a boiling-water bath. After the addition of sulfuric acid (2N, 2.3 ml), the mixture was further heated for 9 hr. After neutralization, an oily product (1.27 g) was fractionated on a column of SiO_2 (20 g; benzene: 2-butanone=5: 1). After the recovery of the unchanged mate-

7) R. Kuhn, H. H. Baer, and A. Seeliger, *Ann. Chem.*, **611**, 236 (1958).

rial (0.44 g; 43%), a hydrolyzed product was eluted in a yield of 0.37 g (37%). This was treated with excess *p*-nitrobenzoyl chloride in pyridine. The crude residue thus obtained (95%) was crystallized with diethyl ether.

Spectral Data: I, ν_{max}^{film} (cm^{-1}): 3490, 3460 (OH), 3090, 3070, 3030, 3010, 1955, 1875, 1810, 1720, 1603, 1584, 1145, 739, 699 (benzyl); δ (ppm): 2.40 (1H, broad, exchangeable with D_2O; 3-OH), 3.37 (3H, singlet; *O*-CH_3), 3.43 (1H, quartet; H-2, $J_{1,2}=4.0$ Hz, $J_{2,3}=8.0$ Hz), 4.13 (1H, quartet; H-3, $J_{3,4}=10.0$ Hz). II, ν_{max}^{film} (cm^{-1}): 1746, 1233 (*O*-acetyl); δ (ppm): 1.99 (3H, singlet; *O*-acetyl), 3.43 (3H, singlet; *O*-CH_3), 3.54 (1H, quartet; H-2, $J_{2,3}=10.0$ Hz), 4.77 (1H, doublet; anomeric, $J_{1,2}=3.8$ Hz), 5.63 (1H, quartet; H-3, $J_{3,4}=8.0$ Hz). III, ν_{max}^{KBr} (cm^{-1}): 1729, 1523, 1349 (*p*-nitrobenzoyl). IV, ν_{max}^{KBr} (cm^{-1}): 1714, 1277 (ester). V, δ (ppm): 3.43 (3H, singlet; *O*-CH_3), 3.72 (3H, singlet; *O*-CH_3). VI, ν_{max}^{KBr} (cm^{-1}): 1731, 1529, 1347 (*p*-nitrobenzoyl). δ (ppm): 6.75 (1H, doublet; anomeric, $J_{1,2}=3.4$ Hz).