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Note

Preparation of the 3,4-di-*O*-benzyl and 3,4-di-*O*-(4-phenylbenzyl) derivatives of benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside

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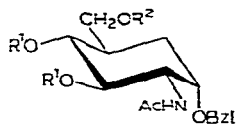
The synthesis of 2-acetamido-2-deoxy-6-*O*-(*N*-acetyl-D-neuraminyl)-D-glucose[1] required the preparation of the aglycons benzyl 2-acetamido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**4**) and benzyl 2-acetamido-2-deoxy-3,4-di-*O*-(4-phenylbenzyl)-α-D-glucopyranoside (**5**).



1 $R^1 = R^2 = H$
2 $R^1 = H$, $R^2 = Tr$
3 $R^1 = Bzl$, $R^2 = Tr$
4 $R^1 = Bzl$, $R^2 = H$
5 $R^1 = 4\text{-PhBzl}$, $R^2 = H$
6 $R^1 = 4\text{-PhBzl}$, $R^2 = Ac$
4-PhBzl = 4-phenylbenzyl

Compound **4** has been prepared[2] in a 35–40% overall yield from benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside (**1**) by benzylation of the 6-trityl ether **2** with benzyl bromide, barium oxide, and barium hydroxide octahydrate in *N*,*N*-dimethylformamide, followed by detritylation. We improved this yield to 74% by modification of the benzylation procedure.

It has been reported[3] that *O*-benzylation of allyl 2-acetamido-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside with benzyl chloride and sodium hydride in boiling benzene was accompanied by the formation of considerable amounts of allyl 3,4,6-tri-*O*-benzyl-2-(*N*-benzylacetamido)-2-deoxy-β-D-glucopyranoside. However, the formation of *N*-benzylated product could be circumvented[4] by treatment of *N*-benzoylated amino-sugar derivatives with the same reagents in boiling tetrahydrofuran. It was concluded[3] that the combination benzyl chloride–sodium hydride is suitable for *O*-benzylation of *N*-benzoyl derivatives of amino sugars, but unfavourable for their *N*-acetyl analogues.

On treatment with sodium hydride and benzyl bromide in boiling tetrahydro-

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furan, benzyl 2-acetamido-2-deoxy-6-*O*-trityl-α-D-glucopyranoside (**2**) reacted completely within 2–3 h (t.l.c.), and gave almost exclusive formation of a less polar compound. This compound was 2-acetamido-3,4-di-*O*-benzyl-2-deoxy-6-*O*-trityl-α-D-glucopyranoside (**3**), since only **4** was obtained after work-up and detritylation. It was shown by t.l.c. that **3** was slowly converted into a faster-moving compound after prolonged exposure to the benzylation conditions. The structure of **4** was confirmed by i.r. and ^{1}H-n.m.r. spectroscopy as well as by comparing its physical constants with those reported in the literature[2]. The ^{1}H-n.m.r. spectrum contained resonance signals for the NH proton and the aromatic protons in the expected intensity ratio.

Similarly, **5** was prepared from **1** in 51% yield by using 4-phenylbenzyl bromide in the alkylation step. Compound **5** could be converted into the 6-*O*-acetyl derivative **6**, the ^{1}H-n.m.r. spectrum of which showed the anticipated three-proton singlet for one *O*-acetyl group.

Thus, derivatives of 2-acetamido-2-deoxy-α-D-glucopyranose can be *O*-benzylated with benzyl bromide or 4-phenylbenzyl bromide and sodium hydride in tetrahydrofuran without extensive formation of *N*-benzylated side-products, provided that the reaction time is controlled.

EXPERIMENTAL

General methods. — Melting points were determined with a Meopta melting-point microscope and are uncorrected. Evaporations were conducted *in vacuo* at <40° (bath). Elemental analyses were carried out at the Institute for Organic Chemistry TNO, Utrecht, The Netherlands. Specific rotations were measured with a Perkin–Elmer 241 polarimeter, using a 10-cm micro-cell. I.r. spectra (KBr discs) were recorded with a Perkin–Elmer Model 457 spectrophotometer. ^{1}H-N.m.r. spectra were recorded with a Varian EM-390 (90 MHz) spectrometer for solutions in chloroform-*d* (tetramethylsilane as internal standard). T.l.c. was performed on silica gel (Merck DC-Plastikrolle Kieselgel 60 F254) and detection was effected by u.v. light, or by spraying with 20% conc. sulphuric acid in methanol, followed by charring at 130° for 5–10 min. The following solvents (v/v) were used: *A*, chloroform–methanol (85:15); *B*, chloroform–methanol (25:1). Short-column chromatography under medium pressure[5] was performed on silica gel (Merck Kieselgel 60, 230–400 mesh). Conventional column chromatography was performed on Merck Kieselgel 60, 70–230 mesh. In all cases, the eluate was monitored by charring with 20% conc. sulphuric acid in methanol on t.l.c. plates.

*Benzyl 2-acetamido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside* (**4**). — A solution of benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside[6] (**1**; 3.00 g, 9.6 mmol) and chlorotriphenylmethane (3.20 g, 11.5 mmol) in dry pyridine (24 ml) was kept at 100° until t.l.c. (solvent *A*) showed that the reaction was complete (3–4 h). The cooled solution was poured into ice-cold, 5% aqueous sodium dihydrogenphosphate. After extraction with chloroform (three times), the combined organic layers were washed

with water, dried (sodium sulphate), and evaporated. After evaporation of toluene to remove traces of pyridine, the syrupy residue was chromatographed on silica gel (165 g). Triphenylmethanol was eluted first with chloroform. The product was then eluted with chloroform–methanol (4:1), and the eluate was evaporated to dryness. A solution of the residue, benzyl bromide (14.00 g, 81.9 mmol), and sodium hydride (1.70 g) in dry tetrahydrofuran (44 ml) was boiled under reflux for 2–3 h until t.l.c. (solvent *B*) indicated the presence of one main component and traces of a slower-moving compound. Methanol (10 ml) was added slowly to the cooled mixture to destroy the excess of sodium hydride, and the inorganic salts were filtered off and washed with chloroform. The combined filtrate and washings were evaporated and a solution of the residue in chloroform was washed with water (three times), dried (sodium sulphate), and evaporated. The syrupy residue was chromatographed on silica gel (190 g) with toluene (1 litre) and with chloroform (500 ml); finally, the product was eluted with chloroform–methanol (25:1). After evaporation, a solution of the resulting residue in 3:7 chloroform–methanol (100 ml) was stirred at 35° and 2M hydrochloric acid (20 ml) was added dropwise. After stirring overnight at room temperature, the mixture was evaporated. A solution of the residue in chloroform was washed with 10% aqueous sodium carbonate (twice) and water (twice), dried (sodium sulphate), and concentrated. The residue was crystallized from chloroform, to give **4** (3.48 g, 74%), m.p. 203–204°, $[\alpha]_D^{20}$ +119° (*c* 0.7, chloroform); lit.[2] m.p. 204–205°, $[\alpha]_D^{20}$ +121° (chloroform); ν_{max}^{KBr} 3300 (NH), 1650 (Amide I), and 1550 cm^{-1} (Amide II); ^{1}H-n.m.r. data (90 MHz): δ 1.78 (s, 3 H, NAc), 2.13 (s, 1 H, OH), 5.35 (d, 1 H, $J_{2,NH}$ 9.6 Hz, NH), and 7.35 (s, 15 H, 3 Ph).

4-Phenylbenzyl bromide. — Phosphorus tribromide (21.39 g, 79.0 mmol) was added under nitrogen, within 10 min, to a stirred solution of 4-phenylbenzyl alcohol (25.00 g, 135.7 mmol) in 1,2-dimethoxyethane (450 ml) at 5°. Stirring was continued for 3 h at room temperature under nitrogen, and the mixture was then diluted with chloroform (400 ml) and poured into ice–water. The organic layer was separated and the aqueous layer was extracted with chloroform (three times). The combined organic layers were washed with saturated, aqueous sodium hydrogencarbonate, dried (magnesium sulphate), and concentrated. The residual solid was recrystallized from methanol and dried over P_2O_5 *in vacuo*. Yield 24.56 g (99.4 mmol, 73%); m.p. 82–83°; lit.[7] m.p. 84–85°.

Benzyl 2-acetamido-2-deoxy-3,4-di-O-(*4-phenylbenzyl*)-α-D-*glucopyranoside* (**5**). — Compound **1** (3.00 g, 9.6 mmol) was tritylated as described for the preparation of **4**. A mixture of the residue obtained after column chromatography, 4-phenylbenzyl bromide (9.50 g, 38.4 mmol), and sodium hydride (1.60 g) in dry tetrahydrofuran (40 ml) was stirred for 1.5 h at 60–65° until t.l.c. (solvent *B*) indicated the presence of one main component and one faster-moving, minor component. Methanol (10 ml) was slowly added to the cooled mixture to destroy the excess of sodium hydride. After the addition of water, the layers were separated and the aqueous layer was extracted with chloroform. The combined organic layers were evaporated, and a solution of the residue in chloroform was washed with water (three times), dried

(sodium sulphate), and evaporated. A solution of the syrupy residue in chloroform (100 ml) was stirred at room temperature and 0.05M methanolic hydrochloric acid (50 ml) was added. After stirring for 1.5 h at room temperature, the mixture was cooled to 0° and solid sodium carbonate (300 mg) was added. After evaporation, a solution of the residue in chloroform (250 ml) was washed with water (three times), dried (sodium sulphate), and evaporated. The solid residue was recrystallized from chloroform, to give **5** (3.14 g, 51%), m.p. 212–213°, $[\alpha]_D^{25}$ +38° (*c* 0.5, chloroform); ν_{max}^{KBr} 3580, 3480, 3420 (shoulders, OH), 3310 (NH), 1650 (Amide I), 1550 (Amide II), 823, 759, 732, and 698 cm^{-1} (Ph): ^{1}H-n.m.r. data [90 MHz, $(CD_3)_2SO$]: δ 1.90 (s, 3 H, NAc), 7.20–7.80 (m, 23 H, aromatic protons), and 8.14 (d, 1 H, $J_{2,NH}$ 9.0 Hz, NH).

Anal. Calc. for $C_{41}H_{41}NO_6$: C, 76.49; H, 6.42; N, 2.18; O, 14.91. Found: C, 76.40; H, 6.39; N, 2.10; O, 15.11.

*Benzyl 2-acetamido-6-*O*-acetyl-2-deoxy-3,4-di-*O*-(4-phenylbenzyl)-α-*D*-glucopyranoside* (**6**). — A solution of **5** (398 mg, 0.62 mmol) in 1:1 acetic anhydride–pyridine (11 ml) was kept overnight at room temperature, and then evaporated. Ethanol and then toluene were evaporated several times from the residue. After final purification by short-column chromatography (column: 4 × 4.5 cm) with 100:1 chloroform–methanol (100 ml) and 96:4 chloroform–methanol, the syrupy product crystallized from ethyl acetate, to give **6** (331 mg, 78%), m.p. 196–197°, $[\alpha]_D^{25}$ +45°, (*c* 0.8, chloroform); ν_{max}^{KBr} 3310 (NH), 1740 (OAc), 1650 (Amide I), 1548 (Amide II), 824, 760, 732, and 698 cm^{-1} (Ph); ^{1}H-n.m.r. data (90 MHz): δ 1.82 (s, 3 H, NAc), 2.03 (s, 3 H, OAc), 5.45 (d, 1 H, $J_{2,NH}$ 9.6 Hz, NH), and 7.20–7.70 (m, 23 H, aromatic protons).

Anal. Calc. for $C_{43}H_{43}NO_7$: C, 75.31; H, 6.32; N, 2.04; O, 16.33. Found: C, 75.28; H, 6.52; N, 1.95; O, 16.24.

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