Carbohydrate Research, 45 (1975) 299–301

Note

Preparation of benzyl 2,3,4-tri-*O*-(chloroacetyl)-β-D-glucopyranosiduronic acid*

NIRMOLENDU ROY AND CORNELIS P. J. GLAUDEMANS

Department of Macromolecules, Indian Association for the Cultivation of Science, Jadavpur, Calcutta 32 (India), and the National Institutes of Health, Bethesda, Maryland 20014 (U. S. A.)

(Received February 12th, 1975; accepted for publication, March 18th, 1975)

The synthesis of glycosides usually involves the condensation of a protected glycose derivative with an appropriate aglycon derivative. Following this, the protecting groups are removed from the glycosyl moiety by treatment with an acid (*e.g.*, isopropylidene groups) or a base (acyl groups), or by catalytic hydrogenolysis (benzyl ethers). The synthesis of 1-*O*-acylglycoses in which the acyl group bears an alkenic bond has long been hampered by the lack of suitably protected glycose intermediates. Earlier work by Bertolini and Glaudemans[1] provided a solution to the problem by the use of the chloroacetyl group, a group that can be removed, at neutral pH, by thiourea in methanol at room temperature, thus avoiding the alkalinity or acidity, or reductive conditions, which would remove 1-*O*-acyl groups or reduce alkenic linkages. One of us has already reported the preparation of 2,3,4,6-tetra-*O*-(chloroacetyl)-D-glucopyranose[1], a compound that is a possible intermediate in the preparation of 1-*O*-acyl-D-glucoses in which the acyl group bears an alkenic bond. We now report the preparation of benzyl 2,3,4-tri-*O*-(chloroacetyl)-β-D-glucopyranosiduronic acid (**2**), a fairly stable intermediate for the preparation of 1-*O*-acyl-D-glucopyranuronic acid derivatives where in the 1-*O*-acyl group is unsaturated. (It has already been shown that benzyl ether groups may be reductively removed without affecting the chloroacetyl group[1].)

Benzyl β-D-glucopyranoside[2] was tritylated at O-6 and the resulting ether was chloroacetylated to yield benzyl 2,3,4-tri-*O*-(chloroacetyl)-6-*O*-trityl-β-D-glucopyranoside (**1**). Detritylation yielded a mixture of (mainly two) compounds from which a crystalline compound having the composition $C_{19}H_{21}Cl_3O_9$ was isolated; this may be benzyl 2,3,6-tri-*O*-(chloroacetyl)-β-D-glucopyranoside, arising from O-4 → O-6 acyl migration. Consequently, a further portion of **1** was detritylated, and the reaction mixture was *immediately* treated with potassium permanganate in acetic acid, so that oxidation of the hydroxymethyl group to a carboxyl group would occur without delay. From the resulting mixture, crystalline benzyl 2,3,4-tri-*O*-(chloro-

*Dedicated to the memory of Dr. Hewitt G. Fletcher, Jr.

acetyl)-β-D-glucopyranosiduronic acid (**2**) was isolated. When treated with diazomethane, this acid afforded a crystalline methyl ester (**3**).

EXPERIMENTAL

Benzyl 2,3,4-tri-O-(chloroacetyl)-6-O-trityl-β-D-glucopyranoside (**1**). — D-Glucose (75 g) was treated with acetic anhydride, bromine, and red phosphorus in the presence of perchloric acid[3] to give tetra-*O*-acetyl-α-D-glucopyranosyl bromide (130 g, 75%), m.p. 88–89°, $[\alpha]_D$ +196° (chloroform) (lit. m.p. 88–89°, $[\alpha]_D$ +198°). The bromide was allowed to react with benzyl alcohol in dichloromethane in the presence of silver carbonate, iodine, and Drierite, to give benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, which was crystallized from ethanol (70 g, 66%), m.p. 99–100°, $[\alpha]_D$ −48° (*c* 2.5, chloroform) (lit.[4] m.p. 96–97°; $[\alpha]_D$ −53.2°).

This tetraacetate (17.6 g) was deacetylated with 0.05M sodium methoxide in methanol (50 ml) for 2 h, and the solution was de-ionized with Amberlite IR-120 cation-exchange resin, and evaporated to a crystalline mass from which pyridine was distilled several times in order to remove all traces of methanol. The residue was dissolved in pyridine (100 ml), chlorotriphenylmethane (17.5 g) was added, the solution was kept for 5 days at room temperature and then evaporated *in vacuo*, and the residue was purified by column chromatography to yield 17 g (81%) of benzyl 6-*O*-trityl-β-D-glucopyranoside, $[\alpha]_D$ −50° (*c* 1.7, chloroform), as an amorphous powder.

A solution of this tritylated D-glucoside (10 g) in dichloromethane (80 ml) was cooled in an ice–salt bath, and pyridine (7 ml) was added. Chloroacetyl chloride (7 ml, 1.5 equiv.) in dichloromethane (40 ml) was slowly added to the vigorously stirred mixture during 45 min; examination by t.l.c. then showed complete acylation. The excess of chloroacetyl chloride was decomposed by adding cold water (60 ml), more dichloromethane (50 ml) was added, and the organic layer was separated, washed thrice with ice–water, dried (anhydrous sodium sulfate), filtered through a bed of charcoal, and evaporated under diminished pressure to a syrup. Ethanol (30 ml) was added, and the resulting crystals were collected, and recrystallized from ethanol–chloroform, to yield **1**; 12 g (83%), m.p. 163–164°, $[\alpha]_D$ +9.5° (*c* 1.69, dichloromethane), $[\alpha]_D$ +5° (chloroform).

Anal. Calc. for $C_{38}H_{35}Cl_3O_9$: C, 61.56; H, 4.75; Cl, 14.33. Found: C, 61.33; H, 4.70; Cl, 14.95.

Benzyl 2,3,4-tri-O-(chloroacetyl)-β-D-glucopyranosiduronic acid (**2**). — Compound **1** (7 g) was stirred with acetic acid (40 ml) for ~20 min, but most of the solid remained undissolved. Hydrogen bromide (780 mg, 1 equiv.) in acetic acid (10 ml) was added dropwise to the vigorously stirred suspension. The original crystals were gradually replaced by precipitated trityl bromide, which was removed by filtration. To the filtrate was quickly added potassium permanganate (3 g), and the mixture was stirred for 4 days at room temperature*. Sodium oxalate was added to decompose

*In one experiment, compound **1** was detritylated as described, but, after removal of the trityl bromide, the filtrate was poured into ice–water. The mixture was extracted with chloroform, and the

the excess of permanganate, water (4 vol.) was added, the mixture was extracted with chloroform, and the extract was washed with water, dried (sodium sulfate), and evaporated to a syrup which was chromatographed on a column of silica gel with benzene as eluant (to remove the triphenylmethane). The eluant was then changed to (*a*) 4:1 (v/v) benzene–ether and (*b*) 40:10:1 benzene–ether–acetic acid to yield the acidic material. The product crystallized partly from benzene. This compound (500 mg) was unstable and could not be freed entirely from trace impurities; m.p. 131–134°, $[\alpha]_D$ −25.5° (*c* 1, dichloromethane). Chemical-ionization mass-spectroscopy showed an (M+1) peak of 513 corresponding to acid **2** (three chlorine isotopes).

Anal. Calc. for $C_{19}H_{19}Cl_3O_{10}$: C, 44.42; H, 3.72; Cl, 20.70. Found: C, 44.18; H, 3.53; Cl, 19.99.

*Methyl [benzyl 2,3,4-tri-*O*-(chloroacetyl)-β-*D*-glucopyranosid]uronate* (**3**). — The methyl ester of **2** was prepared by the addition of diazomethane. The product was purified on a chromatography column of silica gel, to yield crystals of **3**, m.p. 123–125°, $[\alpha]_D$ −21° (*c* 0.4, dichloromethane). The n.m.r. spectra of **2** and **3** had the expected peaks; that of **2** had signals for three chloroacetyl groups and one phenyl group, and that of **3** had a distinct signal for the methyl ester at 220 Hz, apart from the signals for the chloroacetyl and phenyl groups.

Anal. Calc. for $C_{20}H_{21}Cl_3O_{10}$: C, 45.51; H, 4.01; Cl, 20.15. Found: C, 45.36; H, 3.74; Cl, 19.76.

ACKNOWLEDGMENTS

We are grateful to the Section on Microanalytical Services and Instrumentation of the National Institutes of Health for microanalyses and mass spectra. Our thanks are also due Dr. U. R. Ghatak of the Indian Association for the Cultivation of Science for recording one n.m.r. spectrum. One of us (N. R.) expresses his appreciation to Drs. S. K. Dutta, D. K. Roy, and A. Sengupta of the Department of Pharmacy, Jadavpur University, for providing facilities in the Department.

REFERENCES

1 M. Bertolini and C. P. J. Glaudemans, *Carbohydr. Res.*, 15 (1970) 263–270.
2 K. H. Slotta and H. Heller, *Ber.*, 63 (1930) 1024–1028.
3 M. Bárczai-Martos and F. Kőrösy, *Nature (London)*, 165 (1950) 369–370.
4 B. Lindberg, *Acta Chem. Scand.*, 3 (1949) 151–156.

extract was successively washed with water, saturated sodium hydrogen carbonate, and water, dried (sodium sulfate), and evaporated under diminished pressure. The residue was separated on a column of silica gel with 1:3 hexane–ether, to yield two compounds. The faster material (prisms) preponderated and had m.p. 137–138°.

Anal. Calc. for $C_{19}H_{21}Cl_3O_9$: C, 45.66; H, 4.24; Cl, 21.28. Found: C, 45.85; H, 4.33; Cl, 21.03.

The slower material (needles) could not be purified (m.p. 115–132°). The faster material, when treated with chromium trioxide in 1.5M sulfuric acid, gave mostly a product that was indistinguishable from the starting material by t.l.c. The product also showed the same rate of movement in t.l.c. in the presence of pyridine, suggesting that it was not an acid, and, hence, that the starting material was benzyl 2,3,6-tri-*O*-(chloroacetyl)-β-D-glucopyranoside.