BENZOYL DERIVATIVES OF D-GLUCONOLACTONES AND THEIR REACTION WITH ALCOHOLS*

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ABSTRACT

Benzoylation of D-glucono-1,4-lactone and D-glucono-1,5-lactone afforded the corresponding tetra-O-benzoyl derivatives. They showed the optical rotation and i.r. spectral absorption characteristic for 1,4 or 1,5-lactones, respectively. Opening of the lactone ring was effected by treatment with alcohols to give tetra-O-benzoyl-D-gluconates having an unesterified hydroxyl group at C-4 or C-5, respectively.

RESULTS AND DISCUSSION

Benzoylation of D-glucono-1,4-lactone and D-glucono-1,5-lactone afforded the corresponding tetra-O-benzoyl derivatives, which showed the optical rotation and i.r. spectral absorption¹ characteristic for 1,4 or 1,5-lactones, respectively.

The fact that the 2,3,4,6-tetra-O-benzoyl-D-glucono-1,5-lactone (1) could be obtained by direct benzoylation of the 1,5-lactone is of interest, since almost all known derivatives of 1,5-lactones have been obtained by oxidation of the corresponding aldose derivatives^{2,3}. Upson and Bartz⁴ reported that the acetylation of D-glucono-1,5-lactone in the presence of zinc chloride gave a tetra-O-acetyl-D-gluconic acid monohydrate.



On benzoylation of D-glucono-1,4-lactone, the 2,3,5,6-tetra-O-benzoyl-Dglucono-1,4-lactone (2) was obtained. When the crude product was dissolved in

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methanol, opening of the lactone ring took place, and after a few days crystalline methyl 2,3,5,6-tetra-O-benzoyl-D-gluconate (5) was obtained. Treatment of the benzoylated lactone with ethanol afforded the crystalline ethyl ester (6). The opening of the lactone ring was probably catalyzed by traces of acid that still remained in the crude product. Ethyl 2,3,5,6-tetra-O-benzoyl-D-gluconate (6) was also obtained by heating at boiling pure 2 in ethanol containing a catalytic amount of hydrogen chloride until dissolution. However, the reaction was slow and was completed only after ten days. As reported for the unsubstituted lactones⁵, opening of the 1,5-lactone ring was faster than that of the 1,4-lactone. Alcoholysis of 1 was completed in a few hours, and it could be easily followed by t.l.c. on silica gel, as the ester having one hydroxyl group free has a much lower R_F value than the benzoylated lactone.

The n.m.r. spectra of substances 3-6 were measured in chloroform-d. They all showed the presence of four O-benzoyl groups ($\tau 2.1$, 2.6). The methyl ester protons appeared at $\tau 6.38$ for compound 3 and at $\tau 6.4$ for 5. The ethoxy carbonyl group of both ethyl esters (4 and 6) was observed as a triplet of intensity 3 at $\tau 8.88$, and as a quartet of intensity 2 at $\tau 5.9$.

As Horton and Wander⁶ reported for other acyclic derivatives of sugars, H-3 is the lowest-field signal for all four compounds. This signal appeared as a triplet at τ 3.7, J 3.2 Hz for substances 3 and 4, whereas it was superposed with the H-5 signal, at a higher field, for compounds 5 and 6, because of the stronger deshielding effect of the adjacent benzoate group at C-4 of 3 and 4 compared with the hydroxyl group of substances 5 and 6. The H-2 signal showed as a sharp doublet at τ 4.38, $J_{2,3}$ 3.2 Hz. In the spectra of 3 and 4 the H-2 doublet overlapped the H-4 signal. At higher field, all derivatives showed a 3-proton multiplet due to the superposed signals of H-6, H-6', and the proton at the carbon atom attached to the unesterified hydroxyl group (H-5 for 3 and 4, and H-4 for 5 and 6). All four compounds showed a broad signal centered at τ 7.1, due to the hydroxyl proton, which disappeared on deuteration.

The partially benzoylated esters having a free hydroxyl group at C-4 or C-5 could be used as intermediates for the preparation of sugar derivatives having a particular substituent at C-4 or C-5.

EXPERIMENTAL

General. — Melting points were determined with a Thomas-Hoover apparatus (Arthur Thomas Co., Philadelphia, Pennsylvania) and are uncorrected. Specific rotations were measured with a 1-dm tube. Infrared spectra were recorded with a Perkin-Elmer Infracord spectrophotometer. N.m.r. spectra were determined in deuteriochloroform with tetramethylsilane as the external reference, by using a Varian A-60 spectrometer. T.l.c. was performed on Silica Gel G (E. Merck, Darmstadt, Germany) using 1:9 ethyl acetate-benzene as the mobile phase; the materials were detected with iodine vapor or by spraying with 5% ethanolic sulfuric acid, followed by heating for 10 min at $110-120^{\circ}$.

2,3,4,6-Tetra-O-benzoyl-D-glucono-1,5-lactone (1). — To a suspension of D-glucono-1,5-lactone (1.0 g) in anhydrous pyridine (5 ml), cooled to 0°, was added

with stirring benzoyl chloride (4.5 ml). After being shaken for 90 min at room temperature, the mixture was poured with stirring into ice-water. The gum that separated was washed several times with water by decantation until it solidified; yield 4.2 g (84%). The dry product was washed with cold ether to remove benzoic acid, and was recrystallized from benzene to give needles, m.p. 178-179°, $[\alpha]_D^{19}$ +112.9 (6 min) \rightarrow +90.0 (4 h) \rightarrow +19.3° (after 51 h, c 0.8, 90% acetone). This mutarotation is comparable to that of 2,3,4,6-tetra-O-methyl-D-glucono-1,5-lactone for which Haworth and coworkers⁷ reported $[\alpha]_D^{18}$ +101 \rightarrow +29.6° (after 8 h,water). I.r. data: ν_{max}^{Nujol} 1755 (1,5-lactone) and 1720 cm⁻¹ (benzoate carbonyl), no hydroxyl peak.

Anal. Calc. for C₃₄H₂₆O₁₀: C, 68.68; H, 4.41. Found: C, 69.00; H, 4.70.

2,3,5,6-Tetra-O-benzoyl-D-glucono-1,4-lactone (2). — D-Glucono-1,4-lactone was prepared by heating at reflux D-glucono-1,5-lactone in acetic acid according to Isbell and Frush⁸. The lactone was recrystallized from p-dioxane; m.p. 134–135°, $[\alpha]_D^{20}$ +65.2 (12 min) \rightarrow +62.3° (after 24 h, c 1, water), in agreement with the reported values. This compound (1 g) was added with stirring to a mixture of benzoyl chloride (5 ml) and pyridine (5 ml) cooled to 0°. After being shaken for 2 h at room temperature, the reaction mixture was poured into ice-water. The oil formed was washed several times with ice-water, and then dried in a vacuum desiccator; yield 4.16 g (83.7%). The product was soluble in ether and benzene. The chromatographically pure compound, R_F 0.69, had $[\alpha]_D^{20} + 44.5°$ (c 0.6, 90% acetone); the rotation did not change after three days. I.r. data: v_{max}^{Nujot} 1790 (1,4-lactone) and 1720 cm⁻¹ (benzoate carbonyl), no hydroxyl peak.

Anal. Calc. for C₃₄H₂₆O₁₀: C, 68.68; H, 4.41. Found: C, 68.87; H, 4.40.

Methyl 2,3,4,6-tetra-O-benzoyl-D-gluconate (3). — Compound 1 (630 mg) was dissolved by shaking with 50 ml of methanol containing two drops of ether saturated with hydrogen chloride. After 3 h, only one spot, R_F 0.44, was detected. The solution was poured into cold dilute sodium hydrogen carbonate, and an amorphous solid precipitated, yield 620 mg (93%). The product could not be crystallized, and it was purified by precipitation with water from a methanolic solution. The chromatographically pure compound, R_F 0.44, had $[\alpha]_D^{23} + 20.2^\circ$ (c 1, chloroform); i.r. data: ν_{max}^{KBr} 3450 (OH), 1720 (benzoate carbonyl), and 1750 cm⁻¹ (Et ester carbonyl); n.m.r. data: τ 2.1, 2.6 (20-proton multiplets, 4 Bz), 3.7 (1-proton triplet, J 3.2 Hz, H-3), 3.85–4.45 (2 proton multiplet, H-2,4), 5.18–5.82 (3-proton multiplet, H-5,6,6'), 6.38 (3-proton singlet, OMe), and 7.08 (1-proton broad signal, disappears on deuteration, OH).

Anal. Calc. for C₃₅H₃₀O₁₁: C, 67.08; H, 4.79. Found: C, 66.80; H, 4.62.

Ethyl 2,3,4,6-tetra-O-benzoyl-D-gluconate (4). — After a solution of compound 1 (200 mg) in abs. ethanol (20 ml) had been heated for 2 h at reflux, t.l.c. showed one main spot (R_F 0.33) and a faint spot corresponding to the starting material that disappeared after 24 h at room temperature. The syrup, obtained on evaporation of the ethanol under reduced pressure, was soluble in cold ethanol, ether, and benzene, and could not be induced to crystallize. Chromatographically pure 4 was obtained

as an amorphous solid by precipitation with water from the ethanolic solution; it showed $[\alpha]_D^{20} + 14.8^\circ$ (c 0.8, chloroform); i.r. data: ν_{max}^{Film} 3400 (OH), 1720 (benzoate carbonyl), and 1750 cm⁻¹ (Et ester carbonyl); n.m.r. data: τ 2.1, 2.6 (20-proton multiplets, 4 Bz), 3.7 (1-proton triplet, J 3.2 Hz, H-3), 3.85-4.5 (2-proton multiplet, H-2,4), 5.2-5.8 (3-proton multiplet H-5,6,6'), 5.9 (2-proton quartet, J 7 Hz, CH₂ of EtO carbonyl), 7.2 (1-proton broad signal that disappeared on deuteration. OH), and 8.88 (3-proton triplet, Me).

Anal. Calc. for C₃₆H₃₂O₁₁: C, 67.49; H, 5.03. Found: C, 67.10; H, 4.94.

Methyl 2,3,5,6-tetra-O-benzoyl-D-gluconate (5). — Crude compound 2, obtained from 1 g of D-glucono-1,4-lactone, was dried in a desiccator, and then dissolved in boiling methanol. Crystals appeared in the solution after approximately one week at room temperature. They were filtered off, and on being kept, more product was obtained from the mother liquors. Total yield 2.33 g (53%) in five crops. Pure 5 was obtained by recrystallization from benzene, m.p. 182–183°, $[\alpha]_D^{20} + 35.5^\circ$ (c 1, chloroform); i.r. data: v_{max}^{Nujol} 3450 (OH), 1720 (benzoate carbonyl), and 1750 cm⁻¹ (Me ester carbonyl); n.m.r. data: $\tau 2.1$, 2.6 (20-proton multiplets, 4 Bz), 4.05 (2-proton multiplet, H-3,5), 4.38 (1-proton doublet, $J_{2,3}$ 3.2 Hz, H-2), 4.85–5.7 (3-proton multiplets, H-4,6,6'), 6.4 (3-proton singlet, OMe), and 7.1 (1-proton broad signal that disappeared on deuteration, OH).

Anal. Calc. for C₃₅H₃₀O₁₁: C, 67.08; H, 4.79. Found: C, 67.14; H, 4.95.

Ethyl 2,3,5,6-tetra-O-benzoyl-D-gluconate (6). — Compound 2 (100 mg) was dissolved by boiling in ethanol (10 ml) containing one drop of ether saturated with hydrogen chloride at 0°. The reaction was followed by t.l.c.; after 10 days at room temperature, the spot of R_F 0.69, corresponding to the lactone, had completely disappeared, and a spot of R_F 0.37 was detected. After pouring the solution into an equal volume of dilute sodium hydrogen carbonate, a crystalline product was obtained; yield 60 mg (58%), m.p. 170–172°. Recrystallization from 2:3 ethanol-acetone gave pure 6, m.p. 175°, $[\alpha]_D^{23} + 30.7°$ (c 0.8, chloroform); i.r. data: v_{max}^{KBr} 3450 (OH), 1720 (benzcate carbonyl), and 1750 cm⁻¹ (Et ester carbonyl); n.m.r. data: $\tau 2.1$, 2.6 (20-proton multiplets 4 Bz), 4.05 (2-proton multiplet, H-3,5), 4.4 (1-proton doublet, $J_{2,3}$ 3.2 Hz, H-2), 4.85–5.65 (3-proton multiplet, H-4,6,6'), 5.92 (2-proton quartet, J 7.1 Hz, CH₂ of EtO carbonyl), 8.88 (3-proton triplet, Me), and 7.1 (1-proton broad signal that disappeared on deuteration, OH).

Anal. Calc. for C₃₆H₃₂O₁₁: C, 67.49; H, 5.03. Found: C, 67.92; H, 5.03.

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