Note

2,3,5-Tri-*O*-benzoyl-1-*O*-(*p*-nitrobenzoyl)-β-D-ribofuranose, a convenient reagent for the preparation of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride and bromide

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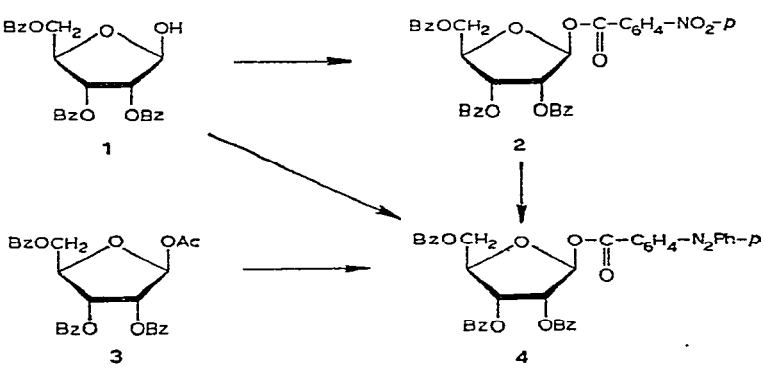
In contrast to the analogous arabinofuranosyl halides[1,2], neither 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride nor the corresponding bromide has as yet been obtained in crystalline form. This fact constitutes a minor handicap in the preparation of these compounds, as they are normally made through the action of hydrogen chloride or bromide on 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[3] (**3**). The removal of acetic acid and excess of hydrogen halide is at best awkward and time-consuming, and must be done with care, inasmuch as the 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl halides are relatively reactive substances. A similar difficulty in the preparation of polydeoxyglycosyl halides was ingeniously overcome by Zorbach and Payne[4] through the use of 1-*O*-(*p*-nitrobenzoyl)-aldose derivatives. When these react with hydrogen bromide or hydrogen chloride in dichloromethane solution, the *p*-nitrobenzoic acid that is released precipitates in almost quantitative yield owing to its low solubility in dichloromethane. After removal of the *p*-nitrobenzoic acid, the glycosyl halide (whether amorphous or crystalline) may be obtained from the solution rapidly and with a minimum of manipulation. This technique has proved especially



useful for the preparation of benzylated glycosyl halides[5–7], and it has been shown that 1-*O*-(*p*-phenylazobenzoyl)-aldoses may be used in the same way[8,9].

In view of these discoveries, the potential value of 2,3,5-tri-*O*-benzoyl-1-*O*-(*p*-nitrobenzoyl)-D-ribofuranose as an intermediate is readily seen, and the preparation of the β anomeric form of this ester (**2**) was undertaken independently in our two laboratories. In one laboratory, pure 2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[10] (**1**) was *p*-nitrobenzoylated to afford the desired ester (**2**) in 93% yield; in the other, a method was developed for the preparation of **2** directly from D-ribose without full purification of intermediates, and the overall yield was 31%. Both procedures are described in the Experimental section.

Although **2** is a readily preparable and highly crystalline compound, and there was no doubt that 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl halides could be prepared from it, we were interested in comparing the convenience of this reagent with that of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[11] (**3**). As usually prepared, 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide is a mixture of anomers[3], and doubtless the same is true of the corresponding chloride; in order to assay these amorphous halides, it seemed most realistic to use them in a condensation reaction. For such a purpose, it is desirable to use a reaction involving steric control, to produce a single product from anomeric halides. Well before neighboring-group participation in displacements was recognized, Tipson[13] drew attention to the fact that, regardless of anomeric configuration, acetylated aldosyl halides react with the silver salts of carboxylic acids to give aldose esters in which the acyloxy group at C-1 is *trans* to the acetoxyl group on C-2. As far as we are aware, no exception to this generalization has ever been observed; indeed, the original statement can reasonably be broadened to include all acylated aldosyl halides, provided that the acyloxy group on C-2 can exert steric control over the displacement. For the purpose under consideration, we chose the silver salt of *p*-phenylazobenzoic acid, inasmuch as previous experience had shown that *p*-phenylazobenzoylated sugars are readily isolable by chromatography and are usually highly crystalline compounds[8,9,14–16]. Authentic 2,3,5-tri-*O*-benzoyl-1-*O*-(*p*-phenylazobenzoyl)-β-D-ribofuranose (**4**) was synthesized through the *p*-phenylazobenzoylation of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**1**); the compound proved to be readily crystallizable, and its n.m.r. spectrum included a low-field singlet that clearly indicated that it had the β-D anomeric configuration[17]. The mother liquor from the preparation was subjected to repeated chromatography, to give an amorphous material that was isomeric with, but more dextrorotatory than, **4**. It is probable that this compound is the α anomer of **4**, but, unfortunately, the quantity available was too small to permit us to record its n.m.r. spectrum.

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**3**) was converted into 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in the conventional way, and the amorphous bromide resulting was condensed with silver *p*-phenylazobenzoate. In two separate experiments, **4** was isolated in 67 and 73% yield. Similarly, **2** was treated in dichloromethane solution with hydrogen bromide, the *p*-nitrobenzoic acid was removed, and syrupy 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide was obtained by evaporation;

condensation with silver *p*-phenylazobenzoate gave **4** in 83% yield. The experiment was repeated, except that hydrogen chloride was used. Although the precipitation of *p*-nitrobenzoic acid was obviously slower, the yield of **4**, after condensation of the 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride with silver *p*-phenylazobenzoate, was unchanged (83%). From these experiments, it appears that **2**, indeed, offers marked advantages over **3** as an intermediate in the preparation of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride and bromide, both as a matter of experimental convenience and in terms of yield.

EXPERIMENTAL

General methods. — Melting points are equivalent to corrected values. Qualitative t.l.c. was performed on Silica Gel GF (250 μm, Analtech, Inc., Wilmington, Delaware) with the solvent systems specified. N.m.r. spectra were recorded, for solutions in $CDCl_3$, at 60 MHz, with tetramethylsilane as the internal standard.

2,3,5-Tri-O-benzoyl-1-O-(p-nitrobenzoyl)-β-D-ribofuranose (**2**). — (*a*) *From 2,3,5-tri-O-benzoyl-D-ribofuranose* (**1**). Compound **1** (1.00 g)[10] was added to a cooled solution of *p*-nitrobenzoyl chloride (0.5 g) in dry pyridine (4.5 ml). After 2 min, pyridinium chloride crystallized, and the mixture was then allowed to warm to room temperature. After 3 min at room temperature, it was treated with water (0.3 ml) and, 20 min later, 20 ml of water was added. The product crystallized spontaneously; water (200 ml) was added, and the crystals were removed by filtration. After being dried in the air, they were dissolved in dichloromethane; the solvent was removed *in vacuo*, and the residue was dissolved in hot absolute ethanol. Crystallization was rapid: yield, 1.23 g (93%), m.p. 136–138.5°. Recrystallized from acetone–pentane, pure **1** was obtained as heavy needles: m.p. 137.5–139.5°, $[\alpha]_D^{20}$ +7.3° (*c* 1.4, chloroform). The n.m.r. spectrum of the compound included a sharp singlet at τ 3.33 (H-1).

Anal. Calc. for $C_{33}H_{25}NO_{11}$: C, 64.81; H, 4.12; N, 2.29. Found: C, 64.53; H, 4.07; N, 2.18.

(*b*) *From D-ribose.* A 1% solution of hydrogen chloride in methanol was prepared by passing 158 g of hydrogen chloride into 20 liters of anhydrous methanol in a 50-liter flask. D-Ribose (1 kg, 6.66 moles) was added, and the mixture was stirred until dissolution was complete. The progress of the reaction was monitored through tests with Benedict solution and, when the mixture no longer gave a positive test for reducing sugar (~45 min at room temperature), further reaction was halted through the addition of 1 liter of pyridine. The solution was evaporated *in vacuo* at 30–35° to a stiff syrup (2.8 kg), which was dissolved in a mixture of 5 liters of pyridine and 5 liters of dichloromethane. The solution was cooled to 0–5° and stirred while benzoyl chloride (3.0 liters, 25.8 moles) was added at such a rate that the temperature of the mixture did not exceed 25° (~1.5 h). After the addition was complete, the temperature of the mixture was allowed to rise to 40°, and was kept at 40° for 2 h. The mixture was then cooled to room temperature, and washed successively with cold water (two 5-liter portions), 1.5 M sulfuric acid, saturated aqueous sodium hydrogen carbonate

solution (~10 liters), and water, dried (sodium sulfate; 0.5 kg), treated with Norit, and evaporated *in vacuo* at 35–40° (bath temp.) to a heavy syrup (5.6 kg).

This crude methyl 2,3,5-tri-*O*-benzoyl-D-ribofuranoside was dissolved in 6 liters of dichloromethane and the solution was cooled to 20°. A solution of hydrogen bromide (2 kg) in 6 liters of glacial acetic acid was prepared in a 22-liter flask, and cooled to 15–20°, and the solution of methyl 2,3,5-tri-*O*-benzoyl-D-ribofuranoside was added to it. The mixture was maintained at 20° until its optical rotation was constant (~25 min), and was then washed successively with cold water (two 5-liter portions), saturated sodium hydrogen carbonate (until slightly basic), and cold water (two 5-liter portions); it was then poured into a vigorously stirred suspension of 1 kg of silver carbonate in a mixture of 15 liters of acetone and 333 ml of water. Stirring was continued for 45 min; the solids were then removed by filtration through a layer of Norit, and the filtrate was evaporated *in vacuo* at 45° (bath temp.) to a heavy syrup (3.64 kg).

The syrup was dissolved in 20 liters of pyridine, and the solution was cooled to −5°; cold water (12.5 liters) was then added slowly. Crystallization was allowed to proceed while the mixture was cooled in an ice–salt bath. Compound **1** was removed by filtration, washed with 4:3 (v/v) cold pyridine–water and dried at room temperature. It was then dissolved in 7 liters of dichloromethane, and the residual moisture was removed from the solution with anhydrous sodium sulfate.

Pyridine (2 liters) was added, and the solution was cooled to 0° and stirred while a solution of *p*-nitrobenzoyl chloride (1.4 kg, 7.54 moles) in a mixture of dichloromethane (5 liters) and pyridine (2 liters) was added at such a rate that the temperature of the mixture did not exceed 10°. After the addition was complete, the mixture was held at 45° for 1 h, and then cooled to room temperature. It was successively washed with two 5-liter portions of water, 1.5 M sulfuric acid (until the pyridine had been removed), saturated aqueous sodium hydrogen carbonate solution, and water, dried (sodium sulfate), treated with Norit, and evaporated to a syrup that was dissolved in dichloromethane (2.5 liters). Upon addition of hot methanol (8 liters), compound **2** crystallized; a second crop was obtained from the mother liquor: yield 1.25 kg (31%, based on D-ribose), m.p. 136–137°.

p-*Phenylazobenzoylation of 2,3,5-tri-*O*-benzoyl-β-*D*-ribofuranose* (**1**). — A solution of **1** (1.00 g) in dry pyridine (10 ml) was treated with *p*-phenylazobenzoyl chloride (0.65 g, 1.23 moles/mole of **1**), the mixture was warmed to 65°, and the progress of the reaction was monitored by t.l.c. in 11:1 benzene–ether. After 1 h, more of the chloride (0.65 g) was added, and, after 4.5 h, a third portion (0.65 g) of the chloride was added. Heating at 65° was continued for a total of 16 h after the final addition of *p*-phenylazobenzoyl chloride; t.l.c. then failed to reveal the presence of **1**. Three drops of water were added to the cooled mixture, and, 20 min later, the mixture was diluted with 800 ml of water. A syrup settled out, and the slightly turbid, aqueous layer was decanted and discarded. The syrup was dissolved in dichloromethane, and the solution was dried (anhydrous magnesium sulfate), and concentrated to a small volume. Solvents were successively added to, and distilled from, the residue in order to remove

pyridine, as follows: 20 ml of toluene (twice), absolute ethanol, and ether. Before evaporation of the ether solution, it was filtered through a layer (0.5 cm) of Silica Gel 7745 (E. Merck, Darmstadt). The residue (1.14 g) was dissolved in a few milliliters of dichloromethane, and the solution was simultaneously boiled and diluted with absolute ethanol (~10 ml). Upon seeding, **4** crystallized: wt 0.72 g (50%), m.p. 151–153°. On t.l.c. in 11:1 benzene–ether, the product was indistinguishable from **4** prepared by the condensation of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride with silver *p*-phenylazobenzoate as described later in this Note.

The mother liquor was concentrated to a syrup that gave a turbid solution with dichloromethane; this was filtered to remove the insoluble material (14 mg), and the filtrate was concentrated to a syrup (0.33 g). Preparative t.l.c. on two plates (20 × 20 × 0.2 cm) of Silica Gel GF (Brinkmann) with 99:1 dichloromethane–methanol separated the major component that migrated at a rate slightly lower than that of **4**. This component was extracted from the silica gel with ether, and further purified by t.l.c. with 50:1 dichloromethane–ethyl acetate and then with 99:1 dichloromethane–methanol. The lower portion of the band obtained in the last chromatography was rechromatographed with 45:2 benzene–ethyl acetate, to give a yellow, amorphous product having $[\alpha]_D^{20}$ +142° and $[\alpha]_{578}^{20}$ +149° (both at *c* 1.7, chloroform).

Anal. Calc. for $C_{39}H_{30}N_2O_9$: C, 69.84; H, 4.51; N, 4.18. Found: C, 69.78; H, 4.78; N, 4.31.

Silver p-*phenylazobenzoate.* — *p*-Phenylazobenzoic acid (15.00 g) was dissolved in 2 liters of hot water containing a slight excess of ammonia, and to this solution was added a solution of 11.4 g of silver nitrate in 400 ml of water. The mixture was kept overnight at ~80° in an open beaker, with stirring; the silver *p*-phenylazobenzoate was then removed by filtration, washed successively with water (1 liter) and methanol (~300 ml), and dried overnight at 120°: wt. 18.26 g (83%).

Anal. Calc. for $C_{13}H_9AgN_2O_2$: C, 46.87; H, 2.72; Ag, 32.39. Found: C, 47.03; H, 2.99; Ag, 32.28.

*2,3,5-Tri-*O*-benzoyl-1-*O*-(p-phenylazobenzoyl)-β-*D*-ribofuranose* (**4**). — (*a*) *From 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-*D*-ribofuranose* (**3**) via *2,3,5-tri-*O*-benzoyl-*D*-ribofuranosyl bromide.* A mixture of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (Calbiochem, Los Angeles, Calif. 90054; 10.00 g, 19.8 mmoles) and 25 ml of glacial acetic acid was treated with 25 ml of a 30–32% solution of hydrogen bromide in glacial acetic acid. After 20 min, dichloromethane (300 ml) was added, and the solution was rapidly washed successively with 1 liter of ice-water and cold, aqueous sodium hydrogen carbonate solution, dried (magnesium sulfate), and evaporated *in vacuo* to a syrup that became a froth when held at 0.3 mm: yield 9.47 g.

A portion (1.70 g) of the 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide thus prepared was dissolved in benzene, and the solution was stirred with silver *p*-phenylazobenzoate (2.06 g). T.l.c. with 11:1 benzene–ether showed the reaction to be essentially complete after 50 min; after 2.25 h, the solids were removed by filtration on a 0.5-cm layer of silica gel, and washed successively with benzene and dichloromethane. The filtrate and washings were combined, and evaporated *in vacuo* to a stiff syrup

(1.94 g). On dissolving in dichloromethane, adding absolute alcohol, and boiling (to remove part of the dichloromethane), the material crystallized spontaneously: wt 1.60 g (67%), m.p. 152–153°. Recrystallization from absolute ethanol entailed very little loss, and failed to change the m.p.; fine needles, $[\alpha]_D^{20}$ −37.9° (*c* 3.6, chloroform). The n.m.r. spectrum of the compound included a sharp singlet at τ 3.37 (H-1).

Anal. Calc. for $C_{31}H_{30}N_2O_9$: C, 69.84; H, 4.51; N, 4.18. Found: C, 69.89; H, 4.54; N, 4.01.

In another experiment, starting with 1.53 g of **3** (3.03 mmoles), the yield of **4** was 73%.

(*b*) *From 2,3,5-tri-*O*-benzoyl-1-*O*-(*p*-nitrobenzoyl)-β-*D*-ribofuranose* (**2**) via *2,3,5-tri-*O*-benzoyl-*D*-ribofuranosyl bromide.* A stream of hydrogen bromide was passed for 2 min into a solution of 1.85 g (3.03 mmoles) of **2** in 10 ml of dichloromethane (dried over Drierite); crystallization of *p*-nitrobenzoic acid began after 1 min. After the reaction mixture had been kept for 5 h at room temperature, the *p*-nitrobenzoic acid was removed by filtration: wt. 0.493 g (97%). The filtrate was evaporated under diminished pressure, and a solution of the residual syrup in 15 ml of benzene was treated with 2.0 g of silver *p*-phenylazobenzoate. The suspension was stirred for 4 h at room temperature, and the silver salts were then removed by filtration on a layer of Filter-Cel, and washed thoroughly with dichloromethane. The filtrate and washings were combined, and evaporated, and the residue was dissolved in dichloromethane. Upon adding absolute alcohol to the boiling solution, crystallization occurred: wt. 1.69 g (83%), m.p. 151–152°.

(*c*) *From 2,3,5-tri-*O*-benzoyl-1-*O*-(*p*-nitrobenzoyl)-β-*D*-ribofuranose* (**2**) via *2,3,5-tri-*O*-benzoyl-*D*-ribofuranosyl chloride.* A stream of hydrogen chloride was passed into a solution of **2** (1.85 g, 3.03 mmoles) in dichloromethane (10 ml) for 2 min. After 10 min, *p*-nitrobenzoic acid began to crystallize and, after 22 h, this was removed by filtration: wt. 0.4788 g (95%). The filtrate was evaporated to a syrup that was treated with silver *p*-phenylazobenzoate as described in (*b*), to give **4**: wt. 1.683 g (83%), m.p. 151–152°.

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