Note

Reinvestigation of the synthesis of β -D-ribofuranosyl β -D-ribofuranoside from 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose using boron trifluoride etherate

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Homogeneous nonreducing disaccharides, sugars whose anomeric carbon atoms are bonded together through an oxygen bridge, are commonly prepared by some variation of the Koenigs-Knorr reaction¹. To accomplish this first requires the preparation of a glycosyl halide from a peracylated monosaccharide, which is then hydrolyzed to the free OH-1 derivative. The latter is then condensed with the freshly prepared glycosyl halide in the presence of an acid acceptor, usually the salt of a heavy metal such as silver carbonate. Recently, the need arose in this laboratory for a shorter, more direct route to homogeneous, nonreducing disaccharides that would be practical to use with small quantities of material. A literature search uncovered a very short communication in which the original intent was to prepare a phenyl derivative at C-1 of D-ribose². When 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose (1) was treated with boron trifluoride etherate $[(C_2H_3)_2O \cdot BF_3]$ in benzene, β -D-ribofuranosyl β -D-ribofuranoside hexabenzoate (3) was obtained instead of D-ribosylbenzene. Unfortunately, this report contains no details about reaction conditions, stoichiometry, purification, yields, etc.; only analytical data were given for 3 and the deblocked disaccharide 4. Originally, 3 was prepared by the Koenigs-Knorr reaction in a 53% yield, which was followed by Zemplén methanolysis to afford noncrystalline β -D-ribofuranosyl β -D-ribofuranoside³ (4). A detailed reinvestigation of the direct self-condensation of a peracyl monosaccharide as promoted by boron trifluoride etherate appeared in order. 1-O-Acetyl-2.3,5-tri-O-benzoyl- β -D-ribofuranose (1) was chosen as the substrate for several reasons: (a) it was easily available either commercially or by synthesis from D-ribose⁴, (b) β -D-ribofuranosyl β -D-ribofuranoside hexabenzoate (3) appeared to be easily crystallizable^{2,3}, and (c) chromatography condition information was available³ for the purification of 3 if such a step was necessary.

Treatment of solutions of 1 in dichloromethane with boron trifluoride etherate afforded mixtures of as many as seven to nine products, as revealed by t.l.c. However, if a significant amount of 3 was present, it would fractionally crystallize as a single crop from solutions of ethanol even without seeding. T.l.c. of the mother liquors showed that, in most cases, there was very little **3** left. In those cases where yields of **3** were very low, the other main crystallizable substance was the substrate **1**, which could be recovered after concentration of the mother liquors. No serious attempts have been made as yet to isolate and identify the other components because of their number and because they migrate so very close to each other on chromatography. The various preparations of **3** afforded white crystals from ethanol with melting points between 141 and 145°, usually having a 2° melting range. The better-formed crystals had m.p. 143–145°. Only yields of **3** having melting points of 141° and above are reported in Table I. Crystals melting lower than this were recrystallized because t.l.c. invariably showed them to contain traces of at least two other components, whereas crystals melting > 141° were homogeneous. All crops of crystals were monitored for identity against the others by at least one other test, such as mixed m.p., specific rotation, t.l.c., and i.r. spectroscopy.

TABLE I

$(C_2H_5)_2O\cdot BF_3$ (mmol)	Molecular sieves (Type, g ^b)	Time (h)	Yield (%)	
3 ^c	None	25	30	
2	3A (1)	24	39	
3	3A (1)	24	47	
4	3A (1)	24	49	
3	3A (1)	6	40	
3	3A (1)	72	47	
3°	3A (1)	24	48	
5 ^d	3A (1)	48	53	
6 ^e	3A (1)	48	51	
31	3A (1)	24	51	
3	4Λ (Ì)	24	42	
3	5A (1)	24	31	
3	3A (3)	24	35	
3	$3A^{g}(1)$	24	30	

Yields of 2,3,5-tri-O-benzoyl- β -D-ribofuranosyl 2,3,5-tri-O-benzoyl- β -D-ribofuranoside (3) from 1-O-ace-tyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose (1)^{*a*}

^{*a*} One mmol of **1** was used and the solvent was dichloromethane (10 mL). ^{*b*} In parentheses. ^{*c*} One mmol was added every 4 h. ^{*d*} Three mmol were added within 24 h, and then 2 mmol within another 24 h. ^{*c*} The addition of $(C_2H_5)_2O$ -BF₃ and molecular sieves 3A was repeated after 24 h. ^{*f*} The starting material was 1,2,3,5-tetra-*O*-benzoyl- β -D-ribofuranose (**2**). ^{*d*} Water (0.15 mL) was added and the mixture was stirred for 1 h prior to addition of $(C_2H_5)_2O$ -BF₃.

Table I shows some of the results obtained when 1 was treated with boron trifluoride etherate in dichloromethane. The yield of 3 was generally $\sim 15\%$ if at least three equivalents of the Lewis acid were used, but could be doubled to 30% if the acid was added periodically in equal increments. In experiments originally intended to protect the reaction mixture from moisture, molecular sieves 3A were employed.

Reaction of 1 with 3–4 equivs. of boron trifluoride etherate increased the yield to $\sim 50\%$. When the amount of boron trifluoride etherate was reduced, the yield of 3 was also reduced. The reaction appears to be complete in less than 24 h, as there was no change in the yield by allowing it to proceed longer. Addition of the Lewis acid in smaller increments or in great excess by further additions did not significantly increase the yield. Moreover, utilization of the 1-O-benzoyl derivative 2 as the substrate in place of the 1-O-acetyl derivative 1 did not affect the yield. The best molecular sieve was Type 3A, and it was further demonstrated that the action was a catalytic type of promotion in two ways. When Drierite was substituted for the molecular sieves, the yield fell < 30%, showing that the results were not dependent upon a drying action. Furthermore, when molecular sieves were recovered from one reaction and immediately placed into another reaction mixture, the yield of this second experiment was not significantly lower than in the first one. When the proportion of molecular sieves 3A was increased, the yield fell significantly, possibly because some of the boron trifluoride was trapped in the microstructure of the sieves and was unavailable for reaction.

The mechanism of this self-condensation is somewhat obscured by the requirement for 3–4 equivs. of boron trifluoride etherate, a ratio of one gram of molecular sieves 3A for every 3–4 mmol of Lewis acid, and because of the large number of unidentified products. One early suggestion was that an OH-1 group would be generated by a small amount of water trapped in the sieves, which would then lead to coupling with the OAc-1 group of another molecule to split off acetic acid. However, experiments with "moist" molecular sieves and with Drierite afforded yields about equal to those obtained by performing the reaction in the absence of either. The best yields ($\sim 50\%$) were always obtained in the presence of dry molecular sieves 3A in the aforementioned proportion to boron trifluoride etherate.

The yields from this self-condensation are competitive with those of the Koenigs– Knorr procedure³ with regard to the actual coupling. Probably, it is somewhat superior because, in the latter, 1 had first to be converted into a glycosyl halide, and then into the OH-1-free derivative prior to coupling with the glycosyl halide.



The preparation of the free disaccharide 4 was easily achieved by stirring 3 with dilute methanolic sodium methoxide at room temperature. Acetylation of 4 afforded the crystalline hexaacetate 5.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler hot-stage and correspond to corrected values. Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter. I.r. spectra were recorded with a Perkin–Elmer Model 21 spectrophotometer. T.l.c. was performed on plates of Silica Gel GF-254, Type 60 (E. Merck, Darmstadt) of 0.25-mm thickness, and developed with 1,2-dichloroethane. Usually 5–10 developments were necessary for best separation. Spots were located with a Minerlight lamp (254 nm). Moist organic solutions were dried over anhydrous MgSO₄. Evaporations were performed under reduced pressure with a rotary evaporator and a bath temperature of 30° . The elemental analysis was obtained at the Spang Microanalytical Laboratory, Eagle Harbor, Michigan.

Materials. — Boron trifluoride etherate was purchased from Aldrich Chemical Company and was distilled one time. Molecular sieves were purchased from Fisher Scientific (Davson). Drierite is the product of W. A. Hammond Drierite Company. Reagent grade dichloromethane and 1,2-dichloroethane were percolated through columns of molecular sieves 3A prior to use. 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose (1) and 1,2,3,5-tetra-*O*-benzoyl- β -D-ribofuranose (2) were prepared by literature methods^{4,5}.

2,3,5-Tri-O-benzoyl- β -D-ribofuranosyl 2,3,5-tri-O-benzoyl- β -D-ribofuranoside (3). — To a solution of 1 (505 mg, 1 mmol) in dichloromethane (7 mL) was added molecular sieves 3A (1 g), followed by a solution of boron trifluoride etherate (426 mg, 3 mmol) in dichloromethane (3 mL). The mixture was magnetically stirred for 24 h, diluted with 1,2-dichloroethane (30 mL), filtered through glass wool into a separatory funnel, and washed with saturated NaHCO₃ (2 × 40 mL) and water (50 mL). The solution was dried, filtered, and evaporated to a light-yellow gum (535 mg), which was dissolved in hot ethanol (7–8 mL). Crystallization started immediately and was usually complete after 4–5 h at room temperature. The crystals of **3** were isolated by filtration, washed with ethanol, and dried (214 mg, 47%); m.p. 143–145°, soft. >130°, $[a]_{D}^{25} + 34.1°$ (c 0.449, chloroform); lit.² m.p. 143–144°, $[a]_{D} + 35.2°$ (c 0.475, chloroform); lit.³ m.p. 142–145°, $[a]_{D}^{25} + 32.5°$ (c 0.1, chloroform).

β-D-Ribofuranosyl β-D-ribofuranoside (4). — To a magnetically stirred mixture of 3 (454 mg, 0.5 mmol) in absolute methanol (10 mL) was added M methanolic sodium methoxide (1 mL), and the mixture was stirred at room temperature. Dissolution was complete after about 2 h. Stirring was continued for a total of 18 h, and the clear, colorless solution was carefully treated with Amberlite CG-120 (H⁺, 100–200 mesh) in small increments until a pH of 6.0–6.5. The resin was removed by filtration and washed three times with methanol. The methanol was evaporated and methyl benzoate was removed by coevaporation with water (four times). The residue was dried by three coevaporations with absolute ethanol, which left a white solid (140 mg, 99%). Crystallization from ethanol (3 mL) at room temperature gave microcrystals which were washed with cold ethanol (86 mg). A second crop (18 mg) was obtained by evaporation followed by crystallization from ethanol (total yield 74%), m.p. 154–155°, $[a]_{\rm D}^{22} - 100^{\circ}$ (c 0.487, water); lit.² m.p. 158–160°, $[a]_{\rm D} - 102^{\circ}$ (c 0.47, water).

2,3,5-Tri-O-acetyl- β -D-ribofuranosyl 2,3,5-tri-O-acetyl β -D-ribofuranoside (5). – Disaccharide 4 (84 mg) was suspended in dry pyridine (2 mL) and acetic anhydride (0.6 mL) was added. The mixture was stirred for 18 h at room temperature and then treated with saturated NaHCO₃ (20 mL). After being stirred for 30 min, the mixture was extracted with chloroform (3 × 20 mL), and the extracts were combined, washed with water (50 mL), and dried. After filtration and evaporation, coevaporation at 40° with toluene removed some residual pyridine to give a gum (189 mg) which crystallized overnight. Recrystallization from ethanol (2 mL) gave 5 (102 mg); additional crops were obtained from the mother liquor (total 155 mg, 97%). The analytical sample was recrystallized from ethanol, to afford long needles (110 mg, 69%), m.p. 107° , $[a]_{\rm p}^{26}$ – 49.5° (c 0.536, chloroform).

Anal. Calc. for C₂₂H₃₀O₁₅: C, 49.44; H, 5.66. Found: C, 49.51; H, 5.88.

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