Note

2-Deoxy sugars
Part XVI. Improved preparation of methyl 2-deoxy-α-D-*arabino*-hexofuranoside*

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Methyl 2-deoxy-α-D-*arabino*-hexofuranoside[1] (**2**) is the starting compound for the preparation of 5,6-*O*-carbonyl-2-deoxy-3-*O*-*p*-nitrobenzoyl-α-D-*arabino*-hexosyl bromide[1], which has utility in the preparation of pyrimidine nucleosides that contain 2-deoxy-β-D-*arabino*-hexofuranose as the carbohydrate residue[1b,c]. The furanoside may be readily prepared in *ca.* 30% yield by the direct methyl glycosidation of 2-deoxy-D-*arabino*-hexose, but its separation from the glycosidation mixture requires column chromatography on powdered cellulose, in which only about 1 g of the mixture can be handled at one time. The method is not suitable, therefore, for large-scale preparations of the furanoside (**2**).

In order to find a way to facilitate the isolation of **2**, we restudied a procedure described by Overend *et al.*[2]. These workers converted 2-deoxy-D-*arabino*-hexose into its dibenzyl dithioacetal (**1**), and demercaptalated the latter in dry methanol[3] to afford (it was claimed) solely "methyl 2-deoxyglucofuranoside" (methyl 2-deoxy-D-*arabino*-hexofuranoside). We repeated their experiment, and our results showed, with the aid of paper-chromatographic analysis, that the product was a mixture, consisting of approximately 50% of methyl 2-deoxy-α-D-*arabino*-hexofuranoside (**2**), the remainder being isomeric pyranoside(s). A similar demercaptalation of the diethyl dithioacetal[4] **1a** gave comparable results.

Nevertheless, the yield of **2** from **1** or **1a** was a marked improvement over that obtained by the direct methyl glycosidation[1] of 2-deoxy-D-*arabino*-hexose, and, because of the greater proportion of **2** formed in the demercaptalation procedure, it was possible to recover about half of the compound by direct crystallization from a solution of the reaction mixture. Technically, in terms of time and effort, this procedure is a more efficient means for large-scale preparations of **2**, *if* total recovery is not a desideratum. The remainder of **2** may be recovered, however, by *p*-nitrobenzoylating the syrupy residue to give the tris-*p*-nitrobenzoate (**2a**), which separates in almost quantitative yield from an acetone solution of the reaction mixture.

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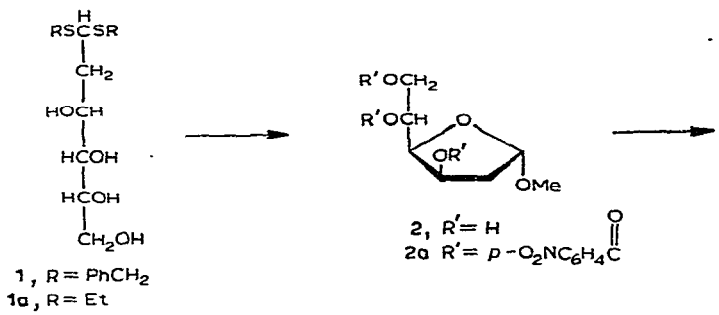
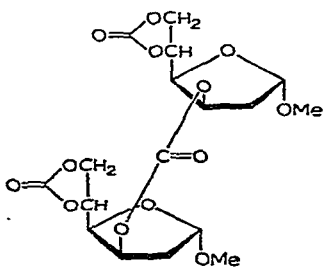
If total recovery of **2** is the objective, it is more efficient to *p*-nitrobenzoylate the demercaptalation product, without prior separation by crystallization; an almost quantitative recovery (corresponding to the proportion of **2** estimated by chromatography) of **2a** is obtained. Deacylation of **2a** to afford crystalline **2** is a simple procedure[1b] to execute; therefore, the conversion consisting of 2-deoxy-D-*arabino*-hexose→dialkyl dithioacetal (**1** or **1a**) →tris-*p*-nitrobenzoate (**2a**)→methyl 2-deoxy-α-D-*arabino*-hexofuranoside (**2**) is a practical method for large-scale preparations of **2**.

By the latter method, we were able to secure an adequate supply of **2**, making possible a scaled-up preparation of methyl 5,6-*O*-carbonyl-2-deoxy-α-D-*arabino*-hexofuranoside, an intermediate in the synthesis of the previously reported furanosyl halide[1] employed in nucleoside syntheses. As more product was formed on this occasion during the carbonylation of **2**, another water-insoluble product was isolated which, from its elemental composition and i.r. spectrum, has been tentatively identified as 3,3′-*O*-carbonylbis(methyl 5,6-*O*-carbonyl-2-deoxy-α-D-*arabino*-hexofuranoside) (**3**).



1, R = $PhCH_2$
1a, R = Et



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EXPERIMENTAL

Demercaptalation of the dithioacetals (**1** *or* **1a**). — To 54 mmoles of either **1** or **1a** in 200 ml of dry methanol were added 8 g of Drierite, 30 g of mercuric chloride, and 16 g of yellow mercuric oxide. The mixture was stirred for 3 h at room temperature, and filtered through a pad of Celite, and to the filtrate was added 25 ml of pyridine. The mixture was kept in a refrigerator overnight, the pyridine–mercuric chloride complex was filtered off, and the filtrate was stirred for 7 min with a small

amount of Rexyn 300 (H^+, OH^-) ion-exchange resin*. The mixture was filtered through a pad of decolorizing carbon, the filtrate was evaporated to dryness under diminished pressure, and the resulting clear syrup crystallized on storage in a vacuum desiccator (phosphorus pentaoxide). Paper chromatography of the syrupy product with water-saturated 9:1 butyl alcohol–toluene disclosed about 50% of methyl 2-deoxy-α-D-*arabino*-hexofuranoside (**2**) (R_F 0.43); the remainder consisted of the isomeric α-D-pyranoside (R_F 0.35), slightly contaminated with what was most probably its anomer.

Methyl 2-deoxy-α-D-arabino-hexofuranoside (**2**). — (*a*) Via *its tris-p-nitrobenzoate* (**2a**). To 8.3 g (47 mmoles) of the syrupy product (obtained from the preceding experiment) in 190 ml of dry pyridine at 0° was added 40 g (220 mmoles) of *p*-nitrobenzoyl chloride. The mixture was stirred for 1 h at 0° and for 1 h at room temperature, and was then kept in a refrigerator for 3 days. After being warmed to room temperature, the mixture was slowly added, with efficient stirring, to 300 ml of saturated, aqueous sodium hydrogen carbonate. Ice-cold water (1.5 l) was added, the mixture was stirred for 1 h, and the resulting precipitate was filtered off, washed with water, and dried in a vacuum desiccator (phosphorus pentaoxide). Three recrystallizations from acetone gave 14.5 g of the *p*-nitrobenzoylated furanoside **2a** (m.p. 142–144° and also 168–169°), corresponding to 4.1 g (*ca.* 50%) of the unsubstituted furanoside (**2**) present in the original syrup. Deacylation of **2a** was readily accomplished[1b], affording **2** in almost quantitative yield.

(*b*) *By direct crystallization.* The syrupy mixture of methyl glycosides (8 g) (obtained from the demercaptalation of **1a**) was dissolved in 80 ml of tetrahydrofuran, and ether was added to incipient turbidity, followed by the addition of one drop of tetrahydrofuran. The solution was nucleated, and the inside of the flask was vigorously scratched to prevent the separation of syrupy material. The solution was kept overnight at room temperature, and the crystals that formed were filtered off and recrystallized from tetrahydrofuran–ether to which a few drops of pentane were added; yield of **2**, 1.9 g (23% based on **1a**), m.p. 76–80°. The syrup that remained after separation of crystalline **2** was *p*-nitrobenzoylated as described in the preceding experiment. The resulting tris-*p*-nitrobenzoate (**2a**) was recrystallized three times from acetone, to afford 6.2 g of pure product, corresponding to 1.8 g (21%) of the unsubstituted furanoside (**2**). The total yield of **2** was, therefore, 44%.

3,3'-O-Carbonylbis(methyl 5,6-O-carbonyl-2-deoxy-α-D-arabino-hexofuranoside) (**3**). — A solution of 976 mg (5.5 mmoles) of **2** in 11 ml of dry pyridine and 8 ml of dry carbon tetrachloride was cooled to −10°, and to this solution was slowly added dropwise, with stirring, 4.2 ml of a 15% (w/w) solution of carbonyl chloride in dry toluene. The mixture was stirred for 1 h at −10° and for 1 h at room temperature, and was then poured, with stirring, into a mixture of 4 g of freshly prepared barium carbonate with 150 ml of crushed ice. After the ice had melted, the mixture was filtered through a bed of Celite. (The filtrate contained the desired methyl 5,6-*O*-

*Fisher Scientific Co.

carbonyl-2-deoxy-α-D-*arabino*-hexofuranoside.) The solid residue, which contained Celite, barium carbonate, and by-product (**3**), was repeatedly extracted with hot tetrahydrofuran. The extracts were combined and evaporated to dryness under diminished pressure, and the residue was recrystallized from acetone–ether–pentane to yield 300 mg of **3**, m.p. 163–164.5°, $[\alpha]_D^{23}$ +83.8° (*c* 1.35, acetone); ν_{max}^{KBr} 1815 (cyclic carbonate carbonyl) and 1755 cm^{-1} (acyclic carbonate carbonyl).

Anal. Calc. for $C_{17}H_{22}O_{13}$: C, 47.01; H, 5.10. Found: C, 46.75; H, 4.97.

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