TWO BENZYLATED HYDROXYGLYCALS DERIVED FROM D-FRUCTOFURANOSE*

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ABSTRACT

1,3,4,6-Tetra-*O*-benzyl-D-fructofuranosyl chloride (**2**), readily preparable from 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**1**), undergoes dehydrohalogenation with ease to give two amorphous, unsaturated products (I and II). The 100-MHz p.m.r. spectra of these compounds permitted tentative assignments of structure, and these assignments were confirmed through chemical degradation. Periodate–permanganate oxidation of one of the unsaturated compounds (I) afforded 2,4-di-*O*-benzyl-D-erythronic acid (**7**), an authentic specimen of which was prepared through the periodate–hypoiodite oxidation of 3,5-di-*O*-benzyl-D-ribofuranose (**8**). This unsaturated compound is, therefore, 2,5-anhydro-1,3,4,6-tetra-*O*-benzyl-D-*erythro*-hex-2-enitol (**3**). Similar oxidation of the other unsaturated product (II) afforded the known 1,4-lactone of 2,3,5-tri-*O*-benzyl-D-arabinonic acid (**6**), showing that the double bond is exocyclic and that compound II is 2,5-anhydro-1,3,4,6-tetra-*O*-benzyl-D-*arabino*-hex-1-enitol (**4**).

INTRODUCTION

2,3,5-Tri-*O*-benzyl-α-D-arabinofuranosyl chloride is accessible by several synthetic pathways[1], but is, perhaps, most conveniently prepared through the action of hydrogen chloride and a solid desiccant on a solution of 2,3,5-tri-*O*-benzyl-D-arabinofuranose in an inert solvent[1]. This halide has proved of some utility in the synthesis of cytotoxic and antiviral nucleosides containing the β-D-arabinofuranosyl group[1,2]. As a result of recent research[3], 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**1**), a 2-ketohexose analog of 2,3,5-tri-*O*-benzyl-D-arabinofuranose, has become available in crystalline form, and we now report an investigation of some of the properties of the corresponding glycosyl chloride, namely, 1,3,4,6-tetra-*O*-benzyl-D-fructofuranosyl chloride (**2**).

DISCUSSION

Brief treatment with hydrogen chloride of a solution of 1,3,4,6-tetra-*O*-benzyl-

*Dedicated to Dr. Nelson K. Richtmyer in honor of his 70th birthday.

D-fructofuranose (**1**) in dichloromethane containing anhydrous magnesium sulfate gave, after subsequent removal of the desiccant and solvent, a product having the properties expected for 1,3,4,6-tetra-*O*-benzyl-D-fructofuranosyl chloride (**2**); like other fully benzylated glycosyl bromides and chlorides, the material was amorphous and unstable. Exploratory attempts to use the chloride for the synthesis of glycosides were not wholly satisfactory, but were observed to result in the formation of an unsaturated carbohydrate derivative. In order to pursue this topic further, a deliberate attempt to dehydrohalogenate **2** was carried out by using conditions similar to those employed by Wolfrom and Husted[4] for the conversion of 2,3,4,6-tetra-*O*-methyl-D-glucopyranosyl bromide into 1,5-anhydro-2,3,4,6-tetra-*O*-methyl-D-*arabino*-hex-1-enitol ("3,4,6-tri-*O*-methyl-2-methoxy-D-glucal")—namely, by the action of Drierite and powdered potassium hydroxide in a mixture of *p*-dioxane and ether. With these reagents, chloride **2** afforded a somewhat complex mixture containing not only the unsaturated derivative observed earlier but also a second, isomeric, unsaturated compound. Through preparative, thin-layer chromatography (t.l.c.), the mixture was separated into four components; for convenience, the two unsaturated compounds, representing 83% of the total weight of the separated fractions, were provisionally designated Products I and II, in the order of increasing rate of migration in the t.l.c. system used.

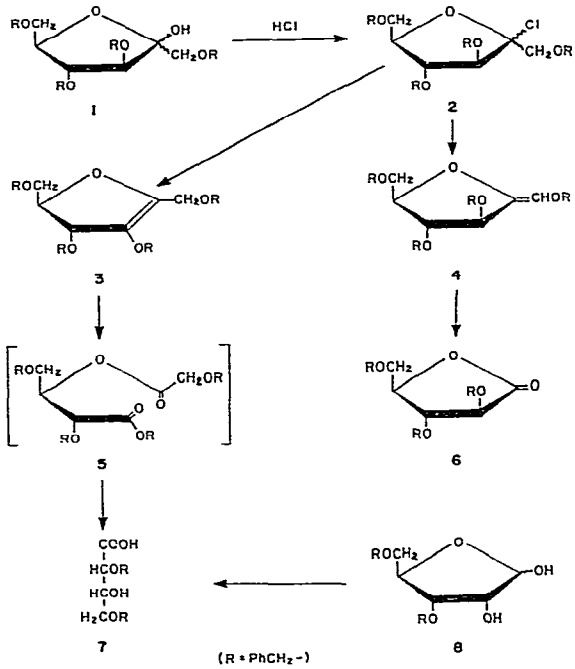
Both of the unsaturated compounds were optically active and had the elemental composition of a dehydrohalogenation product of **2**; they were also amorphous and markedly unstable, even on storage at +5°.

The p.m.r. spectrum of Product I was typical of that of many poly-*O*-benzylated carbohydrate derivatives, in that signals from the allylic benzyl protons tended to obscure the more interesting resonances. However, a well-defined pair of quartets at τ 6.38–7.80 was interpreted as arising from H-6 and H-6′, these protons being coupled with H-5. In addition, a two-proton singlet at τ 5.93 was regarded as arising from H-1 and H-1′. These assignments are in accord with the structure depicted in formula **3**.

Chemical evidence to confirm the structure assigned to Product I was initially sought through reduction over a palladium catalyst, as it was assumed that the benzyl groups would be removed by hydrogenolysis and the double bond reduced, to yield one or more of the known anhydrohexitols. A somewhat similar reaction, the hydrogenolysis–reduction of an enolic benzyl ether in a six-membered ring, has recently been reported from this laboratory[5]. Product I was, however, found to be stubbornly resistant to reduction and, as with some other unsaturated carbohydrate derivatives recently investigated[6,7], we attribute this phenomenon to steric difficulties in the approach of the molecule to the catalyst surface.

Attention was therefore directed to a procedure involving degradation through periodate–permanganate oxidation[8,9]. After treatment of Product I with this combination of reagents and then with a mixture of acetic and hydrochloric acids (to hydrolyze the presumed intermediate, **5**), a crystalline, optically active product was obtained in low yield. Independently, 3,5-di-*O*-benzyl-D-ribofuranose[10] (**8**) was subjected to a two-stage oxidation, periodate being followed by hypoiodite, to give a

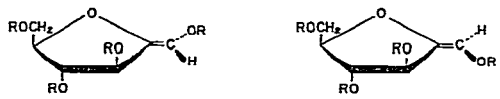
compound identical with that obtained from Product I. The oxidation product is, therefore, 2,4-di-*O*-benzyl-D-erythronic acid (**7**) and Product I is 2,5-anhydro-1,3,4,6-tetra-*O*-benzyl-D-*erythro*-hex-2-enitol (**3**).



Product II was next examined; its p.m.r. spectrum appeared to be more informative than that of Product I. Most significantly, its spectrum included a one-proton singlet at τ 4.41, suggestive of a vinyl hydrogen. An octet at τ 6.20–6.50 was tentatively assigned to H-6,6′. A multiplet, complicated by signals from benzylic protons, appeared at τ 5.30–5.60; irradiation at τ 6.34 affected this area, and irradiation at τ 5.44 collapsed the octet from H-6,6′. It appeared, therefore, that the signal for H-5 was within the multiplet between 5.30 and 5.60. A doublet centered at τ 5.79 was attributed to H-3, and a triplet centered at τ 5.90 was assumed to arise from H-4. On expansion of the 100-MHz spectrum, the singlet at τ 4.41, assigned to H-1, was observed to have a slight shoulder, and the peaks of the doublet at τ 5.79 were somewhat flattened. Irradiation at τ 4.41 sharpened the peaks of this doublet, showing the presence of long-range (vinyl-allylic) coupling between H-1 and H-3. These spectral features are consistent with structure **4** containing an exocyclic double bond between C-1 and C-2.

Unequivocal evidence for the structure of Product II was first sought via catalytic hydrogenation but, as with **3**, this proved impractical. Direct oxidation with periodate–permanganate gave, in low yield, a crystalline degradation product which showed a positive lactone test and proved to be 2,3,5-tri-*O*-benzyl-D-arabinono-1,4-lactone (**6**), a compound recently described[11] as an oxidation product of 2,3,5-tri-*O*-

benzyl-D-arabinofuranose. Hence, Product II is 2,5-anhydro-1,3,4,6-tetra-*O*-benzyl-D-*arabino*-hex-1-enitol (**4**); it should, however, be noted that the geometrical isomerism involved remains unknown, as the evidence available appears insufficient to distinguish between **4a** and **4b**.



Whereas a hydroxyglycal derivative is readily preparable from 1,3,4,5-tetra-*O*-acetyl-α-L-sorbopyranosyl chloride[12], comparable dehydrohalogenations of acylated D-fructopyranosyl and D-fructofuranosyl halides do not appear to have been observed prior to the present work. The mechanism whereby **3** and **4** are formed from **2** cannot, at this stage, be more than a topic for speculation, particularly inasmuch as the anomeric composition of **2** is unknown. Some facts that may be relevant should, however, be noted. Firstly, attempts to form a glycoside from **2** gave a compound later identified as **4**; no **3** was detected. Secondly, exploratory work, monitored solely by t.l.c., indicates that **3** and **4** can be formed in various proportions under diverse conditions. That these compounds are formed when **2** is treated with diethylamine is not surprising, as this reagent was used by Maurer and Mahn[13] in the first synthesis of a hydroxyglycal. More unusual is the apparent formation of these unsaturated derivatives when a solution of **2** or of the *p*-nitrobenzoate[3] of **1** in pyridine is heated for 48 h at 75°.

EXPERIMENTAL

General methods. — Melting points are equivalent to corrected values. Dichloromethane and *p*-dioxane were dried over molecular sieves, type 4A; commercial, anhydrous ether was used without further treatment. Exploratory t.l.c. was conducted on Silica Gel GF (Analtech, Inc.), and preparative t.l.c. was performed with plates (20 × 20 × 0.2 cm) of Silica Gel F-254 (E. Merck, Darmstadt); the solvent systems used are individually specified, proportions being measured by volume. Components were visibilized by illumination under a Gelman–Camag "universal" u.v. lamp, Model 51402. Proton magnetic resonance spectra were measured at 100 MHz for solutions in chloroform-*d*, tetramethylsilane being used as the internal standard.

*Preparation and dehydrohalogenation of 1,3,4,6-tetra-*O*-benzyl-D-fructofuranosyl chloride* (**2**). — To a solution of 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose[3] (**1**, 1.0 g) in dry dichloromethane (15 ml) was added anhydrous magnesium sulfate (0.5 g), the suspension was chilled in an ice bath, and a stream of dry hydrogen chloride was passed through it for 1 min. The mixture was kept in the ice bath for a further 9 min and then filtered, the magnesium sulfate being washed thoroughly with dry dichloromethane. The filtrate and washings were combined, and concentrated *in vacuo*, and the residual, syrupy 1,3,4,6-tetra-*O*-benzyl-D-fructofuranosyl chloride (**2**) was treated

with dry *p*-dioxane (4 ml), dry ether (4 ml), and Drierite (2–3 g). The mixture was stirred for 0.5 h, powdered potassium hydroxide (1.0 g) was added, and the mixture was stirred for a further 2 h. The solid was removed by filtration and washed thoroughly with ether, and the solution and washings were combined, and evaporated *in vacuo* to a syrup which was dissolved in dichloromethane. The solution was washed with water, dried with sodium sulfate, and concentrated *in vacuo* to a syrup which was subjected to preparative t.l.c. on three plates, by use of 30:1 benzene–ether. Four components were observed, and these were individually extracted with ether to give, after removal of solvent, four syrupy products that were designated I to IV in the order of increasing rate of migration in the system used. On t.l.c., Product I (307 mg, 32%) and Product II (178 mg, 18%) rapidly reduced permanganate (applied as a 0.5% spray) and were, therefore, deemed to be unsaturated compounds. Product III (45 mg) was not fully resolved from Product IV (52 mg); neither of these materials reacted promptly with permanganate spray, and they were not investigated further.

Examination of Product I. — The syrupy material showed $[\alpha]_D^{20}$ +43.7° (*c* 1, chloroform) and was markedly unstable, even on storage at +5°. Elemental analysis gave values in agreement with the molecular formula of **2** minus one molecule of hydrogen chloride.

Anal. Calc. for $C_{34}H_{34}O_5$: C, 78.13; H, 6.56. Found: C, 77.92; H, 6.75.

The p.m.r. spectrum of the compound is described earlier in this paper.

*Evidence that Product I is 2,5-anhydro-1,3,4,6-tetra-*O*-benzyl-*D*-erythro-hex-2-enitol* (**3**). — Product I (0.62 g) was stirred with (and partially dissolved in) *tert*-butyl alcohol (60 ml). A solution of sodium metaperiodate (2 g), potassium carbonate (0.5 g), and potassium permanganate (0.06 g) in water (60 ml) was added, and the mixture was stirred for 1 h. Oily drops of starting material were still visible, and so *tert*-butyl alcohol (10 ml) was added and stirring was continued for a further 1.5 h. The insoluble material was removed by filtration and washed with benzene. The filtrate and washings were combined, washed with water, dried (magnesium sulfate), and evaporated *in vacuo* to yield a syrup (0.55 g) which was examined by t.l.c. with 20:1 benzene–ether; products that reduced permanganate spray or gave a positive test with hydroxylamine–ferric chloride spray were not detected. Preparative t.l.c. on two plates resolved the product into three components, the intermediate one (0.23 g) preponderating. This syrupy main product was dissolved in hot glacial acetic acid (2.5 ml), and the solution was diluted with M hydrochloric acid (0.25 ml) and heated on a steam bath for 1 h. More M hydrochloric acid (0.25 ml) was then added, and the heating was continued for a further 1.5 h. The mixture was cooled and evaporated *in vacuo* to a syrup which was successively rubbed with very small portions of cold water, the aqueous washings being discarded. The syrup was then extracted with ~5 ml of water, and the aqueous extract was concentrated *in vacuo* and stored overnight at +5° to afford seed crystals.

The main quantity of syrup, which was clearly heterogeneous (t.l.c. with 20:1:2 benzene–ether–acetic acid), was dissolved in chloroform–pentane, and the solution was seeded. The product that crystallized (30 mg, yield ~8%) was recrystallized

from chloroform–pentane as clusters of needles which melted over a wide range, the final part melting rapidly at 85–88°. A sample dried *in vacuo* overnight at 50° had m.p. 87–89°, suggesting that the material had been hydrated. The product was, therefore, dissolved in chloroform, and the solution was dried with magnesium sulfate; the compound was then crystallized from chloroform–pentane: m.p. 88–89.5°, $[\alpha]_D^{20}$ +42.2° (*c* 0.74, chloroform); a mixed m.p. with a sample of 2,4-di-*O*-benzyl-D-erythronic acid (**7**), prepared from 3,5-di-*O*-benzyl-D-ribofuranose (**8**) as described later, was undepressed. On t.l.c. in 20:1:2 benzene–ether–acetic acid, the samples of **7** from the two sources were indistinguishable.

2,3-Di-O-benzyl-D-erythronic acid (**7**) *from 3,5-di-O-benzyl-D-ribofuranose* (**8**). — A procedure used by Ballou and Fischer[14] for the preparation of 3-*O*-benzyl-D-glyceric acid from methyl 6-*O*-benzyl-α-D-galactopyranoside was modified slightly for this two-step oxidation. A solution of 3,5-di-*O*-benzyl-D-ribofuranose[10] (**8**, 200 mg) in acetone (6 ml) was treated in the absence of direct light during 2 h with a solution of sodium metaperiodate (400 mg) in water (4 ml). The mixture was kept overnight in the dark and the precipitate of sodium iodate that formed was removed by filtration. The filtrate was evaporated *in vacuo* to a residue which was extracted with chloroform. The extract was dried with sodium sulfate, filtered, and evaporated *in vacuo* to afford a syrup that appeared to be free from **8** (t.l.c. with 20:1 dichloromethane–methanol). The syrup was dissolved in *p*-dioxane (3 ml), the solution was diluted with water (1 ml), and a solution of potassium carbonate (0.52 g) and potassium hydrogen carbonate (0.38 g) in water (4 ml) was added. A solution of iodine (0.45 g) and potassium iodide (0.56 g) in water (0.5 ml) was added, and the mixture was stirred for 1 h. *p*-Dioxane (1.5 ml) was added (to dissolve droplets of oil), and the mixture was stirred for a further 1.5 h and then made neutral with dilute sulfuric acid. The inorganic precipitate that formed was removed by filtration, and the excess of iodine in the filtrate was reduced through the addition of solid sodium thiosulfate. The product was extracted from the solution with three portions of ether, and the extracts were combined, dried (magnesium sulfate), and evaporated *in vacuo* to a syrup (120 mg) which was stirred with water (8 ml) for 2 h. The aqueous solution was decanted, and evaporated *in vacuo* to a syrup which crystallized, in part, on storage overnight at +5°. From its solution in chloroform–pentane, the syrup gave 9 mg of crystalline material, and a solution of the water-extracted syrup in the same mixture of solvents yielded 17 mg of crystalline product. The material melted over an extensive range (55–85°), suggestive of an unstable hydrate. The combined batches (14% total yield) were therefore dissolved in chloroform, the solution was dried with magnesium sulfate, the desiccant was removed, the solution was concentrated, and the product crystallized on addition of pentane: m.p. 88–89°, $[\alpha]_D^{20}$ +42.3° (*c* 0.67, chloroform).

Anal. Calc. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.12; H, 6.37.

Examination of Product II. — The syrupy material showed $[\alpha]_D^{20}$ +16.0° (*c* 3, chloroform) and proved to be more stable than Product I on storage at +5°. Its elemental composition showed it to be isomeric with Product I.

Anal. Calc. for $C_{34}H_{34}O_5$: C, 78.13; H, 6.56. Found: C, 78.30; H, 6.71.

The p.m.r. spectrum of the compound is described and discussed earlier in this paper.

*Evidence that Product II is 2,5-anhydro-1,3,4,6-tetra-*O*-benzyl-*D-arabino*-hex-1-enitol* (**4**). — A solution of sodium metaperiodate (570 mg), potassium permanganate (1.7 mg), and potassium carbonate (140 mg) in water (17 ml) was added to a solution of Product II (175 mg) in *tert*-butyl alcohol (17 ml). The mixture was stirred for 4 h, and the insoluble material was then removed by filtration. The filtrate was extracted with two portions of benzene, and the extracts were combined, washed with water, dried (magnesium sulfate), and evaporated *in vacuo* to a syrup (98 mg). T.l.c. (20:1 benzene–ether) showed the material to be heterogeneous, but there was no evidence for the presence of the starting material. One component gave a positive lactone test on spraying with hydroxylamine–ferric chloride[15]. The syrupy product was subjected to preparative t.l.c. with 20:1 benzene–ether, and the component giving the positive test for a lactone was separated, being extracted from the silica gel with ether. On concentration *in vacuo*, the extract afforded a syrup (14 mg, 10%) which crystallized on standing overnight at +5°. After recrystallization from ethanol–pentane, the compound was obtained as needles having m.p. 67–69°; a mixed m.p. with an authentic sample of 2,3,5-tri-*O*-benzyl-D-arabinono-1,4-lactone[11] (**6**) was undepressed. On chromatography in various systems, the products from the two sources proved to be indistinguishable.

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