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## Note

# Synthesis of 2,3-*O*-ethylidene-β-D-erythrofuranosyl 2,3-*O*-ethylidene-β-D-erythrofuranoside, a nonreducing, tetrose-tetrose disaccharide*

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A recent program at this laboratory included investigation of the sweetness of sugars and such derivatives as nonreducing disaccharides. A number of such disaccharides in the hexose–hexose series has long been known[2]. Fewer are known in the pentose–pentose series[2], but they include the naturally occurring β-D-ribofuranosyl β-D-ribofuranoside[3]. The analogue of the latter in the tetrose–tetrose series, β-D-erythrofuranosyl β-D-erythrofuranoside, is unknown. In the following report, the preparations of two crystalline derivatives of this disaccharide are described.

Hydrolysis of periodate-oxidized starch with sulfurous acid has been shown to produce D-erythrose and glyoxal in good yield[4]. Addition of paraldehyde to the hydrolyzate transforms the D-erythrose into its 2,3-ethylidene acetal (**1**), which may be extracted with chloroform[5]. In the present study, **1** was extracted from the hydrolyzate with benzene by liquid–liquid extraction. Unexpectedly, the product isolated from the benzene was a different compound (**2**), which crystallized readily. This product could also be obtained by boiling a solution of **1** in benzene in the presence of *p*-toluenesulfonic acid. Neutral or alkaline solutions of **2** were nonreducing, but they became strongly reducing when acidified with mineral acid and heated. A neutral solution of **2** did not consume periodate. Elemental analysis, *O*-ethylidene and molecular-weight determinations, a highly negative specific rotation, and $^{1}H$- and $^{13}C$-n.m.r. spectra are in accord with the structure 2,3-*O*-ethylidene-β-D-erythrofuranosyl 2,3-*O*-ethylidene-β-D-erythrofuranoside for **2**. Inspection of molecular models indicates that only the β,β linkage of the two ethylidenated D-erythrofuranosyl moieties of **2** is sterically feasible[5].

The known stability of compounds containing the dioxolane–furanose fused-ring system[6] suggested that carefully controlled acid hydrolysis of **2** might permit

*Ethylidene Derivatives of D-Erythrose, Part II. For Part I, see ref. 1.

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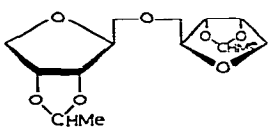
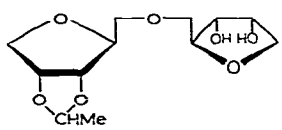
removal of one of the ethylidene groups without excessive hydrolysis of the entire structure. Graded acidic hydrolysis of **2** indeed gave **3**, an alkali-stable product having one fewer ethylidene group. It readily consumed periodate, was nonreducing to Fehling's solution, and showed no mutarotation. Although these properties tended to support for **3** the structure of **2** minus one ethylidene group, it was necessary to consider the possibility of a change in disaccharide linkage during the hydrolysis. A change in the position of linkage of the acetalated moiety to C-2 or C-3 of the deacetalated moiety, for example, would result in exposure of a reducing group. Either product, on catalytic hydrogenation followed by *p*-nitrobenzoylation, would be expected to yield a tri-*p*-nitrobenzoate. Proof that the hydrolysis resulted in no change in position of linkage was afforded by catalytic hydrogenation of **3** followed by *p*-nitrobenzoylation. A di-*p*-nitrobenzoate was the only ester so obtained. It was identical with that obtained from the original **3**. Thus **3**, like **2**, must be a nonreducing disaccharide derivative. Anomeric changes in the glycosidic linkage during the graded acidic hydrolysis appeared unlikely because the product remained highly levorotatory. Elemental analyses of **3** and of its di-*p*-nitrobenzoate and dibenzyl ether, its highly negative specific rotation, and also $^1$H- and $^{13}$C-n.m.r. spectra, all supported the structure β-D-erythrofuranosyl 2,3-*O*-ethylidene-β-D-erythrofuranoside for **3**.




**2**




**3**

To our knowledge, **2** and **3** are the first derivatives of the unknown tetrose–tetrose disaccharide, β-D-erythrofuranosyl β-D-erythrofuranoside, to be described.

## EXPERIMENTAL

*General methods.* — Evaporations were performed under diminished pressure (water pump). Melting points are uncorrected. The cellulose column (5 × 100 cm) was dry-packed with powdered Whatman Ashless Tablets (W. R. Balston, Ltd. England). Eluted fractions were located by chromatography on Whatman No. 1 paper, using the column solvent for development and the Godin[7] spray-reagent for zone detection (u.v. inspection). The activated charcoal was Darco G-60 (ICI United States, Wilmington, DE). $^1$H-N.m.r. spectra were recorded in chloroform-*d* at 100 MHz with a Varian HA spectrometer, with tetramethylsilane as the internal standard. $^{13}$C-N.m.r. spectra were recorded with a Bruker WH-90 spectrometer.

*2,3-O-Ethylidene-β-D-erythrofuranosyl 2,3-O-ethylidene-β-D-erythrofuranoside* (**2**). — (*a*) *From periodate-oxidized starch hydrolyzate.* To an aliquot (225 mL) of a periodate-oxidized starch (22 g) hydrolyzate[8] (675 mL) was added concentrated

sulfuric acid (11 g). The excess of sulfur dioxide was removed and the volume was adjusted to 200 mL by evaporation. Paraldehyde (6 mL) was added, the mixture was kept for 2 days at room temperature and then extracted continuously in a liquid–liquid extractor with benzene (150 mL in the boiling flask) for 18 h. The benzene extract, which was strongly levorotatory, was treated with activated charcoal, filtered, and evaporated to dryness. The residue was extracted with hot water and the hot extract treated with activated charcoal and rapidly filtered. The filtrate was evaporated to a dry, crystalline residue which, after repeated recrystallization from 1:4 (v/v) benzene–heptane, afforded a well crystallized product of constant m.p. 164–165°, $[\alpha]_D^{20}$ −245° (*c* 1, benzene); $^1$H-n.m.r.: $\delta$ 5.34 (s, 2, H-1), 5.01 (q, 2, *J* 4.8 Hz, O-C*H*Me-O), 4.69 (dd, 2, $J_{2,3}$ 6.3, $J_{3,4}$ 3.4 Hz, H-3), 4.41 (d, 2, H-2), 4.08 (d, 2, $J_{4,4'}$ 10.5 Hz, H-4'), 3.86 (dd, 2, H-4), and 1.38 [d, 6, O-CH(C*H*$_3$)-O]; $^{13}$C-n.m.r.: $\delta$ 103.6 (C-1), 101.9 (O-CHMe-O), 85.1 (C-2), 80.4 (C-3), 71.7 (C-4), and 19.1 [O-CH(*C*H$_3$)-O]. The product was nonreducing to Fehling's solution and to Tollens' reagent, and was alkali-stable. It did not consume periodate[10]. On warming in dilute mineral acid, the product became strongly reducing to Fehling's solution.

*Anal.* Calc. for $C_{12}H_{18}O_7$: C, 52.5; H, 6.6; $CH_3CH$, 2 groups; mol. wt., 274. Found: C, 52.5; H, 6.7; $CH_3CH$, 1.8 groups; mol. wt., 274, 268.

(*b*) *From* **1**. — To a solution of compound[5] **1** (0.154 g) in benzene (70 mL) was added *p*-toluenesulfonic acid monohydrate (0.11 g). The mixture was boiled under reflux, and a Dean–Stark trap was used to separate the water condensate. After 11 h, when the optical rotation had become constant ($[\alpha]_D^{20}$ −0.59°, 1 dm tube), the mixture was shaken twice with saturated sodium hydrogencarbonate and evaporated to a solid residue. Recrystallization from 1:4 (v/v) heptane–benzene gave **2**, m.p. and mixed m.p. 162°; yield, 0.076 g (52%).

*Graded acid hydrolysis of* **2**. — A suspension of **2** (1.2 g) in 50mM sulfuric acid (200 mL) was heated for 2.5 h at 85° (bath). The mixture was chilled, diluted with water (200 mL), and shaken with benzene (400 mL) for 5 min. From the benzene layer, 0.51 g of **2** was recovered. The aqueous layer was made neutral with barium carbonate, filtered, and evaporated to dryness. The residue was extracted with abs. ethanol, and the extract was filtered and evaporated to a syrup that was extracted exhaustively with warm benzene. The combined extracts were chilled, filtered, and evaporated to a syrup that crystallized. The product was extracted with boiling heptane and the hot extract decanted from a little undissolved syrup. Evaporation of the extract gave a crystalline residue which, after three recrystaliizations from 4:1 (v/v) heptane–benzene, gave **3**, m.p. 127–128°, $[\alpha]_D^{20}$ −237° (*c* 1, abs, ethanol), −228° (*c* 1, water) (no mutarotation); yield (2 crops), 0.263 g; $^1$H-n.m.r.: $\delta$ 5.30 (s, 1, H-1A), 5.16 (d, 1, $J_{1'A,2'B}$ 1.5 Hz, H-1'B), 4.96 (q, 1, *J* 4.9 Hz, O-C*H*Me-O), 4.67 (dd, 1, $J_{2,3}$ 6.3, $J_{3,4}$ 3.4 Hz, H-3), 4.42 (d, 1, H-2), 4.40 (m, 1, H-3'B), 4.0 (m, 5, H-4A,B, H-4'AB, H-2'B), 2.80 (d, 1, $J_{B,OH}$ 6 Hz, 3-OH), 2.50 (d, 1, $J_{2,OH}$ 6 Hz, 2-OH), and 1.36 (d, 3, O-CHMe-O); $^{13}$C-n.m.r.: $\delta$ 103.5 (C-1A, C-1B), 102.4 (O-*C*HMe-O), 85.1 (C-2A), 80.3 (C-3A), 75.6 (C-2B), 72.5 (C-3'B), 71.6 (C-4A), 70.4

(C-4'B), and 19.1 [O-CH($CH_3$)-O]. It did not reduce Fehling's solution and was alkali-stable. It readily consumed periodate[10].

*Anal.* Calc. for $C_{10}H_{16}O_7$: C, 48.4; H, 6.5. Found: C, 48.3; H, 6.7.

p-*Nitrobenzoylation of* **3**. — To a solution of **3** (0.056 g) in dry pyridine (5 mL) was added *p*-nitrobenzoyl chloride (0.19 g). The mixture was heated for 0.5 h at 80–90° (bath), chilled, and poured into saturated sodium hydrogencarbonate (100 mL). After several h, the mixture was extracted with chloroform and water was distilled from the extract until all chloroform and pyridine had been removed. The resulting suspension was reextracted with chloroform and the extract evaporated to dryness. The remaining residue was extracted with hot heptane, and the hot extract was filtered and evaporated to dryness. The residue, after two recrystallizations from 1:4 (v/v) heptane–benzene, afforded the di-*p*-nitrobenzoate; yield, 0.091 g (74%); m.p. 147–148°, $[\alpha]_D^{20}$ −125° (*c*, 0.08, benzene); $^1$H-n.m.r.: $\delta$ 8.15 (m, 8, aromatic), 5.82 (dd, 1, $J_{3B,4B}$ 6, $J_{3B,4'B}$ 4 Hz, H-3B), 5.55 (m, 2, H-1B, H-2B), 5.40 (s, 1, H-1), 5.00 (q, 1, *J* 4.9 Hz, O-*C*HMe-O), 4.73 (dd, 1, $J_{2,3}$ 6, $J_{3,4'}$ 3 Hz, H-3), 4.52 (d, 1, H-2), 4.46 (dd, 1, $J_{4B,4'B}$ 10 Hz, H-4B), 4.16 (dd, 1, H-4'B), 4.10 (d, 1, $J_{4,4'}$ 10 Hz, H-4), and 3.89 (dd, 1, H-4'); $^{13}$C-n.m.r.: $\delta$ 103.8 (C-1), 102.6 (O-*C*HMe)-O), 100.6 (C-1'), 85.1 (C-2), 80.3 (C-3), 76.8 (C-2'), 72.9 (C-3'), 71.9 (C-4), 69.7 (C-4'), and 19.1 [O-CH($CH_3$)-O].

*Anal.* Calc. for $C_{24}H_{22}N_2O_{13}$: C, 52.8; H, 4.1; N, 5.1. Found: C, 52.7; H, 4.0; N, 5.1.

*Benzylation of* **3**. — To a stirred solution of **3** (0.15 g) and benzyl bromide (5 mL) in *N*,*N*-dimethylformamide (20 mL) was added, portionwise, freshly prepared silver oxide (5 g) during 1 h. The mixture was stirred vigorously for an additional 16 h and then diluted with a large volume of benzene and filtered. The filtrate was shaken with water and was then evaporated to a syrup to which was added pyridine (5 mL). The mixture was warmed (steam bath) for 0.5 h and then diluted with a large volume of benzene, shaken twice with water, and evaporated to a syrup that was dissolved in a small volume of 1:1 heptane–benzene containing 1% of *N*,*N*-dimethylformamide. The solution was poured onto a cellulose column. Development was with the same solvent, 30-min fractions being collected. The appropriate fractions, as ascertained by paper chromatography, were combined. Impure fractions were evaporated to a syrup and again passed through the column as before. A chromatographically pure product was thus obtained that, after two recrystallizations from ethanol–water, afforded the dibenzyl ether; yield 0.17 g (64%); m.p. 75–76°; $^1$H-n.m.r.: $\delta$ 7.30 (m, 10, aromatic), 5.32 (m, 2, H-1A, H-1B), 4.97 (q, 1, *J* 5 Hz, O-*C*HMe-O), 4.62 (s, 2, O-C$H_2$Ar), 4.5 (m, 1, H-3A), 4.52 (ABq, 2, OC$H_2$Ar), 4.36 (d, 1, $J_{2,3}$ 6 Hz, H-2A), 4.0 (m, 6, 2B, 3B, 4A, 4'A, 4B, 4'B), and 1.36 [d, 3, O-CH(C$H_3$)-O]; $^{13}$C-n.m.r.: $\delta$ 103.7 (C-1A), 102.8 (O-*C*HMe-O), 101.4 (C-1B), 85.3 (C-2A), 80.7 (C-2B), 80.4 (C-3A), 77.1 (C-3B), 71.7 (C-4A), 69.9 (C-4B), and 19.2 [O-CH($CH_3$)-O].

*Anal.* Calc. for $C_{24}H_{28}O_7$: C, 67.3; H, 6.6. Found: C, 67.6; H, 6.8.

*Attempted hydrogenation of* **3**. — To a solution of **3** (0.20 g) in abs. ethanol (70 mL) was added freshly prepared, pyrophoric, Raney nickel. The mixture was

hydrogenated at 2600 lb.in.$^{-2}$ for 5 h at 110°. Filtration and evaporation gave a syrup that was dissolved in dry pyridine (5 mL). *p*-Nitrobenzoyl chloride (0.4 g) was added, the mixture was heated at 80–90° (bath) 0.5 h, chilled, and poured into saturated sodium hydrogencarbonate (200 mL). The mixture, processed as before, gave the di-*p*-nitrobenzoate of **3**, m.p. and mixed m.p. 146–147°, $[\alpha]_D^{20}$ −125° (*c* 0.08, benzene).

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