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Note

α-D-Glucopyranosyl 1,3-anhydro-β-D-*xylo*-hexulofuranoside: an intermediate in the alkaline hydrolysis of α-D-glucopyranosyl 3,4-anhydro-β-D-*lyxo*-hexulofuranoside

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Recently, we found[1,2] that methanolysis of α-D-glucopyranosyl 3,4-anhydro-β-D-*lyxo*-hexulofuranoside (**1**) yields, besides 4′-*O*-methylsucrose, α-D-glucopyranosyl β-D-*xylo*-hexulofuranoside 2,1′-anhydride (**2**) which was isolated as its hexa-acetate **3**. According to our proposed mechanism, the hydroxyl group at C-1 on the furanose part of **1** attacks the oxirane ring at position 3, giving α-D-glucopyranosyl 1,3-anhydro-β-D-*xylo*-hexulofuranoside (**4**). Subsequent attack of the hydroxyl group at C-2 of the pyranose moiety leads to compound **2**. This paper deals with the proof of this reaction scheme.

The starting material, 3,4,6,1′,6′-penta-*O*-acetylsucrose (**5**), was obtained as a minor component of the penta-*O*-acetylsucrose fraction from the partial deacetylation of octa-*O*-acetylsucrose[2]. Its reaction with diethyl azodicarboxylate–triphenylphosphine gave the anhydro derivative **6**. Coupling of H-2 to a doublet at 2.194 ppm in the ^{1}H NMR spectrum of **6** confirms the free OH group at C-2. Characteristic chemical shifts[3] of C-3′ and C-4′ (56.25 and 55.03 ppm), together with the upfield shifts for H-3′ and H-4′ with respect to the ^{1}H NMR spectrum of sucrose octa-acetate, indicate a 3′,4′-oxirane ring. Its configuration was determined by acetylation, affording the known[2,4] 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl 1,6-di-*O*-acetyl-3,4-anhydro-β-D-*lyxo*-hexulofuranoside (**7**). Reaction of **6** with 3,4-dihydro-2*H*-pyran gave the 2-*O*-tetrahydropyran-2-yl (THP) derivative **8**. Assuming the validity of our proposed mechanism, **8** should also be transformed into a compound having an oxetane ring. The alkali-resistant group at position 2 should,

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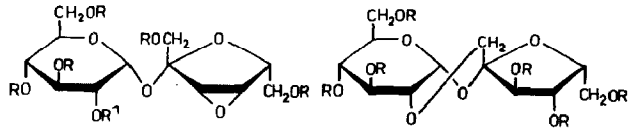
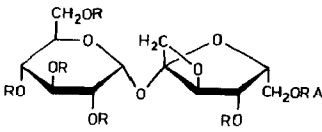
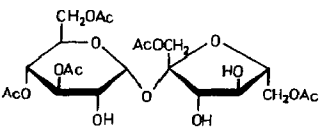


1 $R=R^1=H$
6 $R=Ac$ $R^1=H$
7 $R=R^1=Ac$
8 $R=Ac$ $R^1=$

2 $R=H$
3 $R=Ac$



4 $R=H$
9 $R=Ac$



5

however, prevent its subsequent opening and therefore render possible the isolation of the oxetane in acceptable yield. Compound **8** was at first deacetylated, then heated with 0.1 M sodium hydroxide, and the protecting THP group was removed with cation-exchange resin. Acetylation then gave a hexa-acetate (**9**). Its chemical ionisation (NH_3) mass spectrum revealed a pseudomolecular ion m/z 594 ($C_{24}H_{32}O_{16}$) and many fragment ions derivable by reactions typical of peracetylated sugars[5]. Among them, those arising from the rupture of the glycosidic linkage, m/z 331 (intact pyranose moiety) and m/z 229 (furanose moiety), are of diagnostic value. Both H-1′ signals were shifted downfield; their geminal coupling (7.7 Hz) suggested a four- or five-membered ring[6]. Large downfield shifts for C-1′ and C-3′ clearly pointed to oxygen bridge formation between them. Long-range couplings between H-3′ and both H-1′ protons also supported the structure of a 1′,3′-oxetane derivative **9**.

Oxetane **9** could be distinguished from the 1′,2-anhydro derivative **3** (now obtained in crystalline form, see Experimental) by TLC and by ^{13}C NMR data. Short-time hydrolysis of **1** by 0.1 M sodium hydroxide followed by acetylation afforded, besides the acetate **7** of the starting compound, the oxetane **9** and the 1′,2-anhydro derivative **3** in 15.3 and 16.6% yield, respectively. Methanolysis of **1** (0.1 M sodium methoxide, 1.5 or 7 h) produced the same compounds but at a lower rate: 1.5 h – **7** 92.2%, **9** 1.6%, **3** 1.9%; 7 h – **7** 90%, **9** 2.1%, **3** 5%. Because the hydrolysis of oxetane **9** also gave the 1′,2-anhydro derivative **3** in high yield, the

above-described experiments provide a clear proof of the proposed mechanism[1,2] of methanolysis and hydrolysis of the anhydro derivative **1**.

EXPERIMENTAL

General.—Melting points were determined with a Kofler apparatus and are not corrected. Optical rotations ($c \sim 1$) were measured in 20-cm cuvettes at 20°C. Thin layer chromatography was performed on silica gel (Merck) with the following systems: *A*, 1:4 benzene–*tert*-butyl methyl ether; *B*, 4:1 ether–light petroleum; *C*, 10:15:1.5:1.5 chloroform–ethanol–ammonium hydroxide–water; *D*, 100:5 benzene–ethanol. Detection was achieved through spraying with 1% cerium(IV) sulfate in aq 10% H_2SO_4. Solvents were removed at 50°C under reduced pressure (15 mmHg).

The ^1H and ^{13}C NMR spectra were measured with a Varian VXR-400 spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C) at 25°C. Chemical shifts (± 0.002 and 0.009 ppm) are given on the δ-scale. Me_4Si or the residual solvent signal was used as internal standard. Signals were assigned by combination of $^1H,^1H$-COSY, delayed $^1H,^1H$-COSY, and $^1H,^{13}C$-COSY (HETCOR). A Finnigan MAT-90 mass spectrometer (electron energy, 70 eV; accelerating voltage, 5 kV; ion-source temperature, 250°C; direct inlet at 170°C) was used.

*3,4,6-Tri-*O*-acetyl-α-*D*-glucopyranosyl 1,6-di-*O*-acetyl-3,4-anhydro-β-*D*-lyxo-hexulofuranoside* (**6**).—Triphenylphosphine (662 mg, 3 equiv) and diethyl azodicarboxylate (439 mg, 3 equiv) were added at 0°C to a $CHCl_3$ (EtOH-free) solution (10 mL) of 3,4,6,1′,6′-penta-*O*-acetylsucrose (**5**; 465 mg, 0.84 mmol). The mixture was stirred for 1.5 h at 0°C and then evaporated to dryness. Chromatography on silica gel (80 g, system *A*) afforded, first, compounds not detectable by TLC and then the anhydro derivative **6** (240 mg, 53.5%); $[\alpha]_D$ +84.5° ($CHCl_3$). Anal. Calcd for $C_{22}H_{30}O_{15}$: C, 49.44; H, 5.66. Found: C, 49.66; H, 5.94.

^1H NMR ($CDCl_3$): δ 2.046, 2.068, 2.083, 2.100, 2.138 (5 s, each 3 H, 5 × Ac), 2.194 (d, 1 H, $J_{2,OH}$ 10.1 Hz, HO-2), 3.716 (ddd, 1 H, $J_{1,2}$ 3.9, $J_{2,3}$ 10.1 Hz, H-2), 3.764 (d, 1 H, $J_{3',4'}$ 2.8 Hz, H-3′), 3.803 (dd, 1 H, $J_{4',5'}$ 1.1 Hz, H-4′), 4.802 (dd, 1 H, $J_{5,6a}$ 2.5, $J_{6a,6b}$ 12.1 Hz, H-6a), 4.161 (d, 1 H, $J_{1'a,1'b}$ 11.8 Hz, H-1′a), 4.180 (dd, 1 H, $J_{4,5}$ 10.2, $J_{5,6b}$ 5.1 Hz, H-5), 4.196 (dt, 1 H, $J_{5',6'}$ 5.4 Hz, H-5′), 4.281 (dd, 1 H, H-6b), 4.290 (d, 2 H, H-6′a,6′b), 4.341 (d, 1 H, H-1′b), 5.027 (dd, 1 H, $J_{3,4}$ 9.5 Hz, H-4), 5.225 (dd, 1 H, H-3), and 5.610 (d, 1 H, H-1). ^{13}C NMR ($CDCl_3$): δ 20.37 q, 20.39 q, 20.43 q, 20.49 q, 20.61 q (5 × Ac), 55.03 d (C-4′), 56.25 d (C-3′), 62.24 t (C-6′), 62.40 t (C-6), 65.16 t (C-1′), 68.27 d (C-4), 68.41 d (C-5), 70.20 d (C-2), 73.07 d (C-3), 75.02 d (C-5′), 92.39 d (C-1), 102.60 d (C-2′), 169.33 s, 169.80 s, 170.34 s, 170.37 s, and 170.76 s (5 × C=O).

A mixture of **6** (62 mg, 0.12 mmol), pyridine (2 mL), and acetic acid anhydride (0.1 mL) was left at room temperature overnight and then the solvents were removed. Chromatography of the residue [silica gel (15 g), 100:1 CH_2Cl_2–EtOH]

gave **7** (60 mg, 90%), mp 114–116°C (EtOAc–light petroleum). The NMR spectra were identical to those published[2].

3,4,6-Tri-O-acetyl-2-O-(tetrahydropyran-2-yl)-α-D-glucopyranosyl 1,6-di-O-acetyl-3,4-anhydro-β-D-lyxo-hexulofuranoside (**8**).—A mixture of **6** (198 mg, 0.37 mmol), 1,4-dioxane (10 mL), 3,4-dihydro-2*H*-pyran (0.3 mL), and freshly melted *p*-toluenesulfonic acid (15 mg) was stirred at room temperature for 20 h. Sodium hydrogen carbonate (100 mg) was added, the mixture was stirred for another 30 min and then filtered, and the filtrate was evaporated to dryness. Chromatography of the residue [silica gel (40 g), 7:3 EtOAc–light petroleum] afforded **8** (176 mg, 77%), $[\alpha]_D$ +55° ($CHCl_3$). NMR spectra indicated a mixture of diastereoisomers. Anal. Calcd for $C_{27}H_{38}O_{16}$: C, 52.42; H, 6.19. Found: C, 52.49; H, 6.18.

2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl 4,6-di-O-acetyl-1,3-anhydro-β-D-xylo-hexulofuranoside (**9**).–*(a) From oxirane* **8**. Four drops of M NaOMe were added to a methanolic solution (20 mL) of **8** (320 mg, 0.52 mmol). According to TLC (system *B*), the starting compound was deacetylated after 1 h. TLC (system *C*) exhibited one spot with R_f 0.45. The mixture was neutralised with a stream of CO_2 and evaporated to dryness. Sodium hydroxide (0.1 M, 15 mL) was added to the residue and the mixture was heated to 100°C for 15 h. The compound with R_f 0.45 changed completely into a new one with R_f 0.5 (system *C*). The reaction mixture was passed through an Amberlite IRC 50 (H^+) column (elution with water, 50 mL). Upon evaporation, a syrup (220 mg) was obtained. It consisted of one major component (R_f 0.3, system *C*) and two minor ones with lower R_f values. Pyridine (8 mL) and acetic anhydride (2 mL) were added to the residue. After 16 h, the mixture was evaporated to dryness, toluene was added, and the mixture was evaporated again. Chromatography [silica gel (70 g), 2:1 ether–light petroleum] yielded **9** (20 mg, 60%), $[\alpha]_D$ +79.3° ($CHCl_3$). Anal. Calcd for $C_{24}H_{32}O_{16}$: C, 50.00; H, 5.59. Found: C, 49.72; H, 5.83.

CI (NH_3) mass spectrum: *m/z* 594 ($M + NH_4^+$), 457, 415, 355, 331, 271, 229, 169, 109. ^1H NMR ($CDCl_3$): δ 2.019, 2.045, 2.047, 2.048, 2.084, 2.085 (6 s, each 3 H, 6 × Ac), 4.069 (dd, 1 H, $J_{5,6a}$ 2.1, $J_{6a,6b}$ 12.1 Hz, H-6a), 4.163 (dd, 1 H, $J_{5,6b}$ 6.0 Hz, H-6b), 4.233 (ddd, 1 H, $J_{4,5}$ 10.3 Hz, H-5), 4.279 (dd, 1 H, $J_{5',6'a}$ 6.9, $J_{6'a,6'b}$ 11.7 Hz, H-6'a), 4.401 (dd, 1 H, $J_{5',6'b}$ 4.9 Hz, H-6'b), 4.602 (d, 1 H, $J_{1'a,1'b}$ 7.7 Hz, H-1'a), 4.703 (ddd, 1 H, $J_{4',5'}$ 3.5 Hz, H-5'), 4.821 (dd, 1 H, $J_{1,2}$ 3.9, $J_{2,3}$ 10.4 Hz, H-2), 4.910 (d, 1 H, H-1'b), 5.005 (dd, 1 H, $J_{3,4}$ 9.4 Hz, H-4), 5.052 (d, 1 H, $J_{3',4'}$ 0.9 Hz, H-3'), 5.164 (dd, 1 H, H-4'), 5.491 (dd, 1 H, H-3), and 5.513 (d, 1 H, H-1). ^{13}C NMR ($CDCl_3$): δ 20.47 q, 20.52 q (3 C), 20.62 q, 20.69 q (6 × Ac), 61.15 t (C-6'), 62.23 t (C-6), 68.46 d (C-4), 68.51 d (C-5), 69.42 d (C-3), 69.85 d (C-2), 73.51 d (C-4'), 78.06 d (C-5'), 81.63 t (C-1'), 90.08 d (C-3'), 91.04 d (C-1), 104.99 s (C-2'), 169.57 s, 169.65 s, 170.04 s, 170.13 s, 174.45 s, and 170.63 s (6 × C=O).

(b) From the hydrolysis of the 3',4'-anhydro derivative **1**. Sodium methoxide (four drops, 1 M) was added to a methanolic solution (20 mL) of the 3',4'-anhydro derivative **7** (1.00 g, 1.74 mmol). After 2 h standing at room temperature, the mixture was neutralised with CO_2 and evaporated to dryness. A solution of the

residue in aq NaOH (0.1 M, 15 mL) was then heated for 1.5 h to 100°C, neutralised with CO_2, and evaporated to dryness. Acetylation (pyridine, 10 mL; acetic acid anhydride, 3 mL; 16 h, room temperature) afforded an amorphous product. TLC (system *B*, developed twice) showed three spots: R_f 0.65 (1′,3′-anhydro derivative **9**), 0.6 (1′,2-anhydro derivative **3** and octa-*O*-acetylsucrose), and 0.2 (major component, starting 3′,4′-anhydro derivative **7**). Three spots were also observed when using system *D*: R_f 0.4 (compounds **3** and **9**), 0.37 (octa-*O*-acetylsucrose, traces), and 0.25 (starting **7**). Column chromatography [silica gel (70 g), 2:1 ether–light petroleum] gave (TLC; systems *B* and *D*) pure **9** (152 mg, 15.3%), $[\alpha]_D$ +82.3° ($CHCl_3$), a mixture of **3**, **9**, and (possibly) octa-*O*-acetylsucrose (40 mg), and the 1′,2-anhydro derivative **3** also probably contaminated with octa-*O*-acetylsucrose (230 mg). Recrystallisation of the last fraction from 95% EtOH yielded the 1′,2-anhydro derivative **3** (166 mg, 16%), mp 113–115°C, $[\alpha]_D$ +74.5° ($CHCl_3$), with ^1H and ^{13}C NMR spectra identical to those published for syrupy **3**. Anal. Calcd for $C_{24}H_{32}O_{16}$: C, 50.00; H, 5.59. Found: C, 49.75; H, 5.62.

Elution of the column with light petroleum–EtOAc afforded the starting material **7** (564 mg, 54.6%).

(c) From the methanolysis of anhydro derivative **7**. A mixture of the 3′,4′-anhydro derivative **7** (1 g) and methanolic NaOMe (0.1 M, 15 mL) was heated to boiling for 1.5 h, neutralised with CO_2, evaporated to dryness, and acetylated as described in (*b*). A solution of the product in EtOAc was filtered, and the filtrate was evaporated to dryness. Crystallisation (EtOAc–light petroleum) gave unreacted **7** (724 mg). The mother liquors were subjected to column chromatography [silica gel (40 g), 2:1 ether–light petroleum] that yielded 1′,3′-anhydro derivative **9** (16 mg, 1.6%), 1′,2-anhydro derivative **3** (19 mg, 1.9%), and **7** (198 mg). In an another run, prolonged heating (7 h) produced 2.1% of **9**, 5% of **3**, and 90% of the unreacted epoxide **7**.

Conversion of the 1′,3′-anhydro derivative **9** *into the 1′,2-anhydro derivative* **3**.—A mixture of **9** (137 mg), MeOH (10 mL), and NaOMe (M, four drops) was left for 2 h at room temperature, then neutralised with CO_2, and evaporated to dryness. The residue was heated for 3.15 h with NaOH (0.1 M, 4 mL), again neutralised with CO_2, and evaporated. Acetylation of this residue (pyridine, 3 mL; acetic anhydride, 1 mL; 16 h, room temperature) followed by evaporation and chromatography [silica gel (40 g), 2:1 ether–light petroleum] produced **3** (121 mg, 88%) and a small amount (5 mg) of unreacted **9**.

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