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ACID-CATALYSED MONOACETALATION OF TWO 3-DEOXYHEXITOLS

TREVOR G. BONNER, DAVID GIBSON, AND DAVID LEWIS

Department of Chemistry, Royal Holloway College (University of London), Egham, Surrey TW20 OEX (Great Britain)

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ABSTRACT

Acid-catalysed monobutylidenation of 3-deoxy-D-*ribo*-hexitol yields the 2,4-acetal as the sole, detected product. 3-Deoxy-L-*xylo*-hexitol yields the 4,5-acetals as kinetic products, and the 4,6-acetal as the thermodynamic product.

INTRODUCTION

A monobutylidenation study[1] of three 2-deoxyalditols showed that the kinetic product for each reaction contained a β-ring involving C-1 and C-3, but that the thermodynamic product contained the β-ring involving the other primary carbon; α-*threo* rings were also formed as thermodynamic products where possible. We now report on the monobutylidenation of two 3-deoxyhexitols.

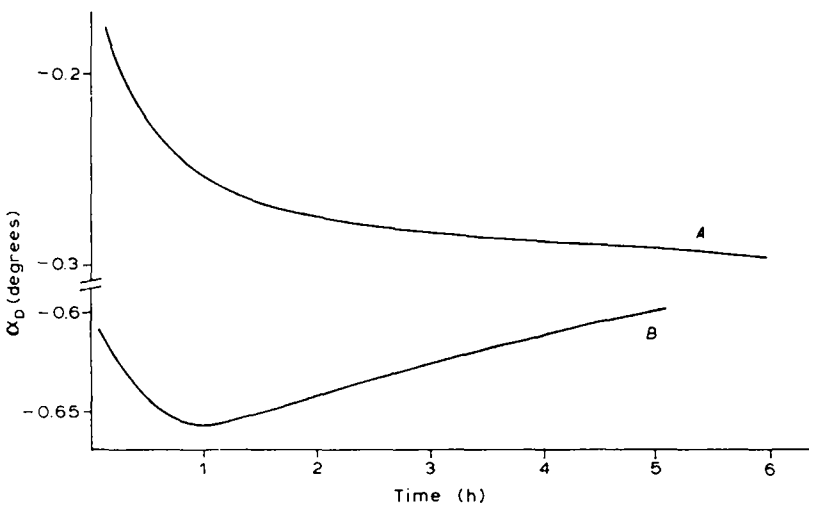
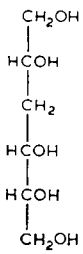


Fig. 1. Plot of α_D (0.1-m path-length) *versus* time for reactions between butyraldehyde (0.1M)–0.5M hydrochloric acid with *A*, 0.1M 3-deoxy-D-*ribo*-hexitol at 22.5°; and *B*, 0.1M 3-deoxy-L-*xylo*-hexitol at 25°.

RESULTS

3-Deoxy-D-*ribo*-hexitol (**1**) and butyraldehyde (equimolar) were condensed in the presence of 0.5M hydrochloric acid. The optical rotation decreased steadily with time (Fig. 1) until reaction equilibrium was reached (1 day). G.l.c. showed only one major, monoacetal peak, the area of which increased with time until equilibrium was reached. Measurement of the g.l.c. peak-area of the deoxyalditol with time gave an initial rate coefficient at 22.5° of 4.3×10^{-3} l.mol^{-1}.sec^{-1}. Work-up of the equilibrium mixture yielded only one monoacetal, namely, the crystalline 2,4-acetal (**2**), in 63% yield. It was characterised as its crystalline tris(toluene-*p*-sulphonate).

The 2,4-acetal (**2**) consumed 1.17 mol of periodate ion per mol of acetal with liberation of 1.08 mol of formaldehyde. P.m.r. spectroscopy in methyl sulphoxide showed an acetal-proton, triplet signal centred at δ 4.49, with ^3J 5.0 Hz, both facts[2,3] being consistent with the presence of a six-membered ring in **2**. After D_2O exchange, the spectrum indicated[4] one secondary and two primary hydroxyl groups. The above information uniquely defines the structure of **2** as the 2,4-acetal.



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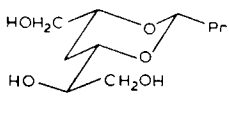

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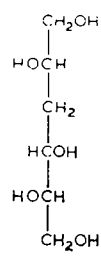

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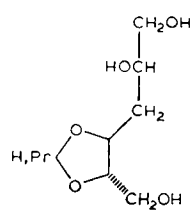

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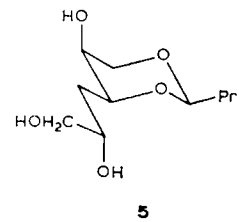

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Acid-catalysed condensation of 3-deoxy-L-*xylo*-hexitol (**3**) with butyraldehyde gave an optical rotation *versus* time curve (Fig. 1) having a minimum after ~1 h. The curve subsequently rose again to the reaction-equilibrium value, which was reached after 1 day. G.l.c. analysis confirmed the formation of a kinetic product, the 4,5-acetals (**4**), followed by the thermodynamic product, the 4,6-acetal (**5**). The initial rate coefficient for **3** at 25°, determined as for **1**, was 1.9×10^{-3} l.mol^{-1}.sec^{-1}. Work-up of the equilibrium reaction-mixture gave **4** (9%) and **5** (28%), both crystalline.

The 4,5-acetals (**4**) consumed 1.04 mol of periodate ion per mol of acetal with the liberation of 1.04 mol of formaldehyde. The p.m.r. spectrum of **4** in methyl sulphoxide showed overlapping, acetal-proton signals centred at δ 4.9, indicating five-membered rings. The above information limits the acetals **4** to having 4,5- or 5,6-rings. The ^{13}C-n.m.r. deshielding[5] of a carbon bearing a hydroxyl group is 1.6 to 7.8 p.p.m. when the oxygen of the hydroxyl group is incorporated into a five-membered, isopropylidene acetal. The ^{13}C-shifts of C-4 and C-5 had been deshielded by ~7 p.p.m. in **4** relative to their shifts in **3**. This defines the structure of **4** as the

4,5-acetals. The intensities of the acetal-carbon signals in the ^{13}C-n.m.r. spectrum showed that the two isomers were present in an ~1:1 ratio in the material isolated; this could not be purified by fractional crystallisation, t.l.c., or g.l.c. The 4,6-acetal (**5**) consumed 1.00 mol of periodate ion per mol of acetal and liberated 0.98 mol of formaldehyde. The p.m.r. spectrum in methyl sulphoxide showed an acetal-proton signal centred at δ 4.52, with ^3J 5.4 Hz, thereby indicating a six-membered ring. The D_2O-exchange technique indicated one primary and two secondary hydroxyl groups. The above facts limit the structure of **5** to the 4,6-acetal.

DISCUSSION

The optical rotation–time curves for the reaction of each of the alditols with butyraldehyde qualitatively fit the observed rotations for the main components present. The reaction of 3-deoxy-D-*ribo*-hexitol[6], $[\alpha]_D$ −10°, to yield its 2,4-acetal, $[\alpha]_D$ −16°, causes a fall in the rotation. For 3-deoxy-L-*xylo*-hexitol, $[\alpha]_D$ −38.7°, the rotation falls as the 4,5-acetals, $[\alpha]_D$ −60.2°, form, and then rises as the 4,6-acetal, $[\alpha]_D$ −13.9°, accumulates.

There is no previously reported study of the acetalation of these two alditols. The Barker–Bourne rules[7] for the preferred acetal at reaction equilibrium correctly predict a *β-erythro* ring for 3-deoxy-D-*ribo*-hexitol (**1**) and a *β*-ring for 3-deoxy-L-*xylo*-hexitol (**3**). The deoxy group in **1** should enhance the nucleophilicity of O-2 and O-4 and so enhance the rate of acetal formation thereat. Hence, the most easily formed acetal is also the thermodynamically most-stable acetal for this alditol. Although the two reactions were studied at marginally different temperatures, the initial rate coefficients imply that the reaction of 3-deoxy-D-*ribo*-hexitol (**1**) with butyraldehyde is faster than that of **3**, agreeing with the qualitative prediction above.

For a 2-deoxyalditol, the monoacetal having a *β*-ring with a hydroxyl group at C-5 of the dioxane ring seems to be more stable than the isomer having a *β*-ring with the dioxane ring unsubstituted[1] at C-5. If this fact also applies to *β-erythro* rings, then the stability of rings will be: *β-erythro* ring with C-5 of the dioxane ring hydroxylated > *β-erythro* ring with C-5 unsubstituted > *β*-ring with an equatorial OH at C-5 in the ring. This last inequality is inferred from the non-detection of any 4,6-acetal of **1**. Some 4,6-acetal may have been expected, since there is some indication, from g.l.c., that monobutylidenation[8] of D-glucitol yields the 4,6-acetal. The deoxy group in **1** is therefore not sufficiently destabilising to cause a reversal of the Barker–Bourne rule that a *β-erythro* ring is more stable than a *β*-ring. The Barker–Bourne rules were based on results from non-deoxyalditols. At equilibrium, the ratio of the g.l.c. peak-areas of **1**:**2** was 29:71, whereas the ratios of **3**:**4**:**5** were 60:10:30. The formation of the stable *β-erythro* ring in **2** drives the reaction equilibrium over to the acetal side (*cf.* > 80% reaction for D-glucitol[8]), but the less-stable *α-threo* ring in **4** and *β*-ring in **5** mean that the equilibrium lies more to the alditol side. The figures show that the thermodynamic stability of the *α-threo* ring in **4** is less than that of the *β*-ring in **5**, a fact predicted by the Barker–Bourne rules.

There is no reported work on the preferred conformation of **1** or **3**. Using the rule[9] that parallel 1,3-interactions are unfavourable, **1** is predicted to have a carbon-chain conformation like that in D-glucitol, whereas **3** should have a planar, zigzag carbon-chain. However, in the acetal **2**, the carbon chain can assume the planar, zigzag conformation. Unfortunately, the 220-MHz, p.m.r. spectra of **2** in methyl sulphoxide or pyridine-d_5 and of the tris(toluene-*p*-sulphonate) of **2** in $CDCl_3$ were too complex to give confirmation of this. Similarly, the p.m.r. spectrum of **5** in methyl sulphoxide could not be analyzed to confirm the prediction that the carbon chain of the alditol should be a planar zigzag. The five-membered ring of **4** should have various conformations[10].

EXPERIMENTAL

Techniques. — These were performed as described previously[1]. Polarimetry was effected with a Perkin–Elmer 141 polarimeter. G.l.c. analysis of the acetalation of **1** and **3** was performed on columns of Apiezon K (7.5%) at 168° and OV-225 (3%) at 140°, respectively. Peak areas were measured on a Hewlett–Packard 3307B integrator.

2,4-O-Butylidene-3-deoxy-D-ribo-*hexitol* (**2**). — 3-Deoxy-D-*ribo*-hexitol (**1**, 1.80 g, 97.5% pure by g.l.c.; obtained by reduction of syrupy 3-deoxy-D-*ribo*-hexose[11] with sodium borohydride) was dissolved in 0.5M hydrochloric acid (110 ml) and freshly distilled butyraldehyde (0.78 g). The solution was kept at room temperature for 48 h, then neutralised with 4M sodium hydroxide, and concentrated *in vacuo*. The solid residue was extracted with hot pyridine, the extract was concentrated, and the syrupy residue was introduced onto a column of alumina (300 g) and eluted with ethanol–water (9:1). The first fraction (1.5 g) was crystallised from methyl acetate, to yield **2**, m.p. 113–114.5°, $[\alpha]_D^{27}$ 4.7° (*c* 1.15, methanol), $[\alpha]_D^{23}$ −16.5° (*c* 2.2, water), R_F 0.41.

Anal. Calc. for $C_{10}H_{20}O_5$: C, 54.52; H, 9.15. Found: C, 54.53; H, 9.15.

The 1,5,6-tris(toluene-*p*-sulphonate) of **2**, prepared conventionally in 54% yield, had m.p. 89–91° (from ethanol), $[\alpha]_D^{23}$ 2.65° (*c* 2.4, chloroform).

Anal. Calc. for $C_{31}H_{38}O_{11}S_3$: C, 54.53; H, 5.6; S, 14.10. Found: C, 54.51; H, 5.64; S, 14.17.

Methyl 2,3,6-tri-O-benzoyl-4-deoxy-α-D-xylo-*hexoside*. — Methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-thiocyanato-α-D-glucoside[12] (32.16 g) and freshly prepared Raney-nickel (75 g) in ethanol (750 ml) were heated under reflux for 6 h. Work-up gave methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-α-D-*xylo*-hexoside (15.0 g), m.p. 112–113°, $[\alpha]_D^{23}$ +123.6° (*c* 2.6, chloroform).

Anal. Calc. for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.31; H, 5.58.

Methyl 4-deoxy-α-D-xylo-*hexoside*. — Zemplén debenzoylation of methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-α-D-*xylo*-hexoside (5.12 g) gave methyl 4-deoxy-α-D-*xylo*-hexoside (1.33 g), m.p. 91–92° (from ethyl acetate); lit.[11] m.p. 90°.

3-Deoxy-L-xylo-*hexitol* (**3**). — Acid hydrolysis of methyl 4-deoxy-α-D-*xylo*-

hexoside (1.33 g) gave syrupy 4-deoxy-D-*xylo*-hexose (1.19 g; lit.[11] m.p. 131–132°), which was reduced with sodium borohydride, to give **3** (75%), m.p. 93–94° (from ethanol), $[\alpha]_D^{23}$ −38.7° (*c* 2.2, water); lit.[13] for D-isomer, m.p. 90–93°, $[\alpha]_D$ +40°.

Anal. Calc. for $C_6H_{14}O_5$: C, 43.36; H, 8.4. Found: C, 43.35; H, 8.1.

4,5-(**4**) *and 4,6-O-butylidene-3-deoxy-*L-xylo-*hexitols* (**5**). — Butyraldehyde and **3** (2.38 g) were condensed as described above for **1**. The neutralised, concentrated mixture was extracted with hot ethanol, and the concentrated, syrupy extract was passed through a column of alumina (250 g), to free the monoacetal fraction from starting material. Fractionation of the monoacetals on a column of Dowex-1 X8 (HO^-) resin (elution with CO_2-free, deionised water) gave **5** (0.9 g), m.p. 107–108° (from ethyl acetate), $[\alpha]_D^{26.5}$ −14.7° (*c* 1.25, methanol), $[\alpha]_D^{23}$ −13.9° (*c* 2.4, water), R_F 0.41.

Anal. Found: C, 54.87; H, 9.22.

Eluted second was **4** (0.29 g), m.p. 79–80° (mixed isomers, from ethyl acetate), $[\alpha]_D^{26.5}$ −55.7° (*c* 0.85, methanol), $[\alpha]_D^{23}$ −60.2° (*c* 1.6, water), R_F 0.49, and single peak in g.l.c.

Anal. Found: C, 54.48; H, 8.83.

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