Monobutylidene Acetals of 1-Deoxy-D-galactitol

By **Trevor G. Bonner,* Edward J. Bourne, David Lewis,** and **Levant Yüceer,** Department of Chemistry, Royal Holloway College (University of London), Englefield Green, Surrey, TW20 0EX

Acid-catalysed monobutylidenation of 1-deoxy-D-galactitol (L-fucitol) yields the diastereoisomeric 2,3-acetals under kinetic control. The main product under thermodynamic control is the 4,6-acetal; the 4,5-acetal (4% yield) was also isolated.

THE aim of this study was to see if 1-deoxy-D-galactitol exhibited a kinetic phase during acid-catalysed monoacetal formation, and to characterise the main acetals produced initially and at equilibrium.

RESULTS

Gas chromatograms (Figure 1) of the products from 1-deoxy-D-galactitol and n-butyraldehyde (0.92 mol. equiv.) in the presence of 1M-hydrochloric acid showed a kinetic phase. This was confirmed by a plot of optical activity against time (Figure 2) for an equimolar (0.5M) solution of the polyol and aldehyde in 1M-hydrochloric acid, which showed a slight minimum after 30 min.

Condensation of the polyol and butyraldehyde (1.35 mol. equiv.) in the presence of 1M-hydrochloric acid for 2 days yielded a syrupy product. The diacetals were extracted with light petroleum. The syrupy extract contained several diacetals, as judged by t.l.c., but none could be crystallised. The light petroleum-insoluble material was dissolved in hot ethanol. Most of the unchanged polyol crystallised, and

the liquors contained a syrupy mixture of monoacetals. This mixture was fractionated on an anion-exchange resin. The 4,6-acetal (I) was eluted first and in highest yield (overall 18%). The mixed 2,3- (II) and 4,5-acetals (III) were

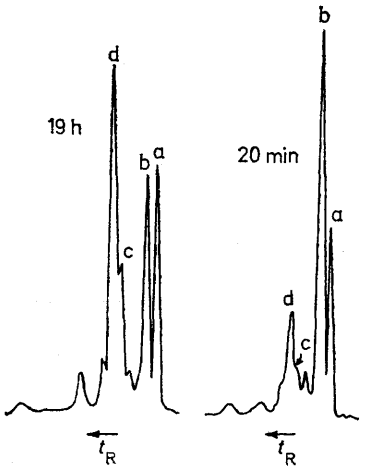


FIGURE 1 Gas chromatograms of reaction of 1-deoxy-D-galactitol with butyraldehyde (0.92 mol. equiv.) in M-hydrochloric acid; a, 1-deoxygalactitol; b, 2,3-; c, 4,5-; d, 4,6-acetal

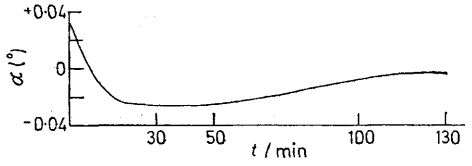
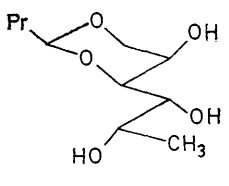


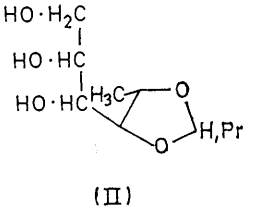
FIGURE 2 Reaction of butyraldehyde (0.5M) with 1-deoxy-D-galactitol (0.5M) in M-hydrochloric acid at 25 °C (rotations for 0.1 m tube at 436 nm)

eluted second, and were purified by fractional crystallisation.

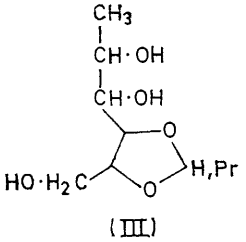
The syrupy 4,6-acetal was obtained on one occasion as a solid. All attempts to recrystallise it failed. The work



(I)



(II)



(III)

reported was done on the syrup. The structure of the 4,6-acetal (I) was determined as follows. It gave a triacetate and a trimethyl ether, both crystalline. It consumed 0.97 mol. equiv. of periodate ion, and liberated acetaldehyde, isolated as its dinitrophenylhydrazone (0.7 mol. equiv.). The acetal structure was therefore limited to the 4,6- or the 4,5-isomer. The ^{1}H n.m.r. spectrum (solvent deuterium oxide at 100 MHz) was complex and poorly resolved. Warming the sample moved the HOD peak upfield to reveal an acetal proton triplet at τ *ca.* 5.3. A 100 MHz spectrum (solvent tetradeuteriomethanol) showed the one-proton triplet at τ 5.40. On the other hand, the ^{1}H n.m.r. spectrum of the triacetate in deuteriochloroform was completely interpreted. The acetal proton triplet shift (τ 5.50) confirmed [1] the presence of a six-membered ring. The magnitudes of the various coupling constants suggested that all the polyol carbon chain was in the planar zig-zag conformation. The shift (τ 5.38) of the acetal proton triplet of the trimethyl ether in deuteriochloroform also confirmed the presence of a six-membered ring. The methoxy proton signals were at τ 6.34, 6.52, and 6.64. The mass spectrum showed medium abundance peaks corresponding to M — 1, M — Pr, loss of C-1 and C-2, and loss of C-1, C-2, and C-3.

The mixed crystalline 2,3-acetals (II) (6% yield) in deuterium oxide showed acetal proton triplets at τ 4.96 and 4.85, which are assigned [1] tentatively to the isomers with the propyl group and C-4 *cis* and *trans* respectively with respect to the ring. The C-1 methyl group gave doublets at τ 8.64 and 8.57, assigned to the isomers with C-1 and the propyl group *trans* and *cis*, respectively. On periodate oxidation, 2.03 mol. equiv. of periodate were consumed, and 1.2 mol. equiv. of formaldehyde and 0.97 mol. equiv. of formic acid were released. These results proved that the acetal ring spanned the 2- and 3-positions.

The structure of the crystalline 4,5-acetal (III) (4% yield) was investigated as follows. The ^{1}H n.m.r. spectrum (solvent deuterium oxide) gave an acetal one-proton triplet at τ 4.89 characteristic of a five-membered ring acetal proton. The proton-decoupled ^{13}C n.m.r. spectrum (solvent deuterium oxide) showed acetal carbon resonances at 106.6 and 107.1 p.p.m., indicating a mixture of stereoisomers. The compound consumed 1.2 mol. equiv. of periodate, but gave neither formaldehyde nor formic acid. The liberated acetaldehyde was isolated as its bisdimedone derivative (0.91 mol. equiv.). These results limit the structure to the 4,5-acetals. The isomer obtained is different from the 4,6-acetal (I). The observed rotation ([α] +18.7°) is consistent with a 4,5-acetal, as a D-*threo*-arrangement of hydroxy-groups yields an acetal with a positive rotation, *e.g.* 3,4-*O*-butylidene-D-glucitol.[2]

DISCUSSION

The shape of the rotation *vs.* time curve (Figure 2) fits qualitatively the observed rotations of the main acetals proved to be present during the polyol–butyraldehyde reaction. Initially, the 2,3-isomers (II) (acetal ring across the L-*threo*-arrangement of hydroxy-groups) build up, causing a downward movement of the rotation. Subsequently (after 30 min) the product of thermodynamic control is building up. This is mainly the 4,6-isomer (I) ([α] −9.6°), along with some 4,5-isomer (III) (acetal ring across the D-*threo*-arrangement of hydroxy-groups); thus the rotation of the reaction solution then slowly increases.

There appears to be no report of monoacetal formation

[1] T. G. Bonner, E. J. Bourne, D. G. Gillies, and D. Lewis, *Carbohydrate Res.*, 1969, **9**, 463.

[2] T. G. Bonner, E. J. Bourne, Miss S. E. Harwood, and D. Lewis, *J. Chem. Soc.*, 1965, 121.

directly from 1-deoxy-D-galactitol, nor indeed from any 1-substituted galactitol. The predicted[3] thermodynamically favoured monoacetal should have a 4,6-ring, as in fact observed. 1-Deoxygalactitol has some similarities[4] to galactitol in its monobutylidenation; both polyols yield αT- and β-rings.[3] However, galactitol does not show a kinetic phase. Under similar conditions, 1-deoxygalactitol formed the 2,3-acetals (II) faster than did galactitol itself, as judged by g.l.c. This increased rate for 1-deoxygalactitol is reasonable, owing to its lack of a deactivating 1-hydroxy-group. A similar situation[5] obtains for glucitol and its 1-deoxy-derivative. In 1-deoxygalactitol there are two possibilities for αT-ring formation and in the kinetic phase the 2,3-acetal is favoured over the 4,5-acetal (which corresponds to the 2,3-acetal in galactitol itself).

EXPERIMENTAL

General techniques were as reported previously.[4] For g.l.c. an Apiezon K column was used at 181 °C. Retention volumes v_R are quoted relative to the trimethylsilyl derivative of 1-deoxy-D-galactitol.

Reaction of 1-*Deoxy*-D-*galactitol with Butyraldehyde*.—(*a*) 1-Deoxy-D-galactitol {3.5 g; $[\alpha]_D^{22}$ +1.3° (*c* 3.4 in H_2O) (lit.,[6] 1.45°; $[\alpha]_{436}^{22}$ +2.9° in H_2O); m.p. 153—155°; obtained[7] (47%) from D-galactose} in 1M-hydrochloric acid (200 ml) at room temperature was mixed with butyraldehyde (1.7 ml). Samples were analysed by g.l.c. at suitable time intervals. Part (150 ml) of the reaction solution was neutralised with sodium hydroxide solution after 48 h and evaporated, and the residue was extracted with hot ethanol. The extract deposited 1-deoxy-D-galactitol (0.15 g). The filtrate was evaporated, and the residue was extracted with warm chloroform. The extract was concentrated and deposited 4,5-O-*butylidene*-1-*deoxy*-D-*galactitol* (0.1 g), m.p. 103—105°, raised to 108.5—110° by recrystallisations from chloroform (10 parts) (Found: C, 54.35; H, 9.0. $C_{10}H_{20}O_5$ requires C, 54.5; H, 9.1%), v_R 1.46, R_F 0.67 in solvent A, $[\alpha]_D^{25}$ +18.7° (*c* 0.5 in MeOH).

(*b*) 1-Deoxy-D-galactitol (7 g) in 1M-hydrochloric acid (400 ml) was shaken with n-butyraldehyde (5 ml) and left at room temperature for 2 days. A water-insoluble oil (diacetals) was extracted with light petroleum, and the water layer was neutralised with 4M-sodium hydroxide and evaporated to a syrup. The syrup was extracted with hot ethanol to leave most of the salt. The concentrated extract yielded unchanged 1-deoxygalactitol. The crystallisation liquor was evaporated to a syrup (4.0 g) which was fractionated on Dowex-1 X8(OH^-) resin (250 g) (elution with deionised, carbon dioxide-free water). Syrupy 4,6-O-*butylidene*-1-*deoxy*-D-*galactitol* (Found: C, 54.0; H, 8.9%) (1.7 g), v_R 1.60, $[\alpha]_D^{25}$ −9.6° (*c* 0.56 in MeOH), R_F 0.65 (single spot in solvent A), was eluted first. On one occasion, a sample of acetal crystallised, m.p. 56—68°, but all attempts to recrystallise the material failed. The fractions containing the mixed five-membered ring acetals (R_F 0.67, solvent A) were combined and evaporated to a syrup (2.0 g), which solidified at −5 °C. Crystallisation from ethanol–diethyl ether (1 : 1 v/v) gave 4,5-*O*-butylidene-D-galactitol (0.4 g), m.p. 105—108 °. The crystallisation liquor was evaporated and the syrup was crystallised from ether–light petroleum to yield material (0.8 g) which after several recrystallisations gave the 2,3-O-*butylidene*-1-*deoxy*-D-*galactitols* (Found: C, 54.8; H, 9.0%) (0.6 g), m.p. 66—68°, $[\alpha]_D^{25}$ −12.8° (*c* 1.1 in MeOH), v_R 1.12.

Derivatives of 4,6-O-*Butylidene*-1-*deoxy*-D-*galactitol*.—(*a*) The acetal (0.1 g) in pyridine with acetic anhydride yielded the 2,3,5-*triacetate* (Found: C, 55.8; H, 7.3. $C_{16}H_{26}O_8$ requires C, 55.5; H, 7.6%) (0.12 g), m.p. 153—156° (from ethanol–water), τ ($CDCl_3$) 8.87 ($J_{1,2}$ 7.0 Hz, H-1), 4.73 ($J_{2,3}$ 2.0 Hz, H-2), 4.82 ($J_{3,4}$ 9.5 Hz, H-3), 6.12 ($J_{4,5}$ 1.5 Hz, H-4), 5.28 ($J_{5,6ax}$ 1.5, $J_{5,6eq}$ 1.0 Hz, H-5), 6.13 ($J_{6ax,6eq}$ −13.0 Hz, H-6*ax*), 5.91 (H-6*eq*), 5.50 (*J* 5.5 Hz, acetal H), *ca.* 8.39 and *ca.* 8.62 (CH_2), 9.11 (CH_3), and 7.89 and 7.93 (OAc).

(*b*) The acetal (0.9 g) in dimethylformamide (20 ml) was stirred at room temperature with silver oxide (5 g) and methyl iodide (5 ml) for 24 h, to yield, after several crystallisations from light petroleum, the 2,3,5-*trimethyl ether* (Found: C, 59.6; H, 9.6. $C_{13}H_{26}O_5$ requires C, 59.5; H, 9.9%), m.p. 61—63°.

Periodate Oxidation of 4,6-O-*Butylidene*-1-*deoxy*-D-*galactitol*.—The acetal (0.25 g) was dissolved in sodium periodate (0.2 g) solution in water (5 ml) and kept at room temperature for 3 h. The solution was neutralised with sodium hydrogen carbonate solution, water (5 ml) was added, and the resulting solution was distilled. The distillate (3 ml) was treated with 2,4-dinitrophenylhydrazine [0.14 g in methanol (2 ml); sulphuric acid added to dissolution]. Acetaldehyde 2,4-dinitrophenylhydrazone (0.18 g) precipitated. Crystallisation gave material of m.p. 140—145°. The m.p. of this compound is variable.[8] Material of m.p. 145—146° is reported.[8]

Periodate Oxidation of 4,5-O-*Butylidene*-1-*deoxy*-D-*galactitol*.—The acetal (0.10 g) in water (10 ml) was treated with sodium periodate (0.10 g, 1.03 mol. equiv.) at room temperature for 40 min. The solution was distilled at atmospheric pressure until 6.5 ml of distillate had been collected. The distillate was treated with a warm solution of dimedone in water. The precipitate acetaldehyde bisdimedone derivative (0.116 g, 0.91 mol.) had m.p. 137—139°, mixed m.p. 139—140.5°.

We thank the P.C.M.U. (Harwell) for recording some of the ^1H n.m.r. spectra, and Dr. D. G. Gillies of this department for discussions. One of us (L. Y.) thanks Royal Holloway College Council and Rank, Hovis McDougall Ltd. for financial support.

[4/2479 *Received*, 27*th November*, 1974]

[3] S. A. Barker, E. J. Bourne, and D. H. Whiffen, *J. Chem Soc.*, 1952, 3865; J. A. Mills, *Adv. Carbohydrate Chem.*, 1955, **10**, 1.
[4] T. G. Bonner, E. J. Bourne, D. Lewis, and L. Yüceer, *Carbohydrate Res.*, 1974, **33**, 1.
[5] T. G. Bonner, E. J. Bourne, P. J. V. Cleare, R. F. J. Cole, and D. Lewis, *J. Chem. Soc.* (*B*), 1971, 957.
[6] E. Votoček and J. Bulíř, *Z. Zuckerind. Böhmen*, 1906, **30**, 333; *Chem. Zentr.*, 1906, 1819.
[7] M. L. Wolfrom and J. V. Karabinos, *J. Amer. Chem. Soc.*, 1944, **66**, 909.
[8] G. J. Karabatsos, B. L. Shapiro, F. M. Vane, J. S. Fleming, and J. S. Ratka, *J. Amer. Chem. Soc.*, 1963, **85**, 2784.