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Note

Synthesis of 2,4-di-*O*-methyl-D-lyxose

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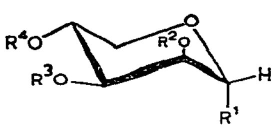
2,4-Di-*O*-methyl-D-lyxose has not, to our knowledge, been reported. We now describe a simple synthesis of this crystalline compound from D-lyxose.

Treatment of methyl α-D-lyxopyranoside[1] (**1**) with one molar equivalent of benzoyl chloride in pyridine at −15° yielded predominantly one product, which was readily crystallised in 46% yield from the reaction mixture. Identification of this product as the 3-benzoate **2** was made on the basis of its n.m.r. spectrum. Thus, the lowest-field signal for aliphatic protons, attributable to the methine proton in the grouping –CHOBz, was a double doublet with *J* 3.5 and 9.5 Hz. Of the three possible monobenzoates of the pyranoside in the $^4C_1$ conformation, only the 3-ester would be expected to exhibit this coupling pattern. The presence of a significant proportion of the alternative $^1C_4$ conformer was precluded by the $J_{1,2}$ value of 2.2 Hz and $J_{4,5}$ values of 10.5 and 5.5 Hz. Selective acylation at HO-3 might reasonably be expected, in view of the reported[2] dimolar acylation of methyl α-D-mannopyranoside to yield mainly the 3,6-dibenzoate.



1 $R^1 = OMe; R^2 = R^3 = R^4 = H$
2 $R^1 = OMe; R^2 = R^4 = H; R^3 = Bz$
3 $R^1 = OMe; R^2 = R^4 = Me; R^3 = Bz$
4 $R^1 = OMe; R^2 = R^4 = Me; R^3 = H$
5 $R^1 = OH; R^2 = R^4 = Me; R^3 = H$

Methylation of **2** with diazomethane–boron trifluoride etherate[3] gave, after two treatments and isolation by p.l.c., the 2,4-di-*O*-methyl derivative **3** in 64% yield. Debenzoylation of **3** gave methyl 2,4-di-*O*-methyl-α-D-lyxoside (**4**) as a syrup, which, on acidic hydrolysis, gave crystalline 2,4-di-*O*-methyl-D-lyxose (**5**). On the basis of the downward mutarotation on dissolution of **5** in water, the crystalline material appears to be the α anomer.

In addition to **3**, methylation of **2** gave a minor amount of a partially alkylated compound, presumably either the 3-*O*-benzoyl-2-*O*-methyl or 3-*O*-benzoyl-4-*O*-methyl derivative of **1**, which underwent facile acyl migration on dissolution in

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deuteriochloroform. Therefore, the originally separated material was immediately benzoylated. A decision between the alternative 3,4-di-*O*-benzoyl-2-*O*-methyl and 2,3-di-*O*-benzoyl-4-*O*-methyl structures was made in favour of the latter, as irradiation of the low-field, two-proton multiplet decoupled H-1. The ease of acyl migration in the monobenzoate is also in agreement with the latter alternative. Therefore, HO-2 in **2** is less reactive than HO-4 towards the diazomethane–boron trifluoride etherate reagent.

EXPERIMENTAL

Preparative layer chromatography (p.l.c.) was carried out on Kieselgel PF_{254}. N.m.r. spectra were measured at 220 MHz unless stated otherwise. Diazomethane solution in dichloromethane was prepared by the method of De Boer and Backer[4], except that dichloromethane was substituted for ether.

Methyl 3-O-benzoyl-α-D-lyxopyranoside (**2**). — To a cooled (−15° bath) and stirred solution of methyl α-D-lyxopyranoside[1] (**1**) (3 g) in pyridine (100 ml), a solution of benzoyl chloride (2.58 g) in pyridine (50 ml) was added dropwise during 15 min. Stirring was continued at −15° for 1 h, at 0° for 1 h, and at room temperature for 2 h. The mixture was then poured into a stirred solution of sodium hydrogen carbonate (5 g) in water (200 ml), and the solution was extracted with chloroform (5 × 50 ml). The combined extracts were dried and concentrated, and pyridine was removed from the residue by azeotropic evaporation with toluene. Crystallisation of the resulting gum from ethyl acetate–light petroleum gave **2** (2.25 g, 46%), m.p. 134–136°, $[\alpha]_D$ +43° (*c* 0.9, chloroform); ν_{max}^{Nujol} 3440, 3350 (OH), 1700 cm^{-1} (C=O). N.m.r. data $[(CD_3)_2CO]$: δ 3.01, 3.04 (2 s, OH), 3.38 (s, OMe), 3.54 (t, $J_{4,5a}$ 10.5 Hz, H-5*a*), 3.74 (dd, $J_{4,5e}$ 5.5, $J_{5a,5e}$ 11 Hz, H-5*e*), 4.11 (t, H-2), 4.25 (m, H-4), 4.65 (d, $J_{1,2}$ 2.2 Hz, H-1), 5.18 (dd, $J_{2,3}$ 3.5, $J_{3,4}$ 9.5 Hz, H-3), 7.40–8.20 (complex, Ar-H).

Anal. Calc. for $C_{13}H_{16}O_6$: C, 58.2; H, 6.0. Found: C, 57.9; H, 6.0.

Methyl 3-O-benzoyl-2,4-di-O-methyl-α-D-lyxopyranoside (**3**). — Freshly distilled boron trifluoride etherate (0.05 ml) was added to a stirred and cooled (bath, −25°) solution of **2** (1.9 g) in chloroform (20 ml), followed, portionwise, by an ~2% solution of diazomethane in dichloromethane[4] (200 ml). More catalyst (2 × 0.05 ml) was added when the reaction became slow, as indicated by the persistence of a yellow colour. T.l.c. (toluene–ethyl acetate, 3:1) then indicated a trace of starting material at the origin, a major fast-running component, and a slower-running compound. The solution was filtered and concentrated to ~20 ml, and the methylation repeated. T.l.c. then indicated the absence of starting material and an increase in the relative amount of the faster-running component. After concentration to ~100 ml, the reaction solution was washed with saturated, aqueous sodium hydrogen carbonate (30 ml), dried, and concentrated. The residue was subjected to p.l.c. (solvent as for t.l.c.), and the major component was crystallised from ethyl acetate–light petroleum to give **3** (1.33 g, 64%), m.p. 89–90°, $[\alpha]_D$ +31° (*c* 0.2, chloroform); ν_{max}^{film} no absorption near 3600 (OH), 1720 cm^{-1} (C=O). N.m.r. data $[(CD_3)_2CO]$: δ 3.36, 3.38 (2 s, 3 MeO), 3.48 (dd, $J_{4,5a}$ 10.5 Hz, H-5*a*), 3.62 (t, H-2), 3.72 (dd, $J_{4,5e}$ 5, $J_{5a,5e}$ 9 Hz, H-5*e*), 3.82 (m, H-4), 4.74 (d, $J_{1,2}$ 3 Hz, H-1), 5.29 (dd, $J_{2,3}$ 3.5, $J_{3,4}$ 8.5 Hz, H-3), 7.40–8.20 (complex, Ar–H).

Anal. Calc. for $C_{15}H_{20}O_6$: C, 60.8; H, 6.8. Found: C, 60.6; H, 6.8.

When the separated minor component [$\nu_{\max}^{\text{film}}$ 3460 (OH), 1720 cm^{-1} (C=O)] was dissolved in deuteriochloroform, the onset of isomerization was indicated by the occurrence of two signals for H-1 (d, δ 4.62 and 4.71) and three signals for OMe (s, δ 3.37, 3.42, and 3.48). T.l.c. confirmed the presence of a second minor component in addition to the initially dissolved material. The original, p.l.c.-purified material was therefore benzoylated to yield an oil [$\nu_{\max}^{\text{film}}$ no absorption near 3600, 1725 cm^{-1} (C=O)], which was identified (n.m.r. spectroscopy with selective decoupling) as methyl 2,3-di-*O*-benzoyl-4-*O*-methyl-α-D-lyxopyranoside. N.m.r. data ($CDCl_3$, 100 MHz): δ 3.42, 3.44 (2 s, OMe), 3.54–4.16 (complex, H-4,5*e*,5*a*), 4.79 (d, H-1), 5.48–5.74 (complex, H-2,3), 7.20–8.14 (complex, Ar–H).

*Methyl 2,4-di-*O*-methyl-α-*D*-lyxopyranoside* (**4**). — A solution of **3** (1.23 g) in methanol (80 ml) to which sodium (0.05 g) had been added was stored overnight at room temperature. The residue obtained on concentration was dissolved in ether (4 ml), and the solution was absorbed onto a short column of silica gel. Elution with ether–light petroleum (1:1, 150 ml) removed methyl benzoate; the column was then eluted with toluene–methanol (2:1, 200 ml) to yield **4** as a chromatographically pure syrup (0.71 g, 89%), $[\alpha]_D$ +41° (*c* 0.1, chloroform); $\nu_{\max}^{\text{film}}$ 3480 (OH), no absorption near 1720 cm^{-1}.

Anal. Calc. for $C_8H_{16}O_5$: C, 50.0; H, 8.4. Found: C, 49.65; H, 8.6.

*2,4-Di-*O*-methyl-*D*-lyxose* (**5**). — A solution of the glycoside **4** (0.63 g) in 0.5M hydrochloric acid (10 ml) was heated at 100° for 6 h. Water (10 ml) was added, and the solution was neutralized with silver carbonate, filtered, saturated with hydrogen sulphide, and then concentrated. The resulting black residue was extracted with boiling ethanol (3 x 50 ml), and the combined extracts were filtered through Kieselguhr and then through filter paper. Evaporation yielded a chromatographically pure solid (0.53 g, 91%), which was crystallised from ethyl acetate containing a little ethanol to give **5**, m.p. 83–85°, $[\alpha]_D$ -5.7 (initial) $\rightarrow$ $-11.1°$ (final) (*c* 0.32, water). Paper chromatography with 1-butanol–acetic acid–water (4:1:5) gave R_F 0.69, R_{Glc} 4.17.

Anal. Calc. for $C_7H_{14}O_5$: C, 47.2; H, 7.9. Found: C, 46.9; H, 7.9.

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