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Note

Selective acetylation of D-galactose*

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Whereas selective acylation of pyranosides and other sugar derivatives has been systematically investigated[1–5], the direct, selective acetylation of monosaccharides has so far received little attention[6,7], presumably because of the difficulties in fractionating the mixtures of products We have previously described[8] the selective acetylation of some benzyl glycopyranosides and we now report on the direct partial acetylation of D-galactose

eq-Hydroxyl groups are esterified at a rate higher than that of *ax* groups, the lower reactivity of *ax* HO-4 in methyl α-D-galactopyranoside and benzyl β-D-galactopyranoside under partial acetylation conditions is well established Partial acetylation of D-galactose with 6 2 molar equivalents of acetic anhydride in the presence of sodium acetate at room temperature afforded a syrupy tetra-acetate fraction (*1*, 16%), from which 1,2,3,6-tetra-*O*-acetyl-β-D-galactopyranose[9] (3%) was isolated by fractional crystallisation Crystalline penta-*O*-acetyl-β-D-galactopyranose (7 5%), a syrupy triacetate fraction (*2*, ~3%), and a diacetate fraction (*3*, ~3%) were also isolated Methylation with diazomethane–boron trifluoride etherate of fraction *1*, which showed two components (t l c , ether), yielded 4-*O*-methyl-D-galactose (major component) together with 3-*O*-methyl and 2-*O*-methyl-D-galactose, and a trace of D-galactose, after deacetylation of the reaction products When the 1,2,3,6-tetra-acetate was methylated with diazomethane–boron trifluoride etherate and the crystalline product deacetylated, 4-*O*-methyl-D-galactose was the only sugar isolated The crystalline 4-phenylcarbamate of the 1,2,3,6-tetra-acetate was readily prepared

Fraction *2* was shown by methylation[10] to contain mainly the 1,3,6-tri-*O*-acetyl-β-D-anomer, with the 1,2,6-isomer present as a minor component T l c showed that one treatment of fraction *3* with diazomethane–boron trifluoride etherate yielded a mixture of products, which was partitioned between benzene and water. The benzene layer contained a syrup (80%) which, on deacetylation, gave crystalline 2,4-di-*O*-methyl-D-galactose in high yield, the 3,4-di-*O*-methyl isomer was also detected The chloroform extract of the aqueous layer yielded a syrup (17%)

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which, on deacetylation, gave 2-*O*, 3-*O*, and 4-*O*-methyl-D-galactose (paper electrophoresis)

Repeated treatment of fraction *3* with diazomethane–boron trifluoride etherate followed by deacetylation gave mainly 2,3,4-tri-*O*-methyl-D-galactose (identified by p c) together with another presumed tri-*O*-methylgalactose

The preparation of 4-*O*-methyl- and of 2,4-di-*O*-methyl-D-galactose exemplifies the synthetic applications of the acetates described above Of the known tetra-*O*-acetyl-D-galactopyranoses, 1,2,3,6-tetra-*O*-acetyl-*β*-D-galactopyranose is obtained by a method[9] which is somewhat complicated, and therefore, to avoid difficulty, the sequence described above provides a useful alternative

O-Benzoylated monosaccharides having two hydroxyl groups free can readily be methylated[11] by the use of diazomethane in the presence of boron trifluoride etherate This procedure is now shown to be effective with *O*-acetylated monosaccharides having two hydroxyl groups free

EXPERIMENTAL

Concentrations were performed under reduced pressure Melting points were determined on a Kofler microscope stage, and are uncorrected Optical rotations were determined with a Bellingham and Stanley Polarimeter Model B Thin-layer chromatography (t l c) was performed on Merck Silica Gel F-254. using benzene–methanol (96 4–9 1) unless otherwise stated The separated materials were detected (*a*) by spraying the dried chromatogram with 10% of sulphuric acid in ethanol and heating, and (*b*) with the ferric hydroxamate reagent[12]. Free sugars were detected with aniline hydrogen phthalate[13] The solvent system 1-butanol–ethanol–water (5 1 4, upper layer), which was suitable for lower acetates, was used with Whatman No 1 and 3MM papers Paper electrophoresis was carried out in borate buffer (pH 9 6), differences in the applied voltage had no significant influence on M_G values

Partial acetylation of D-*galactose* — A mixture of D-galactose (20 g), anhydrous sodium acetate (10 g), and acetic anhydride (65 ml) was stored at room temperature for three weeks, with occasional shaking. T.l.c. then revealed penta- and tetra-acetate (major products), together with small proportions of triacetate and starting material The slurry was filtered, and the solid was washed with chloroform, the combined filtrate and washings diluted with a large volume of ethanol, and the solution concentrated Fractional crystallization of the residue (14 g) from ethanol afforded crystalline penta-*O*-acetyl-*β*-D-galactopyranose (3 3 g), m p 140°, $[\alpha]_D$ +28° (*c* 0 1, chloroform), lit.[14] m p 142°, $[\alpha]_D$ +25° (chloroform)

The mother liquors were concentrated to a syrup, which was extracted with benzene. The filtered solution was extracted several times with water The combined extracts were exhaustively extracted with chloroform T l c then showed that the chloroform extract contained triacetate and a small proportion of tetra-acetate, whereas the benzene solution retained the penta-acetate and tetra-acetate. The dried chloroform solution was concentrated and the residue was partitioned between

benzene and water as described above Extraction of the aqueous phase with chloroform gave, after concentration of the extract, a syrupy triacetate (fraction *2*, 900 mg), $[\alpha]_D$ +56° (*c* 0 19, chloroform)

In an analogous manner, aqueous extraction of the foregoing benzene solution was repeated until all tetra-acetate (fraction *1*, mainly the *β* anomer) was isolated, *via* chloroform extraction of the aqueous layer, as a syrup (6 g), $[\alpha]_D$ +63° (*c* 0 6, chloroform) Fractional crystallisation from di-isopropyl ether yielded 1,2,3,6-tetra-*O*-acetyl-*β*-D-galactopyranose (1 2 g), m p 139–140°, $[\alpha]_D$ +36° (*c* 0 2, chloroform); lit [9] m p 138–140°, $[\alpha]_D$ +38° (chloroform).

The aqueous phase remaining after the chloroform extraction contained (p c) D-galactose, and two components of greater chromatographic mobility which were detected with potassium periodate–cuprate[15]. Fractionation on Whatman 3MM paper gave a syrupy diacetate (fraction *3*, ~600 mg), $[\alpha]_D$ +54° (*c* 0 32, ethanol), R_F 0.53. The presumed monoacetate had R_F 0 26

Methylations with diazomethane–boron trifluoride etherate — (*a*) *1,2,3,6-Tetra-O-acetyl-β-D-galactose* A solution of the title compound (153 mg) in dichloromethane (5 ml) was kept at −5° while boron trifluoride etherate (0 02 ml) was added, and the solution was maintained at the same temperature during the addition of excess of diazomethane in dichloromethane The mixture was kept for 1 h to allow all colour to discharge T l c then showed an almost complete conversion into a faster-moving product. Polymethylene was removed, and the filtrate was washed with water and dried. Concentration left 1,2,3,6-tetra-*O*-acetyl-4-*O*-methyl-*β*-D-galactose (141 mg), m p 102–105° (from di-isopropyl ether), $[\alpha]_D$ +32° (*c* 0 1, chloroform)

Anal Calc for $C_{15}H_{22}O_{10}$ C, 49 7, H, 6 08 Found C, 49 5, H, 6 13

A solution of the foregoing product (98 mg) in methanol (5 ml) was treated with 0 1M methanolic sodium methoxide (0 5 ml) for 2 h at room temperature Cations were removed with Amberlite IR-120(H^+) resin, and the solution was then concentrated The crude, crystalline residue (42 mg, 80%) had R_G 0 26, M_G 0 28 {lit [16] 0 30 for 4-*O*-methyl-D-galactose) A trace of galactose (due to incomplete methylation of the tetra-acetate) was also detected Recrystallisation of the product from ethanol gave 4-*O*-methyl-D-galactose with physical constants {m p 218–220°, $[\alpha]_D$ +84° (*c* 1 18, water)} in agreement with those reported[17]

(*b*) *The triacetate fraction* 2 To a solution of fraction *2* (135 mg) in dichloromethane (6 ml) at 0°, boron trifluoride etherate (0 02 ml) was added The solution was maintained at 0° during the addition of excess of diazomethane in the usual manner, and then kept at 0° for 30 min T l c then showed ~90% conversion into two faster-moving products, designated *B* and *A* in order of increasing R_F values Polymethylene was removed, and the filtrate was concentrated to a syrup (140 mg), which was partitioned between benzene and water Concentration of the organic layer gave *A* as a colourless syrup (112 mg), $[\alpha]_D$ +26 5° (*c* 0 37, chloroform)

Anal Calc for $C_{14}H_{22}O_9$ C, 50 3, H, 6 58 Found C, 51 7, H, 6 77.

Continuous extraction of the aqueous layer with chloroform gave, after concentration of the extract, a syrup (*B*, 24 mg), $[\alpha]_D$ +50° (*c* 0 24, chloroform)

Paper electrophoresis of the syrup, after deacetylation, revealed 2-*O*-methyl (M_G 0 42) and 4-*O*-methyl-D-galactose (M_G 0 28), identified by comparison with authentic samples, together with the 3-methyl ether (M_G 0 66) (lit [16] 0 63)

Fraction *A* (56 mg) was deacetylated, as described above, to give a syrupy product which showed (p c , aniline hydrogen phthalate) two dimethyl ethers with R_G 0 53 (major) and 0 46 (minor) The product with R_G 0 53 did not react with alkaline triphenyltetrazolium chloride[18] After being dried *in vacuo*, the hygroscopic product crystallized slowly from ethyl alcohol to give 2,4-di-*O*-methyl-D-galactose as slightly coloured, sticky crystals with M_G 0 22, identical with that of 2,4-di-*O*-methyl-D-galactose provided by Dr G. A. Adams In addition, 3,4-di-*O*-methyl-D-galactose (M_G 0.19), identified by comparison with an authentic sample provided by the late Dr D J Bell, was detected.

Crystallisation of the mixture from ethanol gave 2,4-di-*O*-methyl-D-galactose (20 mg), m p 92° (shrinking at 68°), $[\alpha]_D$ +80° (*c* 0 3, water), lit.[19] m p 98–99°, $[\alpha]_D$ +86° (water) The anilide had m p 208–210°; lit [20] m p. 214–216°

(*c*) *The diacetate fraction* 3. Two treatments of fraction *3* (150 mg) in dichloromethane (5 ml) with excess of diazomethane, as described above, gave (t l c) a complex mixture of products Polymethylene was removed, and the filtrate was concentrated to a syrup, which was dissolved in benzene (20 ml) Incompletely methylated sugars were removed by extraction with water (3 × 15 ml) Deacetylation of a portion (25 mg) of the syrup (49 mg), $[\alpha]_D$ +21° (*c* 0 5, chloroform), obtained on evaporation of the benzene, gave a syrup (16 mg), $[\alpha]_D$ +68° (*c* 0 7, water), composed of two substances with R_G 0 68 (which was chromatographically identical to 2,3,4-tri-*O*-methyl-D-galactose) and 0 79.

1,2,3,6-Tetra-O-*acetyl-4*-O-*phenylcarbamoyl-β*-D-*galactopyranose* — To a solution of 1,2,3,6-tetra-*O*-acetyl-*β*-D-galactopyranose (200 mg, m p. 138°) in dry toluene (4 ml), phenyl isocyanate (0 5 ml) and dry pyridine (0 75 ml) were added After 24 h at room temperature, t l c showed almost complete conversion into material of higher R_F value The solution was treated with water to decompose excess of phenyl isocyanate and kept for 1 h at room temperature Carbanilide was removed and the filtrate was concentrated to a syrup, which was extracted with chloroform (30 ml) The extract was filtered, washed to remove pyridine, dried, and concentrated The residue was crystallised slowly from the minimal volume of di-isopropyl ether at 0° Recrystallization of the product (210 mg) from di-isopropyl ether gave the title compound, m p. 142–144°, $[\alpha]_D$ +21° (*c* 0 2, chloroform).

Anal Calc for $C_{21}H_{25}NO_{11}$· C, 53 96, H, 5.35, N, 2 99 Found C, 52 85, H, 5 05, N, 2 95

Methylation of fraction 1 — A solution of fraction *1* (77 mg) in dichloromethane (5 ml) was treated with diazomethane–boron trifluoride etherate in the usual manner Polymethylene was removed, and the filtrate was concentrated Paper electrophoresis of the resulting syrup, $[\alpha]_D$ +42° (*c* 1 2, ethanol), after deacetylation, revealed the presence of 4-*O*-methyl-D-galactose (major component) together with the 3-methyl ether, M_G 0 65 (lit [16] 0 63 for 3-*O*-methyl-D-galactose), 2-methyl ether.

M_G 0 40 (lit [16] 0 43 for 2-*O*-methyl-D-galactose), and D-galactose (M_G 0 90) as minor components

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