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Note

A convenient synthesis of D-glucose-2-*C*-*d* derivatives, and of methyl 4,6-*O*-benzylidene-2-*C*-methyl-α-D-glucopyranoside

ALAN H. HAINES
School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ (Great Britain)
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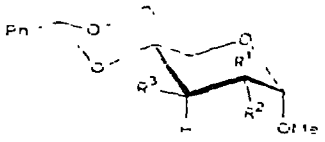
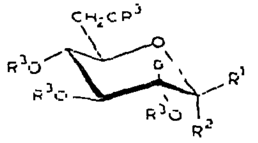
In connection with ^{29}Si-n.m.r. studies[1] on trimethylsilyl ethers of carbohydrates, methyl α-D-glucopyranoside-2-*C*-*d* (6) was required. The published procedures for the preparation of D-glucose, or its derivatives, isotopically substituted with deuterium or tritium at C-2 involve enzyme-controlled incorporation of the isotope from deuterium oxide or tritiated water into D-glucose 6-phosphate[2] or D-fructose 6-phosphate[3–5], and the reduction of sodium D-*arabino*-hexulosonate with lithium borotritiide[6]. In each case, careful separation of the compound having the required *gluco*-configuration is necessary from structural isomers or stereoisomers that are produced concomitantly. Brief reports[7–9] of high stereoselectivity exhibited in reductions of certain α-D-*arabino*-hexopyranosid-2-ulose derivatives prompted the development of a simple, non-enzymic synthesis for D-glucose and its derivatives labelled with deuterium at C-2, starting from the readily available[10] methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**1**).

Oxidation of **1** with methyl sulphoxide–phosphorus pentaoxide in *N*,*N*-dimethylformamide[11] gave a chromatographically homogeneous substance which appeared to be the hydrate (**2**) of methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose (**3**). Although the product had a large m.p. range and no satisfactory elemental analysis was obtained, further recrystallisations and preparative layer chromatography did not alter its physical properties. The n.m.r. spectrum indicated, unequivocally, the structure **2**, and provided no evidence for the presence of any impurities. The i.r. spectrum showed absorptions for hydroxyl groups, in addition to the expected carbonyl absorption.

Complete dehydration of **2**, to afford ketone **3**, was not achieved by repeated azeotropic removal of water with toluene. Although an absorption for hydroxyl groups in the i.r. spectrum of the glassy material so obtained was only just detectable, crystallisation of the substance from dichloromethane–light petroleum gave highly crystalline material (mainly ketone **3**) which melted over a large temperature-range. This range varied with each preparation, but at its narrowest was 54–64°. Prolonged drying of hydrate **2** *in vacuo* produced material which gave an i.r. spectrum very



1 $R^1 = H, R^2 = OH, R^3 = OBz$
2 $R^1 = R^2 = OH, R^3 = OBz$
3 $R^1 = R^2 = O, R^3 = OBz$
4 $R^1 = D, R^2 = R^3 = OH$
5 $R^1 = Me, R^2 = R^3 = OH$



6 $R^1 = H, R^2 = OMe, R^3 = H$
7 $R^1 = H, R^2 = OMe, R^3 = Ac$
8 $R^1 = OAc, R^2 = H, R^3 = Ac$

similar to that of this crystalline material, and which had an elemental analysis close to that expected for **3**.

Collins and his co-workers[12] reported the preparation of **3**, having m.p. 51–52°, by the oxidation of **1** with methyl sulphoxide–dicyclohexylcarbodi-imide[13]. Their n.m.r. data for this compound agree well with the corresponding data for the dehydration product of **2** prepared in this work. In this laboratory, repetition of the described[12] preparation of **3** afforded material having i.r. and n.m.r. spectra indistinguishable from those of the compound obtained *via* the oxidation of **1** with methyl sulphoxide–phosphorus pentaoxide, and similar melting-point behaviour was observed. It is concluded that the complete dehydration of **2** proceeds only with difficulty, and that the hydration of **3** does not occur stoichiometrically.

Reduction of hydrate **2** with sodium borodeuteride in ethanol solution gave an immediate precipitate of the 3-benzoate, which was debenzoylated to afford methyl 4,6-*O*-benzylidene-α-D-glucopyranoside-*2-C-d* (**4**) in 69% overall yield. Catalytic hydrogenolysis of **4** gave methyl α-D-glucopyranoside-*2-C-d* (**6**), in which the extent of deuterium incorporation was shown to be not less than 96% by examination of the mass spectrum of the tetra-*O*-acetyl derivative **7**. Hydrolysis of the glycoside **6** gave D-glucose-*2-C-d*, which was characterised as its penta-acetate **8**.

The high stereoselectivity of the reduction prompted an investigation into the stereochemistry of the reaction of **3** with a Grignard reagent. Treatment of **3** with six molar equivalents of methylmagnesium iodide in ether, with isolation of the major reaction product by p.l.c., gave crystalline methyl 4,6-*O*-benzylidene-2-*C*-methyl-α-D-glucopyranoside (**5**). The configuration at C-2 in **5** was ascertained by measurement of the circular dichroism (c.d.) spectrum of a solution containing equal amounts of the diol and tris(dipivalomethanato)praseodymium[14]. The positive extremum of the c.d. curve at 315 nm indicated the *gluco* configuration of the product; the *manno* isomer would be expected to give a curve having a negative extrenum at this wavelength.

EXPERIMENTAL

Preparative layer chromatography was performed on Kieselgel PF_{254}. N.m.r. spectra were measured with Varian HA-100 or Perkin-Elmer R-12 instruments

(Me_4Si as internal standard). Rotations were measured at ambient temperature with a Perkin-Elmer 141 polarimeter. The c.d. spectrum was measured with a Cary 61 Spectropolarimeter. Light petroleum refers to the fraction having b.p. 60–80°.

Oxidation of methyl 3-O-benzoyl-4,6-O-benzylidene-α-D-glucopyranoside (**1**) *with methyl sulphoxide-phosphorus pentaoxide.* — A solution of **1**[10] (10.6 g) in a mixture of *N,N*-dimethylformamide (300 ml) and methyl sulphoxide (9 ml) containing phosphorus pentaoxide (14.4 g) was stirred at room temperature for 12 h, and then heated in an oil bath at 70° for 6 h. Addition of the reaction mixture to ice-water (1.5 l) afforded a crystalline solid, which was collected, washed with water, and then recrystallised from ethanol-water to afford material (mainly the hydrate **2**: 8.38 g), m.p. 91–102°, $[\alpha]_D$ −4° (*c* 0.5, ethanol); ν_{max}^{Nujol} 3500, 3240 (OH), 1760 (weak), and 1720 cm^{-1} (C=O). N.m.r. data ($CDCl_3$, 100 MHz): δ 1.90 (br, 2 OH), 3.53 (s, OMe), 3.70–4.60 (complex m, H-4,5,6,6'), 4.84 (s, H-1), 5.58 (s benzylic-H), 6.01 (d, $J_{3,4}$ 10 Hz, H-3), 7.20–7.70 and 8.00–8.20 (complex m, Ar-*H*).

An acceptable elemental analysis could not be obtained on this material. On t.l.c. (toluene-ethyl acetate, 9:1: three developments), it was homogeneous (R_F 0.36: **1** had R_F 0.21). Neither repeated recrystallisation nor p.l.c. of the material produced an elevation or narrowing of the melting range, and although intensive drying (80° *in vacuo* over P_2O_5) produced no systematic change in m.p., it caused a significant decrease in the intensities of the i.r. bands for OH, and a marked increase in the intensity of the C=O band at 1760 cm^{-1}. Elemental analysis of dried material was consistent with its being mainly the ketone **3**.

Anal. Calc. for $C_{21}H_{22}O_8$: C, 62.7; H, 5.5. Found: C, 62.2; H, 5.6.

Repeated evaporation of toluene from a sample of the oxidation product (m.p. 91–102°) gave a thick syrup which was reconverted into the original, crystalline material on the addition of water. Crystallisation of the syrup from dichloromethane-light petroleum afforded material having m.p. 54–64°; ν_{max}^{Nujol} 3600–3100 (very broad and weak), 1760, and 1720 cm^{-1} (C=O). N.m.r. data ($CDCl_3$, 60 MHz): δ 3.38 (s, OMe), 3.70–4.60 (complex m, H-4,5,6,6'), 4.76 (s, H-1), 5.50 (s, benzylic-H), 6.01 (d, $J_{3,4}$ 10 Hz, H-3), 7.10–7.60 and 8.00–8.30 (complex, Ar-*H*). Collins and his co-workers[12] reported m.p. 51–52°, $[\alpha]_D$ −18° (*c* 0.5, ethanol), and similar spectral data for **3** prepared by oxidation of **1** with methyl sulphoxide-dicyclohexylcarbodi-imide.

Oxidation of **1** with methyl sulphoxide-dicyclohexylcarbodi-imide, with crystallisation of the product from ethanol-water, gave material, m.p. 100–112°, $[\alpha]_D$ −6° (*c* 0.6, ethanol), the i.r. spectrum of which was indistinguishable from that of the material having m.p. 91–102° described above. The products of the two oxidation procedures, after azeotropic dehydration with toluene, gave indistinguishable n.m.r. spectra ($CDCl_3$ at 60 MHz).

Methyl 4,6-O-benzylidene-α-D-glucopyranoside-2-C-d (**4**). — To a solution of the crystalline oxidation product **2** (2.7 g) in 95% ethanol (25 ml), a solution of sodium borodeuteride (0.2 g) in ethanol (5 ml) was added in one portion. The solution deposited crystals immediately and, after the addition of water (10 ml), these were collected and dried *in vacuo* over phosphorus pentaoxide. The material (2.2 g), which had an R_F value identical to that of **1** (t.l.c.: toluene–ethyl acetate, 4:1), was suspended in methanol (50 ml), and sodium (0.02 g) was added; dissolution of the solid occurred during 15 min. After 65 h at room temperature, solid carbon dioxide was added to the mixture, and the residue obtained on concentration of the solution was triturated with light petroleum. Crystallisation of the resulting solid from ethyl acetate–light petroleum gave **4** (1.3 g, 69% based on **2**), m.p. 167–169°, $[\alpha]_D$ +105° (*c* 0.2, chloroform): lit.[15] for the unlabelled compound, m.p. 163–164°, $[\alpha]_D$ +110° (*c* 2, chloroform). The n.m.r. spectrum of **4** in $(CD_3)_2CO$ was similar to that of the undeuterated compound, but the signal for H-1 was a singlet at δ 4.7 instead of the doublet at δ 4.7 ($J_{1,2}$ 4 Hz) observed in the latter case.

Methyl α-D-glucopyranoside-2-C-d (**6**). — A solution of **4** (0.96 g) in methanol (20 ml) containing one drop of trifluoroacetic acid was stirred under hydrogen in the presence of palladium–charcoal (0.14 g) for 4 h. After filtration through kieselguhr, the solution was concentrated, and the residue was crystallised from ethanol at 4° to give **6** (0.56 g, 85%), m.p. 169–171°. The n.m.r. spectrum in D_2O was similar to that of undeuterated compound, but H-1 appeared as a singlet at δ 4.78, instead of a doublet at δ 4.79 ($J_{1,2}$ 4 Hz) in the latter case.

Treatment of **6** with acetic anhydride in pyridine afforded the tetra-acetate **7**, m.p. 102–103°. In the mass spectrum of **7**, the peak of highest *m/e* value was at 332 (M – OMe). The ratio of intensities of peaks at *m/e* 332 and 331 indicated that **7** was ≥96% monodeuterated.

Penta-O-acetyl-β-D-glucopyranose-2-C-d (**8**). — A solution of **6** (0.2 g) in 0.5M hydrochloric acid was heated under reflux for 13 h. After neutralization with Amberlite IR-45 (HO^-) ion-exchange resin (5 ml), the solution was concentrated, and water was removed from the residue by azeotropic distillation with absolute ethanol. The solid was dissolved in the minimum quantity of water, absolute ethanol (4 ml) added, and the solution was seeded with D-glucose. After 1 week, the crystals (0.12 g) were collected, and acetylated with acetic anhydride–sodium acetate to afford, after two recrystallisations from ethanol, **8** (0.07 g), m.p. 130–132°. N.m.r. data ($CDCl_3$, 100 MHz): δ 1.99, 2.01 (×2), 2.06, 2.09 (4 s, OAc), 3.70–3.94 (m, H-5), 3.96–4.40 (complex m, H-6,6′), 4.96–5.34 (m, H-3,4), and 5.7 (s, H-1). The n.m.r. spectrum in $CDCl_3$ was similar to that of the undeuterated compound[10]: in the latter case, the signal for H-1 is a doublet at δ 5.76 ($J_{1,2}$ 6.9 Hz).

Methyl 4,6-O-benzylidene-2-C-methyl-α-D-glucopyranoside (**5**). — The crystalline oxidation product **2** (1.3 g) was dehydrated by azeotropic removal of water with toluene (5 × 30 ml). A solution of the resulting syrup in ether (50 ml) was added during 1 h, with stirring, to an ethereal solution of methylmagnesium iodide, prepared from magnesium (0.49 g), methyl iodide (1.3 ml), and ether (11 ml). After 12 h, water (2 ml) was added and the ether was evaporated under reduced pressure. Chloroform (75 ml) and water (75 ml) were added, the mixture was filtered through kieselguhr, and the chloroform layer was dried (Na_2SO_4) and concentrated. T.l.c. (ethyl acetate–toluene, 1:1) indicated a major reaction product (R_F 0.2) which was then isolated by p.l.c. Crystallisation of the syrup (0.59 g) from ethyl acetate–light petroleum gave material (0.4 g) which, after two further recrystallisations, gave **5**, m.p. 156–158°, $[\alpha]_D$ +80° (*c* 0.3, chloroform). N.m.r. data ($CDCl_3$, 100 MHz): δ 1.31 (s, C-Me), 2.50–2.70 (br, 2 OH), 3.40 (s, OMe), 3.45–4.34 (complex m, H-3,4,5,6,6′), 4.42 (s, H-1), 5.50 (s, benzylic-H), and 7.20–7.60 (m, Ar-*H*).

Anal. Calc. for $C_{15}H_{20}O_6$: C, 60.8; H, 6.8. Found: C, 60.6; H, 6.7.

The c.d. spectrum of a solution of **5** (3 mg) in carbon tetrachloride (100 ml) containing tris(dipivalomethanato)praseodymium (7 mg) had $\Delta\varepsilon$ +0.73 at 315 nm.

A solution of the dibenzoate of **5** in methanol gave a c.d. spectrum with $\Delta\varepsilon$ +18.13 at 235 nm, confirming[17] the *gluco* configuration.

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