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Note

Reaction of 1,2-*O*-isopropylidene-α-D-glucofuranose and some of its derivatives with diazomethane–stannous chloride: synthesis of 3,5-di-*O*-methyl- and 5-*O*-methyl-D-glucose derivatives

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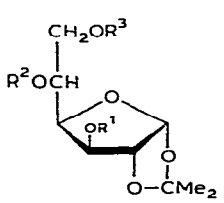
Earlier studies of the partial methylation of glycosides[1–3] and nucleosides[4–6] with diazomethane in the presence of a catalytic amount of stannous chloride dihydrate showed that the reagent exhibits remarkably high specificity towards certain hydroxyl groups. Intramolecular hydrogen-bonding has been suggested as a probable influence[2]. As part of further studies of the selective methylation, 1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) and some of its derivatives have been treated with the reagent, leading to simplified syntheses of 3,5-di-*O*-methyl-D-glucose (**2**), 5-*O*-methyl-D-glucose (**3**), and some derivatives thereof. The ethers **2** and **3**, and their derivatives, have been synthesised previously[7–16], but by more-tedious routes.

Treatment of **1** in methanol–dichloromethane with excess of diazomethane in the presence of stannous chloride dihydrate yielded a syrupy product. T.l.c. (ether) indicated the presence of two compounds, in addition to some unreacted **1**. Column chromatography on silica gel yielded syrupy 1,2-*O*-isopropylidene-3,5-di-*O*-methyl-α-D-glucofuranose (**4**, 21%) and crystalline 1,2-*O*-isopropylidene-5-*O*-methyl-α-D-glucofuranose (**5**, 56%). Compound **4** failed to yield the reported[9] crystalline *p*-phenylazobenzoate and was characterised as the *p*-nitrobenzoate **6**. It was further characterised by mild hydrolysis with acid, to give syrupy **2** that was converted into the known phenylosazone **7**. There was no apparent formation of the reported[10] 1,6-anhydride of **2** under the conditions of hydrolysis.

Compound **5** yielded the crystalline diacetate **8** on treatment with acetic anhydride–pyridine. Acid hydrolysis of **5** gave syrupy **3**, which gave a crystalline *N*-benzyl-*N*-phenylhydrazone **9**.



1 $R^1 = R^2 = R^3 = H$
4 $R^1 = R^2 = Me, R^3 = H$
5 $R^1 = R^3 = H, R^2 = Me$
6 $R^1 = R^2 = Me, R^3 = p$-nitrobenzoyl
8 $R^1 = R^3 = Ac, R^2 = Me$
10 $R^1 = Me, R^2 = R^3 = H$

Similar methylation of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (**10**) with the reagent yielded 61 % of **4**, following column chromatography.

No reaction was observed between compound **5**, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, or 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose and the reagent, showing that isolated hydroxyl groups cannot be methylated by this method. Previous results showed that primary hydroxyl groups of glycosides[1] and nucleosides[4-6] do not react under these conditions.

The foregoing results indicate that a vicinal-diol system, or a system of two hydroxyl groups of sufficiently close proximity to form a disubstituted complex with the catalyst, is a requirement for the reaction. For compound **1**, HO-5,HO-6 and HO-3,HO-5 both fulfil this requirement. An intermolecular complex is unlikely from the foregoing results. The orientation of the hydroxyl groups is also an important factor, since the trans-diaxial diol groups of methyl 4,6-*O*-benzylidene-α-D-altropyranoside and the corresponding α-D-idopyranoside failed to react, presumably due to the unfavorable spatial disposition of the two hydroxyl groups[17].

It is difficult to explain the greater selectivity of HO-5 in compound **1** towards methylation on the basis of intramolecular hydrogen-bonding[2]. In **1**, the HO-3 group is exo to the *cis*-fused, furanose–dioxolane ring-system and is consequently unfavorably situated to form an intramolecular hydrogen-bond with O-2. The relative acidities of the hydroxyl groups participating in the complex probably determine the site of methylation. Initial attack at HO-5 in compound **1** yields **5**, with residual hydroxyl groups at C-3 and C-6 which cannot undergo complex formation and are, in effect, "isolated groups". Methylation of HO-3 in **1** gives **10**, with a diol system at C-5 and C-6, which can react further to yield **4**.

There have been few studies of the reaction of alcohols, especially diols, with tin(II) chloride in non-aqueous media[18-21]. The products are very reactive towards air and moisture. The reaction of a number of monosaccharide derivatives with tin(II) chloride is currently under investigation. In 2',3'-*O*-(dibutylstannylene)ribonucleosides, the dibutylstannylene group activates the 2'- and 3'-oxygen atoms in acylation and alkylation reactions[22]. These derivatives are unusually stable tin(IV) derivatives.

EXPERIMENTAL

I.r. spectra were determined as Nujol mulls. Kieselgel 60 (Merck) was used for column chromatography, and silica-gel plates (Merck DC Fertigplatten) were used for analytical t.l.c.; compounds were detected by charring with sulphuric acid. Dichloromethane was redistilled from phosphorus pentaoxide before use. Evaporations were carried out at 40° *in vacuo*.

Reaction of diazomethane–stannous chloride dihydrate. — (*a*) *With 1,2-O-isopropylidene-α-D-glucofuranose* (**1**). A solution of **1** (5.0 g) in methanol (200 mL) and dichloromethane (120 mL) containing stannous chloride dihydrate (20 mg) was cooled to –10° and treated with a solution of diazomethane [from *N*-nitrosomethyl urea[23] (20 g)]. The mixture was stirred at room temperature overnight; t.l.c. (ether)

then indicated the presence of two major components in addition to **1**. The solvent was evaporated and a solution of the residue in ether was chromatographed on silica gel (65 g). Elution with ether gave 1,2-*O*-isopropylidene-3,5-di-*O*-methyl-α-D-glucofuranose (**4**; 1.17 g, 21%), $[\alpha]_D^{23}$ –25° (*c* 11.7, chloroform); lit.[10] $[\alpha]_D^{20}$ –26.6° (ethanol). Continued elution with ether gave 1,2-*O*-isopropylidene-5-*O*-methyl-α-D-glucofuranose (**5**; 2.95 g, 56%), m.p. 69–71°, $[\alpha]_D^{23}$ –13° (*c* 8, chloroform); lit.[11] m.p. 71–72°; lit.[13] $[\alpha]_D$ –13.1° (chloroform). Subsequent elution with dichloromethane gave **1** (0.65 g), m.p. 158–160° (from ethyl acetate), $[\alpha]_D$ –11.5° (water); lit.[24] m.p. 159–161°, $[\alpha]_D$ –11.8° (water). Treatment of **4** with *p*-nitrobenzoyl chloride in pyridine, in the usual manner, gave the *p*-nitrobenzoate **6**, m.p. 124–126° (from methanol), $[\alpha]_D^{23}$ –20.5° (*c* 2.8, chloroform); lit.[10] m.p. 125–126°, $[\alpha]_D^{20}$ –21.3° (chloroform).

With acetic anhydride–pyridine in the usual manner, **5** gave the diacetate **8**, m.p. 85–87° [from light petroleum (b.p. 60–80°)], $[\alpha]_D^{23}$ –14.8° (*c* 2.7, chloroform); lit.[13] m.p. 87°, $[\alpha]_D$ –15.2° (chloroform).

(*b*) *With* 1,2-O-*isopropylidene*-3-O-*methyl*-α-D-*glucofuranose* (**10**). A solution of compound **10** (2.0 g) in methanol (100 mL) and dichloromethane (50 mL) containing stannous chloride dihydrate (5 mg) was treated with diazomethane as described in (*a*). Chromatography of the syrupy product on silica gel (30 g), with ether as eluant, gave compound **4** (1.28 g, 61%), $[\alpha]_D^{23}$ –24.5° (*c* 5.1, chloroform); lit.[10] $[\alpha]_D^{20}$ –26.6° (ethanol).

3,5-*Di*-O-*methyl*-D-*glucose* (**2**). — A solution of compound **4** (1.0 g) in acetic acid (10 mL), water (1 mL), and trifluoroacetic acid (1 mL) was kept at room temperature for 3.5 h; t.l.c. (ether) then indicated the absence of **4**. Evaporation of the solvents, followed by distillation of methanol (2 × 15 mL) from the residue, afforded **2** (0.82 g, 98%), $[\alpha]_D^{23}$ –20° (*c* 6, water); lit.[8–10] $[\alpha]_D$ –20° (water); lit.[7] $[\alpha]_D^{24}$ –21.3°.

A solution of **2** (0.2 g), sodium hydrogensulphite (0.2 g), and phenylhydrazine (2 mL) in 20% aqueous acetic acid (8 mL) was heated for 3 h on a boiling water-bath. The mixture was cooled in ice–water and diluted with water (5 mL), and the precipitated product was filtered off and recrystallised from aqueous ethanol, yielding 3,5-di-*O*-methyl-D-*arabino*-hexosulose bis(phenylhydrazone) (**7**, 90 mg), m.p. 81–84°, $[\alpha]_D^{23}$ –84.5° (*c* 0.8, methanol); lit.[10] m.p. 82–85°, $[\alpha]_D^{20}$ –86° (ethanol).

5-O-*Methyl*-D-*glucose* (**3**). — A solution of compound **5** (1.5 g) in acetic acid (8 mL), water (4 mL), and trifluoroacetic acid (2 mL) was kept at room temperature for 3 h. Evaporation of the solvents, followed by distillation of methanol (2 × 25 mL) from the residue, afforded **3** as a gum (1.19, 96%), $[\alpha]_D^{23}$ –11.5° (*c* 4.2, water); lit.[13] $[\alpha]_D$ –10.6°.

The product was dissolved in water (10 mL) and treated with *N*-benzyl-*N*-phenylhydrazine hydrochloride (1.5 g). The mixture was heated with stirring for 20 min at 100 °C, with dropwise addition of ethanol to give a homogeneous mixture. The mixture was then cooled, and the crystalline product was collected by filtration, washed with cold ether, dried *in vacuo* (P_2O_5), and recrystallised from benzene to give 5-*O*-methyl-D-*arabino*-hexosulose *N*-benzyl-*N*-phenylhydrazone (**9**; 1.71 g, 71%),

m.p. 149–151°, $[\alpha]_D^{23}$ –14° (*c* 4, methanol); lit.[14] m.p. 151–152.5°, $[\alpha]_D^{20}$ –14.2 ±1° (methanol).

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