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The Preparation of 2-Tetrahydropyranyl β-D-Glucopyranosides and Methyl 4-*O*-(2-Tetrahydropyranyl)-β-D-Glucopyranosides

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Dedicated to Professor *Holger Erdtman* on his 60th birthday

The preparations of the two isomeric 2-tetrahydropyranyl β-D-glucopyranosides and the two isomeric 4-*O*-(2-tetrahydropyranyl)-β-D-glucopyranosides and their polyacetates are described.

Although the reaction of dihydropyran with aliphatic and aromatic alcohols has previously been described by Parham and Anderson [1] this reaction has received little attention in the protection of hydroxyl groups in carbohydrates. Each tetrahydropyran group introduced in the molecule gives rise to an additional asymmetric carbon atom and when several hydroxyl groups are reacted this leads to complex mixtures. Dihydropyran has been used to protect hydroxyl groups in ribonucleotide synthesis [2,3] at an intermediate stage without separating the resulting stereoisomers. Amorphous 2-tetrahydropyranyl derivatives were obtained.

The present paper describes the syntheses of the two 2-tetrahydropyranyl β-D-glucopyranosides and the two methyl 4-*O*-(2-tetrahydropyranyl)-β-D-glucopyranosides. The tetrahydropyran groups are stable in alkaline media but are removed under mild acid conditions, and these substances were desired for partial substitution studies.

The two 2-tetrahydropyranyl β-D-glucosides were prepared by reacting 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (I) with dihydropyran in either acetone or in chloroform solution with hydrochloric acid present as catalyst.

The two isomeric tetraacetates (IIIA and IIIB) could be separated from the crystalline reaction product by fractional crystallisation, by paper chromatography on dimethyl sulphoxide impregnated paper [4] and by chromatography on a silicic acid-dimethyl sulphoxide column [5].

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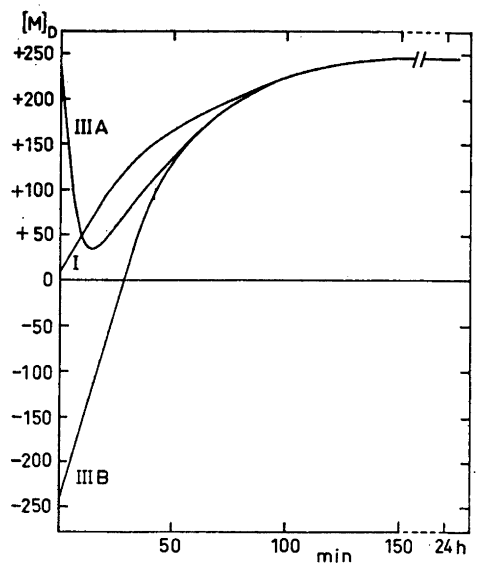


Fig. 1. The rate of hydrolysis in 0.5 N hydrochloric acid in 80 % aqueous acetone at room temperature of (+), IIIA and (−), IIIB, 2-tetrahydropyranyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosides and the rate of mutarotation of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose under the same conditions.

The infrared spectra of the two acetates, using the potassium bromide pellet technique, showed absorption at 905 cm^{-1} as expected for β-D-glucopyranosides and none in the region expected for the α-D-glucopyranosides [6].

The rate of hydrolysis followed by the change in optical rotation of the two isomeric acetates in 0.5 N hydrochloric acid in 80 % aqueous acetone at room temperature is shown in Fig. 1. From this it appears that the (+), IIIA, isomer is hydrolysed faster than the (−), IIIB isomer. The first-order rate-constants under these conditions were approximately 3×10^{-1} (min^{-1}) for IIIA and 3.4×10^{-2} (min^{-1}) for IIIB. The first-order rate-constant for the mutarotation of I under the same conditions was 1.9×10^{-2} (min^{-1}). The hydrolysis curves indicate that both isomers are β-D-glucosides, the initial rapid hydrolysis being followed by a slower mutarotation of the resulting 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose.

The two acetates were deacetylated to yield the two isomeric 2-tetrahydropyranyl β-D-glucosides, of which only the (−) rotating isomer was crystalline. Both deacetylated isomers were cleaved by emulsin as expected for β-D-glucosides.

The two glucosides were easily hydrolysed by N sulphuric, N hydrochloric and 50 % aqueous acetic acid at room temperature in less than 30 min. Some hydrolysis occurred in aqueous solution at pH 5 after a few days.

A paper-chromatographic examination of the reaction of dihydropyran with an equilibrium mixture of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose in aci-

dic solutions of acetone and chloroform, respectively, indicated that the β-form reacted rapidly but the α-form slowly or not at all, and no α-glucosides were found in the reaction mixture. This may indicate a significant difference in reactivity of axial and equatorial hydroxyl groups towards dihydropyran.

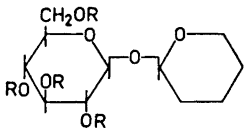
Dihydropyran reacted in the presence of an acid catalyst with methyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside to give an isomeric mixture of methyl 2,3,6-tri-*O*-acetyl-4-*O*-(2-tetrahydropyranyl)-β-D-glucopyranosides (VA and VB). The two isomers could be separated from this mixture by fractional crystallisation albeit in low yield. The (+) rotating isomer separated first and the (−) rotating isomer was obtained by crystallisation of the mother-liquors.

The acetates were deacetylated by shaking overnight with a strong anion-exchange resin, in 95 % ethanol. Both isomeric forms of methyl 4-*O*-(2-tetrahydropyranyl)-β-D-glucopyranoside were hygroscopic and had low diffuse melting points.

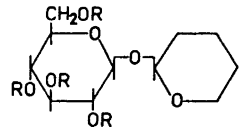
The position of the tetrahydropyranyl group was confirmed by methylation studies. Only glucoses methylated in the 2-, 3- and 6-positions, but not in the 4- position, were found after methylation and hydrolysis.

The tetrahydropyranyl group was very acid labile and was removed in about 20 min. by 0.0125 N sulphuric acid at 23°. The first-order rate-constants for both the isomers under these conditions were the same, *i.e.* 1.3×10^{-1} (min^{-1}).

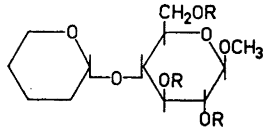
The physical constants of the acetylated tetrahydropyranyl derivatives are shown in Table 1. For each pair of derivatives the difference in optical rotation between the isomers is of the same order of magnitude as that for anomeric pairs of glycosides. A determination of the absolute configuration of the tetrahydropyranyl residue would be most difficult. It seems reasonable, however, to assign to the more dextrorotatory isomers the absolute configuration of α-D (β-L) glycosides and the less dextrorotatory the configuration of the β-D (α-L) glycosides.



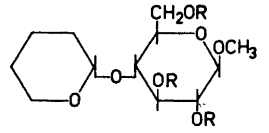
III A: R = −COCH3
IV A: R = −H



III B: R = −COCH3
IV B: R = −H



VA: R = −COCH3
VIA: R = −H



V B: R = −COCH3
VI B: R = −H

Table 1.

Substance	M.p.	$[\alpha]_D^{20}$	$[M]_D$
IIIA	137–138°	+63°	+272°
IIIB	109–111°	−62°	−268°
VA	110–111°	+12°	+ 48.5°
VB	89–90°	−76°	−307°

EXPERIMENTAL

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranose (I) was prepared according to McCloskey and Coleman [7] and methyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (II) according to the method by Levene and Raymond [8]. Dihydropyran was distilled over sodium, b.p. 84–86°.

Evaporations were performed at reduced pressure at a bath temperature below 40°. All melting points are corrected.

Chromatography. Paper: Whatman No. 1. Solvents: 1. Isopropyl ether-light petroleum (40–60°), 1:1 (on dimethyl sulphoxide-impregnated paper [4]). 2. Water-saturated methyl ethyl ketone. 3. Butanol-ethanol-water 10:3:5.

Paper electrophoresis. Paper: Whatman No. 1. Buffers: 0.1 M borate at pH 10 [9], 0.05 M germanate at pH 10 [10]. Spray reagents: Anisidine hydrochloride, silver nitrate and sodium hydroxide.

2-Tetrahydropyranyl β-D-glucopyranosides

*Preparation of 2-tetrahydropyranyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosides. (IIIA and IIIB).* A solution of the tetraacetate I (15 g), dihydropyran (90 ml) and 37 % hydrochloric acid (3 ml) in dry acetone (40 ml) was allowed to stand for 3 h at room temperature, neutralised with sodium hydrogen carbonate, dried over calcium chloride and filtered Concentration to a small volume and addition of ethanol gave crystals (12 g) m.p. 103–105°, $[\alpha]_D^{20}$ 0° (*c*, 1.0 in chloroform). Paper chromatography in solvent 1 gave two spots corresponding to the two isomeric 2-tetrahydropyranyl β-D-glucoside tetraacetates. After several recrystallisations from ethanol, crystals of IIIA were obtained, m.p. 137–138° $[\alpha]_D^{20}$ + 63° (*c*, 1.0 in chloroform). This was the slower-moving compound on paper chromatography in solvent 1.

In another experiment, I (10 g) and dry dihydropyran (10 ml) in anhydrous chloroform (10 ml) containing 0.4 % hydrogen chloride gas was allowed to stand 72 h and worked up as described above. By recrystallisation of the crystalline product a good yield (4.8 g) of almost pure IIIB with m.p. 105–110° and $[\alpha]_D^{20}$ −62° (*c*, 1 in chloroform) was obtained.

The result of the fractional crystallisations is possibly unpredictable and the fact that the above experiments yielded different isomers as pure products may be fortuitous. Better yields of each of the two isomers are obtained by column chromatography.

A silicic acid column (silicic acid, Mallinckrodt AR, 100 mesh, 3 × 28 cm) was prepared according to Lindberg and Wickberg [5] and the mixture (1 g) of the two isomers, from the reaction conducted in acetone solution, was fractionated using solvent 1. IIIB was eluted first (0.35 g) m.p. 109–111°, $[\alpha]_D^{20}$ −62° (*c*, 1.0 in chloroform) after recrystallisation from ethanol, then a mixed fraction which contained both isomers and finally IIIA (0.30 g) with m.p. 137–138° and $[\alpha]_D^{20}$ + 63° (*c*, 1.0 in chloroform) after recrystallisation from ethanol. (IIIA: Found: C 53.0; H 6.60; O 40.5. IIIB: Found: C 52.6; H 6.47; O 41.1. Calc. for $C_{19}H_{28}O_{11}$: C 52.77; H 6.52; O 40.70.)

2-Tetrahydropyranyl β-D-glucopyranosides (IVA and IVB). The acetates were deacetylated in methanolic solutions containing 1.67 % ammonia at room temperature overnight [11]. The solutions were concentrated to dryness. By crystallisation from acetone,

crystals of the glucoside IVB (from IIIB) were obtained with m.p. 176–178°, $[\alpha]_D^{20}$ −110° (*c* 1.0 in water) after recrystallisation from ethanol. (Found: C 50.2; H 7.48; O 42.3. Calc. for $C_{11}H_{20}O_7$: C 49.99; H 7.63; O 42.38.)

The isomer IVA from the acetate IIIA had $[\alpha]_D^{20}$ + 37° (*c*, 1.0 in water) and did not crystallise.

On paper chromatography in solvent 2, IVA had R_F 0.11 and IVB R_F 0.13, on paper electrophoresis in borate[9] IVA had M_G 0.13 and IVB M_G 0.15.

Enzyme hydrolysis. The enzymolyses were conducted in 2 % aqueous solutions buffered at pH 5 and at 25°. The paper chromatograms were run in solvent 3. IVA and IVB and methyl β-D-glucopyranoside were cleaved by emulsin whereas methyl α-D-glucopyranoside was unchanged. Blanks of IVA and IVB in the same buffer containing no enzyme remained mostly unchanged.

A paper chromatographic examination of the reaction of dihydropyran with equilibrated 2,3,4,6-tetra-O-acetyl-D-glucopyranose. The tetraacetate I (2 g) in chloroform containing a few drops 37 % hydrochloric acid was allowed to stand until completely equilibrated, $[\alpha]_D^{20}$ + 80° (*c*, 10.0 in chloroform) (approximately 1 h), neutralised with silver oxide, filtered and separated into two equal volumes which were concentrated to dryness. The reaction with dihydropyran was carried out in acetone and in chloroform solution, respectively, as described above. Samples were withdrawn at intervals and after neutralisation with silver oxide examined by paper chromatography on dimethyl sulphoxide impregnated paper using ethyl ether as solvent. This gave complete separation of 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-glucopyranose with negligible trailing due to mutarotation. The products of the reaction were examined by paper chromatography in solvent 1. It was found that only the α-form of the starting material remained, after 4 h in the experiment conducted in acetone and after 24 h in that conducted in chloroform. Approximately equal amounts of the two tetrahydropyranyl derivatives IIIA and IIIB were formed.

Methyl 4-*O*-(2-tetrahydropyranyl)-β-D-glucopyranosides

Methyl 2,3,6-tri-O-acetyl-4-O-(2-tetrahydropyranyl)-β-D-glucopyranosides. (VA and VB). The triacetate II (1.0 g), dihydropyran (3 ml) and 37 % hydrochloric acid (1 drop) were shaken together for 8 h when no solid material remained. The reaction mixture was diluted with acetone (10 ml), neutralised with silver oxide, concentrated and crystallised from ether-light petroleum (40–60°) overnight to give the mixed isomers VA and VB (0.8 g). Recrystallisation from the same solvent gave the 4-*O*-tetrahydropyranyl derivative VA (0.25 g) m.p. 110–111°, $[\alpha]_D^{20}$ + 12° (*c*, 8.0 in chloroform). (Found: C 53.0; H 6.85. Calc. for $C_{18}H_{28}O_{10}$: C 53.47; H 6.97.) The mother-liquors from above after two recrystallisations from ether-light petroleum (40–60°) yielded the tetrahydropyranyl derivative VB (0.15 g) m.p. 89–90°, $[\alpha]_D^{20}$ −76° (*c*, 0.8 in chloroform). (Found: C 53.2; H 6.77; OCH_3 7.56. Calc. for $C_{18}H_{28}O_{10}$: C 53.47; H 6.97; OCH_3 7.67).

Methyl 4-O-(2-tetrahydropyranyl)-β-D-glucopyranosides. (VIA and VIB). Dowex resin (2-X8 OH^-) was washed with water and then alcohol (95 %). The acetate VA (1.0 g) was shaken with the resin (about 10 g) in ethanol (95 %, 30 ml) overnight. The solution was

Table 2. Rates of hydrolysis of the glucosides VIA and VIB in 0.0125 N sulphuric acid at 23°.

VIA

t (min)	2	4	6	8	10	12	14
$a°_t$	+ 0.16	+ 0.01	−0.06	−0.12	−0.16	−0.19	−0.21
$\log_{10}(a_t - a\infty)$	0.35	0.52	0.64	0.77	0.89	1.00	1.10

VIB

t (min)	3	4	5	6	7	8	9
$a°_t$	−1.74	−1.60	−1.51	−1.43	−1.37	−1.31	−1.26
$\log_{10}(a_t - a\infty)$	0.11	0.20	0.27	0.34	0.40	0.47	0.54

filtered and the resin washed thoroughly with water (made slightly alkaline with ammonia) and then with alcohol. The filtrate and washings were combined and concentrated to give a syrup which crystallised overnight from ethanol-hexane to give needles of the glucoside VIA. This compound was hygroscopic and gave a diffuse m.p. 42—50°, $[\alpha]_D^{20}$ + 39° (*c*, 2.0 in water). (Found: C 52.1; H 8.28. Calc. for $C_{13}H_{22}O_7$: C 51.80; H 7.97.)

The procedure was repeated with the acetate VB to give the glucoside VIB which was also hygroscopic and showed a diffuse m.p. 35—45°, $[\alpha]_D^{20}$ —52° (*c*, 1.2 in water). (Found: C 50.9; H 8.05. Calc. for $C_{13}H_{22}O_7$: C 51.80; H 7.97.)

Rate of hydrolysis of the glucosides. (VIA and VIB). The glucoside (about 0.2 g) was dissolved in water (5 ml). 0.025 N sulphuric acid (5 ml) was added and the rate of hydrolysis followed polarimetrically (Table 2).

Methylations. The glucosides VIA and VIB were methylated in sodium hydroxide with dimethyl sulphate. The products were worked up and hydrolysed as described by Croon [12] and the hydrolysates fractionated by carbon column chromatography. The methyl ethers of glucose were identified by germanate and borate electrophoresis and by paper chromatography in solvents 2 and 3.

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