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ACID-CATALYSED HYDROLYSIS OF 1,2-*O*-ALKYLIDENE-α-D-GLUCOFURANOSES

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ABSTRACT

The rates of acid-catalysed hydrolysis of 1,2-*O*-alkylidene-α-D-glucofuranoses indicate that, for oligosaccharide synthesis, cyclopentylidene and cycloheptylidene acetals are better protecting groups than the isopropylidene residue Hydrolysis was impeded by a nitrate group at position 5 and more so by one at position 3 The hydrolyses were accompanied by a positive drift in optical rotation, except for the 5-*O*-substituted compounds where the formation of D-glucopyranose derivatives cannot occur

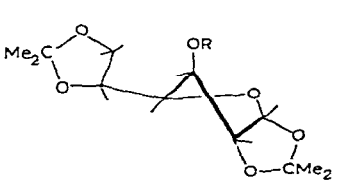
INTRODUCTION

1,2-O-Isopropylidene-α-D-glucofuranose derivatives have been used in the synthesis of (1→3)-[1–5], (1→5)-[1 3 6 7], and (1→6)-linked[8] disaccharides For the removal of the 1,2-*O*-isopropylidene group, various conditions have been described[1–6], but the yields of products never exceeded 75% In a few cases[2 4], the moderate yields of unsubstituted disaccharides have been ascribed to partial hydrolysis of the interglycosidic linkage

In synthesising (1→5)-linked disaccharides[7], quantitative removal of the protecting groups from 5-*O*-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-1,2-*O*-isopropylidene-α-D-glucofuranose by means of dilute, aqueous sulphuric acid also caused considerable rupture of the interglycosidic linkage We have therefore investigated 1,2-acetals of enhanced acid-lability

RESULTS AND DISCUSSION

Reaction of D-glucofuranurono-6,3-lactone with a mixture of *p*-dioxane, cyclopentanone, and its diethyl acetal (generated *in situ* by using triethyl orthoformate) in the presence of mesitylenesulphonic acid gave the 1,2-*O*-cyclopentylidene derivative **2a** The 1,2-*O*-cyclohexylidene (**4**) and 1,2-*O*-cycloheptylidene (**8**) derivatives were prepared in a similar manner



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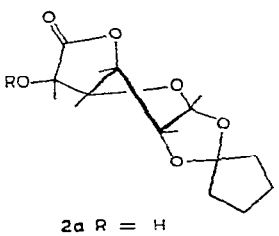
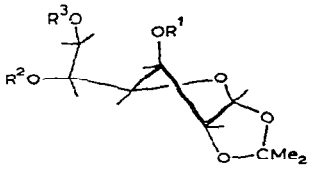
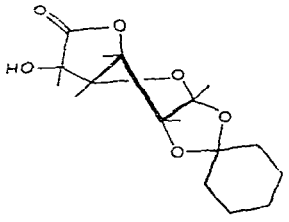
1b R = NO_2



2a R = H
2b R = NO_2



3a R^1 = H, R^2 = H, R^3 = H
3b R^1 = NO_2, R^2 = H, R^3 = H
3c R^1 = H, R^2 = β-D-Glc*p*, R^3 = H
3d R^1 = H, R^2 = α-D-Glc*p*NAc, R^3 = H



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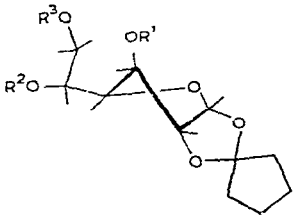
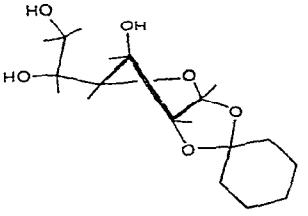


5a R^1 = H, R^2 = H R^3 = H
5b R^1 = H R^2 = NO_2 R^3 = H



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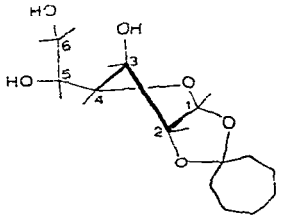

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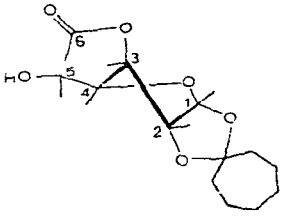

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Reduction of **2a**, **4**, and **8** with borane in tetrahydrofuran gave the corresponding 1,2-*O*-cyclopentylidene (**5a**), 1,2-*O*-cyclohexylidene (**6**), and 1,2-*O*-cycloheptylidene (**7**) derivatives of α-D-glucofuranose as the main products

Since reductive cleavage of 1,3-dioxolanes to hydroxyethers by the borane–tetrahydrofuran complex can occur[9], the identities of **5a**, **6**, and **7** were confirmed by ^{1}H-n m r spectroscopy (Table I) In methyl sulphoxide-d_6, the hydroxylic protons gave sharp doublets (HO-3 and HO-5) and triplets or quartets (HO-6), which disappeared on deuterium exchange Compound **6** has been prepared previously by an alternative route[10].

Methanolysis of **5a**, **6**, and **7** gave glucose only (g l c -analysis[11]) T l c. of the mother liquors revealed other components which were not further investigated.

Treatment of **2a** with acetyl nitrate afforded 1,2-*O*-cyclopentylidene-α-D-glucofuranurono-6,3-lactone 5-nitrate (**2b**), which was reduced with borane in tetrahydrofuran to give 1,2-*O*-cyclopentylidene-α-D-glucofuranose 5-nitrate (**5b**) The structures

TABLE I

^{1}H-NMR (90 MHz, Me_2SO-d_6) DATA FOR 1,2-*O*-ALKYLIDENE DERIVATIVES OF α-D GLUCOFURANURONO 6,3-LACTONES AND α-D-GLUCOFURANOSE

	H-1	*H-2*	*H-3*	*H-4*	*H-5*	$J_{1,2}$[d]	$J_{3,4}$	$J_{4,5}$	*HO-5*	*Alkylidene*
2a	5 95	4 70	4 78	4 88	4 50	3 7	3 1	4 4	3 5	1 6, 2 0
2b	6 01	4 81	5 01	5 19	5 72	3 7	3 1	4 4	[a]	1 4, 2 1
4	6 03	4 84	4 88	4 98	4 59	3 6	3 0	4 3	3 5	1 2–1 9
8	5 97	4 77	4 84	4 92	4 60	3 7	3 1	4 4	3 7	1 3–2 1

	H-1	*H 2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6b*	*HO-3*	*HO-5*	*HO-6*	*Alkylidene*
3a	5 80	4 38	4 04	3 87	3 69	3 52	3 33	5 1	4 6	4 4	1 19, 1 37
3b	5 92	4 87	5 32	4 22	←3 5———	———3 7→[b]	3 31	[a]	5 1	4 6	1 27, 1 44
5a	5 80	4 32	4 07	3 88	3 69	3 57	3 33	5 1	4 6	4 4	1 4–1 9
5b	5 86	4 38	4 03	4 17	5 27	3 84	3 59	5 7	[a]	5 1	1 3–1 9
6	5 80	4 37	4 04	3 85	3 67	3 56	3 32	5 1	4 6	4 4	1 2–1 7
7	5 76	4 31	4 06	3 83	3 66	3 54	3 31	5 1	4 6	4 4	1 2–1 9

	$J_{1,2}$[d]	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	$J_{3,OH}$	$J_{5,OH}$	$J_{6a,OH}$	$J_{6b,OH}$
3a	3 7	2 4	8 1	2 8	5 8	−11 5	4 8	5 4	5 7	5 7
3b	3 9	3 3	8 9	[a]	6 0	−11 7	[a]	5 6	5 6	5 3
5a	3 8	2 4	8 2	2 7	6 0	−11 4	5 3	5 4	5 9	5 9
5b	3 8	3 0	8 0	2 7	5 7	−12 9	5 3	[a]	6 2	5 3
6	3 8	2 4	8 2	2 7	5 8	−11 5	4 8	5 5	[c]	[c]
7	3 7	2 4	8 2	2 5	5 9	−11 4	4 8	5 5	5 7	5 7

[a]Not present [b]Complex multiplet [c]Partially masked by H-2 resonances [d]$J_{1,3}$ spacings in all compounds studied were <0 3 Hz

of **2b** and **5b** were confirmed by ^{1}H-n m r spectroscopy (Table I), the nitrate ester causes a large downfield-shift of the H-5 doublet in **2b** as well as of the H-5 multiplet in the reduced compound **5b**

1,2-*O*-Isopropylidene-α-D-glucofuranose 3-nitrate (**3b**) was obtained by treatment of 1,2 5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1a**) with acetyl nitrate followed by selective hydrolysis of the 5,6-*O*-isopropylidene group The ^{1}H-n m r data for **3b** are given in Table I

The acid-catalysed hydrolysis of cyclic acetals involves an A-1 mechanism[12–15] For 1,2-*O*-alkylideneglucofuranoses, protonation of the 1,3-dioxolane oxygen atoms is followed by unimolecular heterolysis, with the formation of a transition state having much carbonium-ion character[15] Water adds rapidly to yield glucose and the ketone

The hydrolyses of **3b**, **5a**, **5b**, **6**, and **7** in acidified, aqueous propan-2-ol were followed polarimetrically, the compounds are insufficiently soluble in aqueous acid Good first-order plots were obtained, and $t_{0.5}$ values are given in Table II T l c showed that no 2-propyl glucosides or other species were formed

TABLE II

HALF-LIVES (*h*) OF 1 2-*O*-ALKYLIDENE-α-D-GLUCOFURANOSES AND DERIVATIVES THEREOF

Compound	*0 53M H_2SO_4 in water–propan-2-ol (65 35)*[a]	*Compound*	*0 52M H_2SO_4 in water*[b]
3a	19 68	**3a**	5 47[a]
3b	92 9	**3c**[3]	3 2[c]
5a	7 78	**3d**[7]	5 6[d]
5b	11 27		
6	124 1		
7	9 53		

[a]At 19 3 , deviation from the mean <2% [b]At 20 0°, estimated error 10% [c]Recalculated to be valid at an H_0 value of +0 11 [d]The rate was determined by time-dependent quantitative g l c after trimethylsilylation estimated error 20%

The rate for **3a** is considerably larger in aqueous acid than in the mixed solvent (Table II) No data are available for Hammett's acidity function (H_0)[13] of sulphuric acid in propan-2-ol–water mixtures However, Braude and Stern[16] demonstrated that $-H_0$ went through a minimum with changing water content at a fixed concentration of mineral acid in ethanol, *p*-dioxane, and acetone Similar behaviour for acidified propan-2-ol–water mixtures would be expected

The nitrate group at position 3 resulted in a marked decrease of the rate ($k_{3a}/k_{3b} = 4\ 76$), whereas the same substituent at C-5 has little effect ($k_{5a}/k_{5b} = 1\ 45$) Electron-withdrawing substituents in the sugar moiety may affect the overall rate by (*a*) lowering the standing concentration of the conjugate acid, and (*b*) facilitating or retarding the unimolecular heterolysis, depending on the site of protonation These effects cancel out in the overall rate in related, acid-catalysed, hydrolytic systems[14 17]

The isopropylidene group in **3b** is almost as stable as the cyclohexylidene group in **6**, yet it can be removed under milder conditions after removal of the nitrate ester

The cyclopentylidene (**5a**) and cycloheptylidene (**7**) acetals hydrolyse more rapidly than the cyclohexylidene acetal (**6**) The differences in the rates of hydrolyses of related cyclic acetals have been discussed[12 15] in terms of changes of ring-torsional and bond-angle strains in the transition state However, cycloheptylideneuridine hydrolyses faster than cyclopentylideneuridine[12], whereas the reverse order of reactivity holds true in the present series This finding strongly indicates that the changes in bond angle in the transition state are mediated by the sugar moiety and do not follow the general trend[12] for the diethyl acetals of the ketones

If HO-5 is blocked ($R^2 \neq H$), as in the monosaccharide derivatives **5b** and in the (1→5)-linked disaccharides **3c**[3] and **3d**[7], a glucopyranose derivative cannot be formed and there is a negative drift in optical rotation during the reaction ^{1}H-N m r spectroscopy of the (1→5)-linked disaccharides in deuterium oxide demonstrated that both anomeric furanose forms were present in about equal amounts[7 19] Thus, the observed molecular rotation roughly equals its B value ($0\,5[M]_\alpha + 0\,5[M]_\beta$) In accordance with Hudson's rule, the molecular rotation of a (1→5)-linked disaccharide should be considerably lower than the values for the respective (1→2)-, (1→3)-, (1→4)-, and (1→6)-linked pyranoid analogues (*cf* Ref 18)

EXPERIMENTAL

General methods — Melting points were determined on a Mettler FP5/FP51 photoelectric melting-point apparatus Specific rotations were determined at ambient temperature with a Perkin-Elmer 141 Polarimeter ^{1}H-N m r spectra (internal Me_4Si) were recorded with Varian EM360 and EM390 spectrometers, and i r spectra with a Pye Unicam SP1100 spectrophotometer Solutions were concentrated at 40° (bath)/~12 mmHg T l c was performed on silica gel (Schleicher & Schull T L C Ready Plastic Foil FR-1500), with conventional detection by charring with sulphuric acid Column chromatograpny was performed on silica gel (Merck Kieselgel 60 230–400 mesh) with *A*, ethyl ether, *B*, ethyl ether–light petroleum (b p 40–60°) (1 3) and *C*, as in *B*, ratio 3 1

Kinetic methods — Reactions were followed at 546 nm by using a Zeiss precision polarimeter Jacketed tubes were used to ensure a constant temperature (±0 1°) Half lives ($t_{0\,5}$, h) were computed by regression analysis of ln $|\alpha_t - \alpha_\infty|$ *versus* time (t) straight-line plots using a Hewlett-Packard 9100B calculator The method of Guggenheim[20] gave the same results In most cases, the optical rotations to be expected at infinite time were checked by actual measurements

A poor correlation constant (r) and a large standard-deviation on $t_{0\,5}$ was obtained for **3d** Therefore, the rate for **3d** was calculated by measuring peak areas in g l c after trimethylsilylation[7]

1,2-O-Cycloalkylidene derivatives of α-D-*glucofuranurono-6,3-lactone* — (*a*) Freshly distilled cyclopentanone (60 ml) was added dropwise to a stirred solution

(0°) of mesitylenesulphonic acid (1 g) in *p*-dioxane (100 ml) and triethyl orthoformate (15 ml). The mixture was then kept at room temperature for 2 h. Finely powdered D-glucofuranurono-6,3-lactone (10 g, 56 8 mmol) was added, and the suspension was vigorously stirred until a clear solution was obtained (24–48 h). The solution was neutralized with triethylamine, and concentrated. A solution of the syrupy residue in chloroform (100 ml) was washed with water (100 ml). The aqueous layer was extracted with chloroform (3 × 50 ml). The combined chloroform layers were dried ($MgSO_4$), treated with decolourizing carbon, filtered through diatomaceous earth, and concentrated. Treatment of the residue with ethyl ether afforded crystalline **2a**. The mother liquor was chromatographed on a column of silica gel (solvent *A*) to give more **2a**. Recrystallisation from ethanol gave 1,2-*O*-cyclopentylidene-α-D-glucofuranurono-6,3-lactone (**2a**, 8 3 g, 60%), m p 112 5–114 5°, $[\alpha]_D$ +53° (*c* 6, chloroform), ν_{max}^{KBr} 3420 (OH, sharp) and 1780 cm^{-1} (C=O, lactone) (Found: C, 54 45, H, 5 88, O, 38 98. $C_{11}H_{14}O_6$ calc. C, 54 54, H, 5 83, O, 39 63%).

The ^{1}H-n m r. data (Table I) were consistent with the allocated structure.

(*b*) Using a procedure similar to that in (*a*), but with 60 ml of cyclohexanone, 1,2-*O*-cyclohexylidene-α-D-glucofuranurono-6,3-lactone (**4**, 3 8 g, 26%) was obtained, m p. 145–146° (from ether–hexane), $[\alpha]_D$ +47° (*c* 2 6, chloroform), ν_{max}^{KBr} 3450 (OH, sharp) and 1780 cm^{-1} (C=O, lactone) (Found: C, 56 41, H, 6 25, O, 36 82. $C_{12}H_{16}O_6$ calc. C, 56 25, H, 6 29, O, 37 46%).

For ^{1}H-n m r. data, see Table I.

(*c*) Using a procedure similar to that in (*a*), but with 40 ml of cycloheptanone, 1,2-*O*-cycloheptylidene-α-D-glucofuranurono-6,3-lactone (**8**, 8 5 g, 55%) was obtained, m p. 121 5–122° (from ether–hexane), $[\alpha]_D$ +48° (*c* 3, chloroform), ν_{max}^{KBr} 3415 (OH, sharp) and 1780 cm^{-1} (C=O, lactone) (Found: C, 57 77, H, 6 70, O, 35 53. $C_{13}H_{18}O_6$ calc. C, 57 77, H, 6 71, O, 35 52%).

For ^{1}H-n m r. data, see Table I.

1,2-O-Isopropylidene-α-D-glucofuranose 3-nitrate (**3b**). — A solution of acetyl nitrate [prepared at −15° from fuming nitric acid (8 ml, sp. gr. 1 50) and acetic anhydride (20 ml)] was added dropwise with stirring to a suspension of **1a** (20 g, 77 mmol) in acetic anhydride (45 ml). The temperature was kept below 0°. After a further 10 min at 0°, the solution was poured into ice–water (750 ml). The oil which separated was dissolved in ether (200 ml), and the solution was successively washed with 100-ml portions of ice–water, cold 15% aqueous potassium carbonate (2 ×), and water, then dried ($MgSO_4$), and concentrated to give 1,2 5,6-di-*O*-isopropylidene-α-D-glucofuranose 3-nitrate (**1b**, 23 g, 98%), as an oil, $[\alpha]_D$ −38° (*c* 3, chloroform), which contained acetic anhydride, ether, and other products, but was suitable for the preparation of **3b**.

A mixture of **1b** (23 g, 75 mmol), methanol (110 ml), and 0 5% aqueous sulphuric acid (50 ml) was stirred vigorously until the solution became clear (~20 h). T l c. (solvent *C*) after 40 h indicated the presence of **1b** and D-glucose 3-nitrate (R_F 0 0) in about equal, but small, amounts. The solution was neutralized with

Dowex 1 X 2 (HO^-) resin, filtered and concentrated A solution of the resulting, clear syrup in ethyl ether was treated with silicic acid (0 5 g) to remove D-glucose 3-nitrate and water, filtered, and diluted with hexane to give **3b** (17 g, 85%), m p 70–70 5°, $[\alpha]_D$ −25° (*c* 2, *p*-dioxane), ν_{max}^{KBr} 3450, 3500 (OH, sharp). 1640, and 1275 cm^{-1} (nitrate) (Found C, 40 90, H, 5 83, N, 5 19 $C_9H_{15}NO_8$ calc C, 40 76, H, 5 70, N, 5 28%)

For ^{1}H-n m r data, see Table I

1,2-O-Cyclopentylidene-α-D-glucofuranurono-6,3-lactone 5-nitrate (**2b**) — A solution of acetyl nitrate [prepared from nitric acid (1 ml) and acetic anhydride (4 ml)] was added to a solution of **2a** (2 4 g, 10 mmol) in acetic anhydride (6 ml) The mixture was kept at 0° for 10 min, then poured into ice–water (100 ml), and vigorously shaken for 5 min The product was collected, washed with ice–water, and dried over KOH *in vacuo* to give **2b** (2 5 g, 88%), m p 112–113° (from chloroform–ether), $[\alpha]_D$ +76° (*c* 3, chloroform), ν_{max}^{KBr} 1800 (C=O, lactone), 1650 and 1275 cm^{-1} (nitrate) (Found C, 46 05, H, 4 51, N, 4 69, O, 44 48 $C_{11}H_{13}NO_8$ calc C, 46 00, H, 4 56, N, 4 88, O, 44 56%).

For ^{1}H-n m r data, see Table I

1,2-O-Cyclopentylidene-α-D-glucofuranose (**5a**) — A solution of **2a** (4 8 g, (20 mmol) in dry tetrahydrofuran was flushed with nitrogen and cooled to −60° M Borane in tetrahydrofuran (38 ml) was slowly added with stirring at below −40° The mixture was allowed to reach room temperature in 3 h, methanol was then added to destroy the excess of borane, and the solution was concentrated Boric acid was removed from the residue by evaporation of methanol three times therefrom Crystallization of the product from ethanol–light petroleum (b p 40–60°) afforded **5a** (2 5 g, 51%), m p 163–164°, $[\alpha]_D$ +6° (*c* 3, *p*-dioxane) (Found C, 53 50, H, 7 41, O, 39 08 $C_{11}H_{18}O_6$ calc C, 53 63, H, 7 37, O, 38 98%)

For ^{1}H-n m r data, see Table I

1,2-O-Cyclohexylidene-α-D-glucofuranose (**6**) — Compound **4** (5 g, 20 mmol) was reduced, as described for **2a**, to give **6** (2 4 g, 47%), m p 151–151 5° [from ethanol–light petroleum (b p 40–60°)], $[\alpha]_D$ +2 5° (*c* 3, *p*-dioxane), lit [10] m p 152–153°, $[\alpha]_D$ +4° (acetone)

For ^{1}H-n m r data, see Table I

1,2-O-Cycloheptylidene-α-D-glucofuranose (**7**) — Compound **8** (5 4 g, 20 mmol) was reduced, as described for **5a**, to give **7** (4 55 g, 83%), m p 151 5–152 5° (dec) [from ethanol–light petroleum (b p 40–60°)], $[\alpha]_D^{50}$ +6° (*c* 3, *p*-dioxane) (Found C, 56 72, H, 8 08, O, 35 08 $C_{13}H_{22}O_6$ calc C, 56 92, H, 8 08, O, 34 99%)

For ^{1}H-n m r data, see Table I

1,2 O-Cyclopentylidene-α-D-glucofuranose 5-nitrate (**5b**) — A solution of **2b** (4 3 g, 15 mmol) in tetrahydrofuran (15 ml) was reduced with borane–tetrahydrofuran complex (22 ml), and further processed as described for **5a**, to give **5b**, (4 1 g, 94%), m p 118–119° (from ethyl acetate–hexane), $[\alpha]_D$ +7° (*c* 3, chloroform), ν_{max}^{KBr} 3450 (OH, sharp), 1640 and 1275 cm^{-1} (nitrate), no lactone absorption was observed

(Found C, 45 01, H, 5 94, N, 4 55, O, 43 21 $C_{11}H_{17}NO_8$ calc C, 45 36, H, 5 88, N, 4 81, O, 43 95%)

For ^{1}H-n m r data, see Table I

ACKNOWLEDGMENTS

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