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Note

Selectivity in cyclic acetal hydrolyses: a comparison between *cis*- and *trans*-fused benzylidene rings

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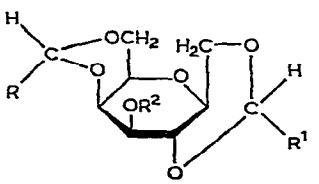
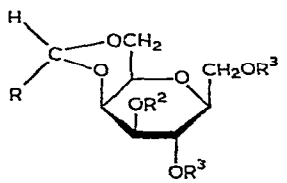
In order to synthesise 2,6:3,4-dianhydro-1-deoxy-D-*talo*-hept-1-enitol, an irreversible inhibitor for β-D-galactosidase, it is necessary to start with a suitably 4,5,7-blocked 2,6-anhydro-1-deoxy-D-*galacto*-hept-1-enitol[1]. We now describe an improved method employing differential hydrolysis of cyclic acetals. It is well known that the rate of hydrolysis of benzylidene and substituted benzylidene groups can be strongly influenced by substituents on the aromatic ring. For example, anisylidene groups are hydrolysed by acids at much higher rates than are benzylidene groups[2]. The rates of acid-catalysed hydrolysis depend on the size and position of the acetal ring in a polyhydric system, and this dependence has been reviewed[3]. It is also known that *trans*-fused 4,6-benzylidene acetals of hexopyranosides are hydrolysed three times faster than *cis*-fused rings[4].

2,6-Anhydro-D-*glycero*-L-*manno*-heptitol[5] (**1**) forms a 1,3:5,7-di-*O*-benzylidene derivative (**2**) which contains *cis*- and *trans*-fused acetal rings. 1-^{3}H-Labelled **1** was used to study quantitatively the selectivity of acetal-group hydrolysis.

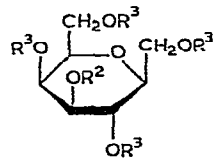
Graded hydrolysis of 1-^{3}H-labelled **2** with dilute acetic acid gave two ^{3}H-labelled products, namely a monobenzylidene derivative and **1**. The reaction was monitored by scanning t.l.c. After 6 h, the monobenzylidene fraction was shown, by acetylation and co-crystallisation of the product with authentic 1,3,4-tri-*O*-acetyl-



2 R = R^1 = Ph, R^2 = H
5 R = R^1 = Ph, R^2 = Ac
8 R = Ph, R^1 = PhOMe-*p*, R^2 = H
9 R = Ph, R^1 = PhOMe-*p*, R^2 = Ac



3 R = Ph, R^2 = R^3 = H
4 R = Ph, R^2 = R^3 = Ac
7 R = Ph, R^2 = Ac, R^3 = H



1 R^2 = R^3 = H
6 R^2 = Ac, R^3 = H

2,6-anhydro-5,7-*O*-benzylidene-D-*glycero*-L-*manno*-heptitol[6] (**4**), to contain 82–85% of 1-^{3}H-labelled 2,6-anhydro-5,7-*O*-benzylidene-D-*glycero*-L-*manno*-heptitol (**3**).

Equally selective, but much slower, was the hydrolysis of 4-*O*-acetyl-2,6-anhydro-1,3:5,7-di-*O*-benzylidene-D-*glycero*-L-*manno*-heptitol (**5**). The *trans*-fused 1,3-dioxane ring was preferentially hydrolysed; after 22 h, using the above procedure, it was shown that the monobenzylidene fraction contained 70% of 4-*O*-acetyl-2,6-anhydro-5,7-*O*-benzylidene-D-*glycero*-L-*manno*-heptitol (**7**). Isolation of **7** after reaction on a 5–10-g scale proved difficult.

In an alternative approach, **3** was converted into 2,6-anhydro-1,3-*O*-*p*-anisylidene-5,7-*O*-benzylidene-D-*glycero*-L-*manno*-heptitol (**8**) by reaction in 1,4-dioxane with *p*-anisaldehyde in low concentration in order to avoid acetal exchange with the 5,7-*O*-benzylidene group. 1-^{3}H-Labelled **8** and 4-*O*-acetyl-2,6-anhydro-1,3-*O*-*p*-anisylidene-5,7-*O*-benzylidene-D-*glycero*-L-*manno*-heptitol (**9**) were subjected to graded hydrolysis with acid, as described for **2** and **5**. After 20 min, the anisylidene group was quantitatively removed from **8** without loss of the benzylidene ring. Here, the relative acid lability of a *trans*-fused 1,3-acetal ring is amplified by the *p*-methoxyl group. Details of the graded hydrolyses are given in the Experimental.

On a preparative scale, crystalline **8** was acetylated to give **9**, which could be hydrolysed without loss of the 5,7-*O*-benzylidene group to yield **7** almost quantitatively.

EXPERIMENTAL

General methods. — Optical rotations were measured at ambient temperature in a 1-dm cell with a Perkin–Elmer 141 automatic polarimeter. Monitoring of reactions was carried out by t.l.c. on silica gel F_{254} (Merck), using benzene–methanol (4:1) and detection by charring with sulphuric acid. Melting points were taken on a Kofler hot-stage microscope and are uncorrected. N.m.r. spectra ($CDCl_3$, internal Me_4Si) were obtained with Varian A-60 D (60 MHz) or EM 390 (90 MHz) spectrometers, and i.r. spectra (KBr) with a Perkin–Elmer 137 spectrometer. Radiochromatograms were scanned with a Packard 7200 scanner, and radioactive samples were assayed in a Berthold BF 815 liquid scintillation counter (LSC) by using PPO (5 g) and POPOP (62.5 mg) in toluene (1 litre).

*2,6-Anhydro-1,3:5,7-di-*O*-benzylidene-*D-glycero-L-manno-*heptitol* (**2**). — A mixture of **3**[6] (17 g, 0.06 mol), powdered $ZnCl_2$ (35 g), and benzaldehyde (110 ml) was shaken for 7 h and then stirred with ice–water–light petroleum (b.p. 60–70°) (1 litre, 1:1). The solid was collected, and washed with light petroleum (b.p. 60–70°) and then water. A solution of the crude material in chloroform (500 ml) was washed with water (2 × 100 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue crystallised from ethanol to give **2** (15 g, 68%), m.p. 178°, $[\alpha]_{578}^{25}$ +80° (*c* 1, chloroform); ν_{max}^{KBr} 3450 (OH), 2870 (CH), 730 and 695 cm^{-1} (aromatic CH). N.m.r. data: δ 3.3–4.53 (m, 10 H), 5.55 (s, 2 H, 2 PhCH), and 7.42 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{21}H_{22}O_6$: C, 68.11; H, 5.98. Found: C, 68.24; H, 6.03.

The acetate **5** of **2** had m.p. 176° (from ethanol), $[\alpha]_{578}^{25}$ +150° (*c* 1, chloroform); ν_{max}^{KBr} 2850 (CH), 1750 (C=O), 698 and 742 cm^{-1} (aromatic CH).

Anal. Calc. for $C_{23}H_{24}O_7$: C, 66.98; H, 5.86. Found: C, 66.83; H, 5.97.

*2,6-Anhydro-1,3-*O*-*p*-anisylidene-5,7-*O*-benzylidene*-D-glycero-L-manno-*heptitol* (**8**). — To a solution of **3** (3 g, 0.01 mol) in 1,4-dioxane (150 ml) were added freshly distilled *p*-anisaldehyde (100 ml) and powdered $ZnCl_2$ (3 g), and the mixture was shaken for 18 h at room temperature. After addition of ice–water (200 ml), the mixture was extracted with chloroform (3 × 100 ml), the extract was concentrated to dryness, and the residual yellow oil was extracted continuously with light petroleum (b.p. 30–50°) to remove anisaldehyde. Crystallisation from methanol then gave **8** (3.1 g, 74%), m.p. 211°, $[\alpha]_{578}^{25}$ +85° (*c* 1.2, chloroform); ν_{max}^{KBr} 3450 (OH), 1610, 1580, 1520 and 1450 (aromatic), and 1250 cm^{-1} (PhOMe). N.m.r. data: δ 3.74 (s, 3 H, OMe), 3.5–4.33 (m, 10 H), 5.46 and 5.50 (2 s, each 1 H, 2 PhC*H*), 6.73–6.92 and 7.22–7.6 (m, 9 H, aromatic H).

Anal. Calc. for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04. Found: C, 65.84; H, 6.01.

The acetate **9** of **8** had m.p. 169° (from methanol–ethanol, 1:3), $[\alpha]_{578}^{23}$ +146° (*c* 0.58, chloroform); ν_{max}^{KBr} 1740 (C=O), 1620, 1580, 1520 and 1470 (aromatic), and 1250 cm^{-1} (PhOMe).

Anal. Calc. for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92. Found: C, 65.02; H, 5.74.

*4-*O*-Acetyl-2,6-anhydro-5,7-*O*-benzylidene*-D-glycero-L-manno-*heptitol* (**7**). — A solution of **9** (2.8 g, 6.3 mmol) in acetone (50 ml) and 80% aqueous acetic acid (50 ml) was kept for 5 min at 90°, pyridine (50 ml) was then added, and the cooled (40°) solution was concentrated *in vacuo*. Distillation of pyridine (3 × 50 ml) and then toluene (4 × 10 ml) from the residue yielded an oil (1.9 g, 93%) which was crystallised from ethyl acetate–light petroleum (b.p. 60–70°), to give **7**, m.p. 170°, $[\alpha]_{578}^{23}$ +115° (*c* 0.57, chloroform); ν_{max}^{KBr} 3450 (OH), 2920 and 2850 (CH), and 1710 cm^{-1} (C=O). N.m.r. data: δ 2.08 (s, 3 H, OAc), 3.05–4.30 (m, 10 H), 4.77 (dd, 1 H, H-4), 5.43 (s, 1 H, PhC*H*), and 7.37 (m, 5 H, Ph).

Anal. Calc. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.11; H, 6.31.

Radioactive samples. — 1-^{3}H-Labelled compounds **8** and **9** were prepared in the same way as described above, and labelled **2** and **5** by slightly modified methods from 1-^{3}H-**3** obtained by reduction of methyl 3,4-di-*O*-acetyl-2,6-anhydro-5,7-*O*-benzylidene-D-*glycero*-L-*manno*-heptonate[6] with $LiAl^3H_4$. By dilution with **3** and crystallisation, a sample having 0.1 mCi/mmol was obtained.

A mixture of 1-^{3}H-**3** (57 mg, 0.2 mmol), benzaldehyde (2 ml), and $ZnCl_2$ (300 mg) was stirred for 8 h, pyridine (4 ml) and acetic anhydride (3 ml) were added, and stirring was continued for 16 h. The mixture was stirred into ice–water (50 ml) and light petroleum (b.p. 30–50°) (50 ml). The product was collected, washed exhaustively with water and light petroleum, dried, and crystallised from ethanol to give 1-^{3}H-**5** (55 mg, 67%).

Compound 1-^{3}H-**5** (41 mg, 0.1 mmol) was stirred with 0.02M methanolic sodium methoxide (4 ml). The mixture was concentrated and the residue was crystallised from ethanol to yield 1-^{3}H-**2** (36 mg, 97%).

TABLE I

HYDROLYSIS DATA[a]

1-^{3}H-2				*1-^{3}H-5*			
Time (h)	*A (%)*	*B (%)*	*C (%)*	*Time (h)*	*A (%)*	*B (%)*	*C (%)*
0.25	91.4	8.6	—	0.33	93	7	—
0.5	71.1	28.9	—	0.6	92	8	—
0.75	61.1	32.4	6.5	0.83	86	14	—
1	49.1	34.9	16	1.08	81	19	—
1.5	47.8	38.5	13.7	1.58	79	21	—
2.5	19.3	41.9	38.8	2.25	59	31	10
3.5	21.4	36.5	42.1	3.42	50	38	12
4.5	9.4	46.2	44.4	9.4	22	61	17
5.5	9.2	37.7[b]	53.1	11.5	20	61	19
8	3.7	31.6	64.7	22	—	80[b]	20
9.5	—	24.8	75.2	26.5	—	77	23

1-^{3}H-8			*1-^{3}H-9*		
Time (min)	*A (%)*	*B (%)*	*Time (min)*	*A (%)*	*B (%)*
1	63.8	36.2	1	79.6	20.4
3	35.5	64.5	3	67.8	32.2
5	17.7	82.3	5	56.7	43.3
7	8.8	91.2	7	42	59
13	1	99	13	21.9	78.1
20	0	100	20	10.5	89.5
30	0	100	30	0	100

Key: A, Substrate; B, partially hydrolysed product; C, fully hydrolysed product.

[a]Aqueous acetic acid at 56°. [b]These samples were acetylated, and used for the identification of **4** by co-crystallisation with an authentic sample.

The reaction of 1-^{3}H-**3** (28.6 mg, 0.1 mmol), 1,4-dioxane (10 ml), *p*-anisaldehyde (3 ml), and $ZnCl_2$ (200 mg) for 1.5 h gave 1-^{3}H-**8** (32 mg, 80%).

Treatment of 1-^{3}H-**8** (16 mg, 0.04 mmol) with pyridine (3 ml) and acetic anhydride (3 ml) for 24 h yielded 1-^{3}H-**9** (15.5 mg, 89%). For the graded hydrolyses, solutions of 1-^{3}H-**8**, 1-^{3}H-**9**, 1-^{3}H-**2**, or 1-^{3}H-**5** (15 mmol in acetone (300 μl) at 60° were treated with 80% aqueous acetic acid (300 μl) also at 60°. The mixtures were kept at 56° and samples (40 μl) were monitored by t.l.c. The radioactivity was expressed in relative peak areas. The results are given in Table I. Starting material and products of hydrolysis could be well separated, as shown by t.l.c. of the corresponding unlabelled samples: **1** R_F 0.06, **2** 0.66, **3** 0.41, **4** 0.71, **5** 0.85, **6** 0.16, **7** 0.53, **8** 0.64, and **9** 0.82.

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