Carbohydrate Research, 154 (1986) 296–300
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Catalytic-transfer hydrogenolysis of benzylidene acetals with palladium–carbon and ammonium formate or hydrazine hydrate*

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(Received Steptember 16th, 1985; accepted for publication in revised form, February 18th, 1986)

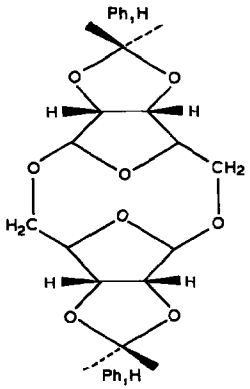
The cyclic acetals of carbohydrates are especially useful as temporary protecting groups in synthesis, as they provide a convenient means of specific and partial blocking[1]. Among the selective deprotection procedures that are available to carbohydrate chemists, the partial hydrolysis of acetals is the most familiar[2]. It should be noted that some limitations exist on hydrolysis, such as, for example, with methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside, in which the two benzylidene groups are removed at similar rates during acid hydrolysis[3]. Recently, we reported a method for the selective removal of a 2-phenyl-1,3-dioxolane group in the presence of a 2-phenyl-1,3-dioxane group by catalytic-transfer hydrogenation. This can be achieved by the action of ammonium formate[4] or hydrazine hydrate[5] in the presence of palladium-on-carbon as the catalyst. The object of the present study was to examine the influence of the size of the acetal ring and the configuration of the acetal carbon atom on the rate and the direction of the reductive cleavage of benzylidene acetals.

The catalytic transfer hydrogenation of benzylidene acetals was conducted by using ammonium formate or hydrazine hydrate as the hydrogen donor and palladium-on-carbon as the catalyst. The course of the reaction depends on the conditions. After long treatment of di-(2,3-*O*-benzylidene-β-D-ribofuranose) 1,5′:1′,5-dianhydride (**1**), as well as methyl 3,4-*O*-benzylidene-β-L-arabinopyranoside (**2**) or its 2-benzoate (**3**), with the ammonium formate–Pd–C reagent, the benzylidene acetal groups are completely removed. By hydrogenolysis of 1,5:2,3-di-*O*-benzylidene-β-D-ribofuranose (**6**) under controlled conditions, the 1,5-*O*-benzylidene is cleaved in preference to the 2,3-*O*-benzylidene group. The results reported here confirm our earlier observation[4] that the catalytic-transfer hydrogenolysis is a highly chemoselective reaction and that the reagent Pd–C–ammonium formate can distinguish between a 2-phenyl-substituted 1,3-dioxepane and a dioxolane ring, or a 1,3-dioxolane and a 1,3-dioxane ring.

Evaluation of the reaction of an equimolar mixture of *endo*-phenyl and *exo*-

*Presented at the Third European Symposium on Carbohydrates, Grenoble, September 16–20, 1985.

0008-6215/86/$ 03.50



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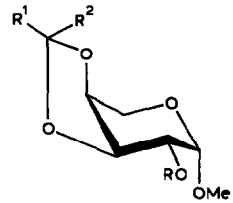
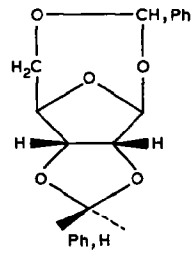


	R	R^1	R^2
2	H	Ph	H
3	Bz	Ph	H
4	H	H	Ph
5	Bz	H	Ph



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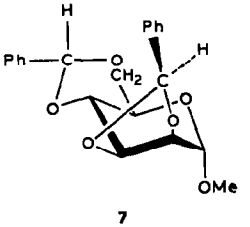
phenyl methyl 3,4-*O*-benzylidene-β-L-arabinopyranosides showed that the *endo* isomer is cleaved the faster, and selective hydrogenolysis led to isolation of the *exo*-phenyl acetal in 25% yield. The first step of the catalytic-transfer hydrogenation of 2-phenyl-1,3-dioxolanes is opening of the acetal ring and formation of benzyl ethers. For our model compounds, it clearly appeared that the regioselectivity of the ring cleavage was determined by the configuration of the acetal carbon atom. Thus, when treated with ammonium formate, methyl (*endo*-Ph)-2-*O*-benzoyl-3,4-*O*-benzylidene-β-L-arabinopyranoside (**5**) gave a mixture of the methyl 3-*O*- and 4-*O*-benzyl derivatives, in yields of 3 and 22%, respectively. The situation was reversed for the *exo*-Ph benzylidene acetal **3**, and the 3-benzyl ether was the main product. Hydrogenolysis of methyl (*exo*-Ph)-2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (**7**) gave methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside. Finally, methyl (*exo*-Ph)-3,4-*O*-benzylidene-β-L-arabinopyranoside (**2**) was mainly converted, as expected, into the 3-benzyl ether.



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The present results show that the direction of the hydrogenolytic ring-cleavage of 2-phenyl-1,3-dioxolanes is determined by the configuration of the acetal carbon atom. For the *exo*-Ph isomer, the hydrogen mainly ruptures the axial oxygen–carbon bond, giving an ether having an equatorial benzyl group. For the *endo*-Ph isomer, the reverse direction of the reaction is observed. The stereoselectivity seen in the present work for the opening of the dioxolane ring is the

same as that previously reported for the lithium aluminum hydride–aluminum chloride reagent[6,7] and for sodium cyanoborohydride–hydrogen chloride[8].

EXPERIMENTAL

General. — Melting points were determined on a Boetius melting-point apparatus and are uncorrected. Optical rotations were measured with a Polamat A automatic polarimeter at 20 ±1°. ^{1}H-N.m.r. spectra were recorded at 60 MHz for solutions in chloroform-*d* or D_2O with tetramethylsilane and sodium 2,2,3,3-tetradeuterio-4,4-dimethyl-4-silapentanoate, respectively, as the internal standards. T.l.c. was performed with Kieselgel G (Merck) as the adsorbent; the developed plates were air-dried, sprayed with 25% methanolic sulfuric acid, and heated on a hot plate. Palladium-on-carbon, 5% or 10% (Degussa, type E10N), was used as the catalyst.

General procedure. — A mixture of the benzylidene acetal (1 mmol), methanol (20–30 mL), palladium-on-carbon (0.6–1.5 g, see Table I), and the hydrogen donor (see Table I) was boiled under reflux. The reaction was monitored by t.l.c. and, when it was complete, the catalyst was removed, the filtrate was evaporated, and the residue was subjected to column chromatography on silica gel.

*Methyl 3-O-benzyl-β-*L*-arabinopyranoside.* — Methyl (*exo*-Ph)-3,4-*O*-benzylidene-β-L-arabinopyranoside (**2**) (378 mg, 1.47 mmol) was converted into the 3-benzyl ether as described under *General procedure*. The residue was purified on a column (1.2 × 20 cm) of silica gel eluted with 7:3 benzene–ether (80 mL) and then 1:1 benzene–ether (200 mL). The second fraction was evaporated, and the 3-benzyl ether crystallized from ethyl acetate–hexane (91 mg, 24%); m.p. 118–119°, $[\alpha]_D^{20}$ +176.4° (*c* 0.7, chloroform); R_F 0.28 (1:2 benzene–ethyl acetate); n.m.r. (in $CDCl_3$): δ 7.30 (m, 5 H, Ph), 4.74 (d, 1 H, H-1, $J_{1,2}$ 3.5 Hz), 4.70 (s, 2 H, PhCH_2), 4.05–3.46 (m, 5 H, H-2–5), 3.32 (s, 3 H, OCH_3), and 2.43 (br s, 2 H, O*H*).

Anal. Calc. for $C_{13}H_{18}O_5$: C, 61.41; H, 7.13. Found: C, 61.30; H, 7.09.

*Methyl 2-O-benzoyl-3-O-benzyl-β-*L*-arabinopyranoside.* — Methyl 2-*O*-benzoyl-(*exo*-Ph)-3,4-*O*-benzylidene-β-L-arabinopyranoside (**3**) (356 mg, 1 mmol) was converted into the 3-benzyl ether as described under *General procedure*. The residue was chromatographed on a column (1.2 × 25 cm) of silica gel (35–70 mesh), using 20:1 benzene–ether (100 mL) and 3:1 benzene–ether (100 mL) as eluants. The third fraction eluted, identified as the 3-benzyl ether, was obtained as a syrup (61 mg, 17%); $[\alpha]_D^{20}$ +146.3° (*c* 0.5, chloroform); R_F 0.41 (2:1 benzene–ethyl acetate); ^{1}H-n.m.r. ($CDCl_3$): δ 8.00 (2 H, *o*-Bz), 7.58–7.25 (3 H, *m*-, *p*-Bz), 7.16 (5 H, PhCH_2), 5.40 (dd, 1 H, H-2, $J_{1,2}$ 3.5, $J_{2,3}$ 10 Hz), 4.95 (d, 1 H, H-1), 4.62 (br s, 2 H, PhCH_2), 4.13–3.66 (m, 4 H, H-3–5), 3.30 (s, 3 H, OCH_3), and 2.61 (br s, 1 H, O*H*).

Anal. Calc. for $C_{20}H_{22}O_6$: C, 67.03; H, 6.18. Found: C, 67.10; H, 6.30.

The benzyl ether (36 mg, 0.1 mmol) was kept overnight at room temperature in 1% methanolic sodium methoxide (2 mL). Work-up in the usual way gave methyl

TABLE I

CATALYTIC-TRANSFER HYDROGENATION OF BENZYLIDENE ACETALS[a]

	Starting material	*Reaction time (min)*	*Product*	*Yield[b] (%)*	*Hydrogen donor (mmol)*	*Catalyst (g)[c]*
1	Di-(2,3-*O*-benzylidene-β-D-ribofuranose) 1,5′:1′,5-dianhydride[9,d]	30	di-β-D-ribofuranose 1,5′:1′,5-dianhydride[10,11]	92	HCO_2NH_4 (5)	1.0
2+4	Methyl 3,4-*O*-benzylidene-β-L-arabinopyranoside[12,e]	12	methyl (*exo*-Ph)-3,4-*O*-benzylidene-β-L-arabinopyranoside[12]	25	HCO_2NH_4 (2.4)	0.5
		40	methyl β-L-arabinopyranoside[13]	95	HCO_2NH_4 (5)	1.5
3+5	Methyl 2-*O*-benzoyl-3,4-*O*-benzylidene-β-L-arabinopyranoside[14,e]	45	methyl 2-*O*-benzoyl-β-L-arabinopyranoside[14]	88	HCO_2NH_4 (5)	1.5
6	1,5:2,3-Di-*O*-benzylidene-β-D-ribofuranose[9,f]	15	2,3-*O*-benzylidene-β-D-ribofuranose[9,g]	62	HCO_2NH_4 (6)	1.5
5	Methyl 2-*O*-benzoyl-(*endo*-Ph)-3,4-*O*-benzylidene-β-L-arabinopyranoside[12,15]	20	methyl 2-*O*-benzoyl-4-*O*-benzyl-β-L-arabinopyranoside	22	HCO_2NH_4 (5)	1.0[h]
3	Methyl 2-*O*-benzoyl-(*exo*-Ph)-3,4-*O*-benzylidene-β-L-arabinopyranoside[12,15]	20	methyl 2-*O*-benzoyl-3-*O*-benzyl-β-L-arabinopyranoside	17	HCO_2NH_4 (5)	1.0[h]
7	Methyl (*exo*-Ph)-2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside[3,15]	15	methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside[16,17]	25	HCO_2NH_4 (3.2)	0.6
2	Methyl (*exo*-Ph)-3,4-*O*-benzylidene-β-L-arabinopyranoside[12]	30	methyl 3-*O*-benzyl-β-L-arabinopyranoside	24	N_2H_4–H_2O (80%, 0.3 mL)	0.7[h]

[a]All compounds were characterized by m.p., $[\alpha]_D^{20}$, and ^{1}H-n.m.r. data. [b]Pure isolated product. [c]Amounts of 10% Pd–C per mmol of starting material. [d]An 11:9 mixture of the *exo* and *endo* isomers. [e]A 1:1 mixture of the *exo* and endo isomers. [f]A 3:2 mixture of the *exo* and *endo* isomers. [g]An 83:17 mixture of the *exo* and *endo* isomers. [h]5% Pd–C.

3-*O*-benzyl-β-L-arabinopyranoside (22 mg, 88%). The n.m.r. spectrum was identical to that of the product obtained by hydrogenolysis of **2**, and a mixture melting point was undepressed.

Methyl 2-O-benzoyl-4-O-benzyl-β-L-arabinopyranoside. — Methyl 2-*O*-benzoyl-(*endo*-Ph)-3,4-*O*-benzylidene-β-L-arabinopyranoside (**5**) (356 mg, 1 mmol) was converted into the 4-benzyl ether, as described for the preparation of the 3-*O*-benzyl derivative. The 4-benzyl ether (79 mg, 22%) had $[\alpha]_D^{20}$ +189.3° (*c* 0.43, chloroform); R_F 0.57 (2:1 benzene–ethyl acetate); ^{1}H-n.m.r. ($CDCl_3$): δ 8.00 (2 H, *o*-Bz), 7.35 (3 H, *m*-, *p*-Bz), 7.25 (m, 5 H, PhCH_2), 5.24 (dd, 1 H, H-2, $J_{1,2}$ 3.5, $J_{2,3}$ 9.5 Hz), 4.93 (d, 1 H, H-1), 4.71, 4.47 (qAB, 2 H, PhCH_2, J_{AB} 12 Hz), 4.40–3.60 (m, 4 H, H-3–5), 3.30 (s, 3 H, OCH_3), and 2.50 (br s, 1 H, O*H*).

Anal. Calc. for $C_{20}H_{22}O_6$: C, 67.03; H, 6.18. Found: C, 66.95; H, 6.09.

The 3- and 4-benzyl ethers of methyl 2-*O*-benzoyl-β-L-arabinopyranoside were *O*-debenzoylated with methanol containing catalytic amount of sodium methoxide, and each product was treated with sodium metaperiodate. Oxidative glycol-cleavage was observed only for the product from the 4-*O*-benzyl derivative.

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