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Note

The acid-catalyzed interconversion of diastereoisomeric methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranosides

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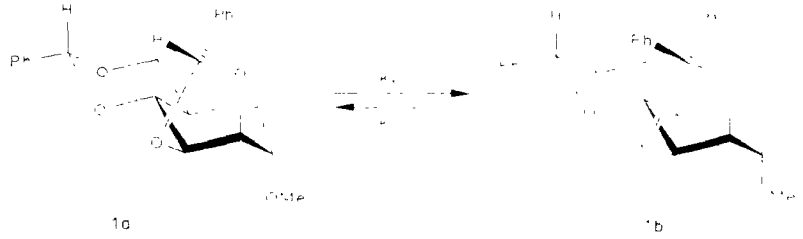
Methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (**1**) was needed as a starting material for our synthetic studies. Reductive ring-cleavage of 2-phenyl-1,3-dioxolane derivatives of carbohydrates with the $LiAlH_4$–$AlCl_3$ reagent[1] has been reported to depend on the configuration of the acetal carbon atom. With *exo*-phenyl derivatives, the reagent attacks O-2, which is the axial oxygen atom of the dioxolane ring, whereas, with the *endo*-phenyl diastereoisomer, the attack occurs at O-3, which is the equatorial atom.

Bhattacharjee and Gorin[2] applied this reaction to **1**, and obtained methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside as the main product, but no information was given as to the starting isomer.

When we used this reaction with the methyl 2,3(*S*),4,6-dibenzylidene acetal (**1a**), with the aim of obtaining methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside, g.l.c. after 30 min showed that the diastereoisomer **1b** was the main product in the mixture. In order to acquire an explanation of this isomerization, we studied the behavior of the two methyl di-*O*-benzylidene-D-mannopyranosides (**1a** and **1b**) in the presence of aluminum trichloride.



1a 1b

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Benzylidenation was conducted by the method of Evans[3,4], using α,α-diethoxytoluene instead of α,α-dimethoxytoluene. Both diastereomers could be isolated in similar yields (total yield, 57%). Compound **1b** was the first to crystallize on addition of 1-propanol, and compound **1a** was recovered from the mother liquors on standing. Characterization was effected by comparison of their physical constants, including ^{1}H-n.m.r.- and ^{13}C-n.m.r.-spectroscopic data, with those described in the literature[5-7].

The isomerization reactions were conducted in chloroform, and in chloroform–ether, solutions, starting with **1a** or **1b**, respectively. The acid catalyst ($AlCl_3$) was added in ether solution. The molar ratio of substrate to catalyst was 25:1 in all experiments. Table I shows the results obtained for the two isomers. When $\ln [\mathbf{1a}]_e/[\mathbf{1a}]_e - [\mathbf{1a}]_t$ and $\ln [\mathbf{1b}]_e/[\mathbf{1b}]_e - [\mathbf{1b}]_t$ were plotted against time, straight lines were obtained; here, $[\mathbf{1}]_e$ = concentration of compound **1** at equilibrium, and $[\mathbf{1}]_t$ = concentration of compound **1** at time t. This result indicated a first-order dependence on the acetal concentration, and enabled us to calculate k_1 and k_{-1} from the slope: $k_1 = 9.30 \times 10^{-4}$ min^{-1} ($CHCl_3$); $k_1 = 7.12 \times 10^{-4}$ min^{-1} (4:1 $CHCl_3$–ether); $k_{-1} = 7.38 \times 10^{-4}$ min^{-1} ($CHCl_3$); $k_{-1} = 4.99 \times 10^{-4}$ min^{-1} (4:1 $CHCl_3$–ether). The equilibrium constant in $CHCl_3$ ($K = [\mathbf{1b}]/[\mathbf{1a}] = k_1/k_{-1}$) gave a value of 1.31 when calculated from the final concentrations (mean value of data at 48, 72, and 96 h), and of 1.26 on considering the ratio of rate constants. In chloroform–ether, the values obtained were 1.37 and 1.42, respectively.

The difference in the rate of isomerization observed when the reaction was conducted in chloroform or 4:1 chloroform–ether may be explained by taking into account the fact that the ethereal oxygen atom competes with the acetal oxygen atoms in the coordination of aluminum. The isomer ratio at equilibrium ([**1b**]/[**1a**]) under either set of conditions is ~1.35:1, which would account for the greater stability of compound **1b**. Nevertheless, this difference cannot explain previous reports[5,8,9] that described this isomer as being the favored or exclusive product on benzylidenation of methyl α-D-mannopyranoside. The differences observed in the solubilities of the two isomers accounts better for this fact. Compound **1b** proved to be less soluble in the solvents tested, and, in particular, it was found to be almost insoluble in ether at room temperature. Taking advantage of this result, we treated an ethereal solution of **1a** with catalytic amounts of $AlCl_3$. The precipitation of **1b** (as fast as it was formed) displaced the equilibrium, and the *exo*-phenyl isomer could be obtained in 85% yield.

The fact that, when we tried to hydrogenolyze **1a** with $LiAlH_4$–$AlCl_3$, the isomer **1b** was formed before the benzyl ether expected would indicate that isomerization was faster than reductive ring-cleavage under the conditions used. Similar considerations would explain the results of Subero *et al.*[10], who obtained the 3-benzyl ether starting from either *exo*- or *endo*-1,6-anhydro-3,4-*O*-benzylidene-β-D-galactopyranose. Although the authors[10] gave no evidence, the referee of that paper suggested the possibility of isomerization.

While our investigation was in progress, Harangi *et al.*[11] reported the Lewis acid-catalyzed isomerization of several derivatives of methyl 2,3-*O*-benzylidene-α-L-rhamnopyranoside and methyl 3,4-*O*-benzylidene-β-L-arabinopyranoside.

EXPERIMENTAL

General. — Melting points were determined on a Kofler apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 automatic polarimeter. ^{1}H-N.m.r. and ^{13}C-n.m.r. spectra were recorded with a Varian XL-100 instrument at 100 MHz and 25.2 MHz, respectively, for solutions in $CDCl_3$ (internal Me_4Si). G.l.c. was performed in a Hewlett–Packard 5830 A instrument fitted with glass columns (180 × 0.2 cm) packed with 2% of OV-101 on Chromosorb W-AW-DMCS (60–80 mesh). Nitrogen was used as the carrier gas at 30 mL/min; T_i 250°; T_d 300°; T_c programmed from 200 to 280° (5°/min). Compound **1a** showed T_r 7.13 min, and compound **1b**, T_r 8.24 min.

*Methyl 2,3-(S). (***1a***) and 2,3-(R): 4,6-di-O-benzylidene-α-D-mannopyranoside (***1b***).* — To a solution of methyl α-D-mannopyranoside (5 g) in *N,N*-dimethylformamide (30 mL) were added α,α-diethoxytoluene (11 g) and *p*-toluenesulfonic acid (0.1 g), and the mixture was treated according to the literature[3,4]. The crude product was dissolved in hot 1-propanol and, on cooling, compound **1b** crystallized (2.7 g, 28.5%). On recrystallization from the same solvent, it showed m.p. 180–182°, $[\alpha]_D^{20}$ 0.00 ($CHCl_3$); lit.[5] m.p. 181–182°, $[\alpha]_D$ +0.03° ($CHCl_3$).

From the mother liquors, compound **1a** crystallized on standing (2.7 g, 28.5%). On recrystallization, it showed m.p. 95–97°, $[\alpha]_D^{20}$ −69.0° ($CHCl_3$); lit.[5] m.p. 97–98°, $[\alpha]_D$ −61.3° ($CHCl_3$).

^{1}H-N.m.r. and ^{13}C-n.m.r. data for both diastereomers agreed with those described in the literature[6,7]. The only difference observed was in the ^{13}C-n.m.r. spectrum of compound **1a**, in which the two signals corresponding to the quaternary carbon atoms of the phenyl group could be distinguished (at 137.16 and 137.00 p.p.m.).

Hydrogenolysis of **1a**. — Compound **1a** (100 mg) was dissolved in 1:1 dichloromethane–ether and treated with $LiAlH_4$–$AlCl_3$ at 45°, as described in the literature[1]. After 30 min, the reaction was stopped, and the mixture was analyzed by t.l.c. with 19:1 benzene–ethyl acetate, and g.l.c. (for the conditions, see general methods).

$AlCl_3$-catalyzed isomerization (**1a** ⇄ **1b**). — The isomerizations were conducted at room temperature with 0.1M $AlCl_3$ in ether (0.4 mL) that was added to the following solutions: (*A*) 0.2M compound **1a** (or **1b**) in chloroform (5 mL), (*B*) 0.2M compound **1a** (or **1b**) in 4:1 chloroform–ether (5 mL), and (*C*) 0.2M compound **1a** in ether (5 mL).

Aliquots (0.2 mL) of (*A*) and (*B*), respectively, were taken at appropriate time intervals, and the reaction was stopped by pouring the solution into $NaHCO_3$ solution, and extracting the products with dichloromethane. The organic layer was washed to neutrality, dried ($MgSO_4$), and evaporated. The ratio of the isomers in

TABLE I

ACID-CATALYZED ISOMERIZATION OF **1a** AND **1b**

Time (h)	*Reaction conditions*[a]	*Starting material*	[1a]		[1b]	
			mmol/L	%	*mmol/L*	%
0	A	**1a**	185	100	0	0
	A	**1b**	0	0	185	100
	B	**1a**	185	100	0	0
	B	**1b**	0	0	185	100
3	A	**1a**	155	83.78	30	16.22
	A	**1b**	22	11.89	163	88.11
	B	**1a**	165	89.20	20	10.80
	B	**1b**	17	9.19	168	90.81
6	A	**1a**	143	77.30	42	22.70
	A	**1b**	34	18.38	151	81.62
	B	**1a**	144	77.84	41	22.16
	B	**1b**	26	14.05	159	85.95
24	A	**1a**	90	48.65	95	51.35
	A	**1b**	74	40.00	111	60.00
	B	**1a**	97	52.43	88	47.57
	B	**1b**	61	32.97	124	67.03
48	A	**1a**	82	44.32	103	55.68
	A	**1b**	79	42.70	106	57.30
	B	**1a**	77	41.62	108	58.38
	B	**1b**	77	41.62	108	58.38
72	A	**1a**	80	43.24	105	56.76
	A	**1b**	79	42.70	106	57.30
	B	**1a**	80	43.24	105	56.76
	B	**1b**	80	43.24	105	56.76
96	A	**1a**	80	43.24	105	56.76
	A	**1b**	78	42.16	107	57.84
	B	**1a**	77	41.62	108	58.38
	B	**1b**	77	41.62	108	58.38

[a]See Experimental section.

the mixture was determined by g.l.c. under the conditions described in General methods. The results obtained are given in Table I.

For (*C*), compound **1b** began to precipitate from the reaction mixture in the first hour, and therefore the aliquots taken were not representative of the isomeric composition. After 24 h, the mixture was diluted with enough dichloromethane to dissolve the organic compound, and processed as for (*A*) and (*B*). Compound **1b** crystallized in 85% yield on addition of 1-propanol.

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