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LEWIS-ACID-CATALYSED ISOMERISATION OF BENZYLIDENE ACETALS OF METHYL α-L-RHAMNOPYRANOSIDE AND METHYL β-L-ARABINOPYRANOSIDE DERIVATIVES

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ABSTRACT

The Lewis-acid-catalysed isomerisation of several derivatives of methyl 2,3-*O*-benzylidene-α-L-rhamnopyranoside and methyl 3,4-*O*-benzylidene-β-L-arabinopyranoside has been investigated. The presence of equatorial substituents vicinal to the benzylidene ring decreases the rate of isomerisation, and *exo* isomers isomerise more quickly than the corresponding *endo* isomers. The occurrence of isomerisation during the reductive cleavage reaction of acetal rings with $LiAlH_4$–$AlCl_3$ has been demonstrated.

INTRODUCTION

The phenyl group of dioxolane-type benzylidene acetals, involving vicinal *cis*-hydroxyl groups of pyranosides, may be *exo* or *endo* with respect to the bicyclic ring system. Reductive ring-cleavage of such benzylidene derivatives with the $LiAlH_4$–$AlCl_3$ reagent is selective and the direction of the reaction is dependent on the configuration at the acetal carbon atom[1–3]. However, a second benzyl-ether product was always detected in these reactions, which was identical to the major product of ring cleavage of the acetal having the opposite configuration at the acetal carbon. The formation of this by-product may be explained either by a non-selective reaction or by isomerisation preceding ring cleavage. The isomerisation of five- and six-membered cyclic acetals in the presence of Lewis acids has been investigated[4–16].

For dioxane-type benzylidene acetals, the phenyl group is generally equatorial. Benzylidenation under alkaline conditions also gives acetals having an axial phenyl group for both *cis*- and *trans*-decalin-type compounds[17,18]. However, the presence of a catalytic amount of hydrochloric acid results in isomerisation to the thermodynamically more-stable equatorial isomer. For dioxolane-type benzylidene acetals[19], the kinetic phase of acetal formation yields the *endo*-phenyl derivative, which gradually equilibrates with the *exo*-phenyl analogue.

Only a few studies have been published on the isomerisation of dioxolane-type benzylidene acetals. The acid-catalysed isomerisation of the *exo* isomer of 3,4,6-tri-*O*-acetyl-1,2-*O*-benzylidene-α-D-glucopyranose in the presence of toluene-*p*-

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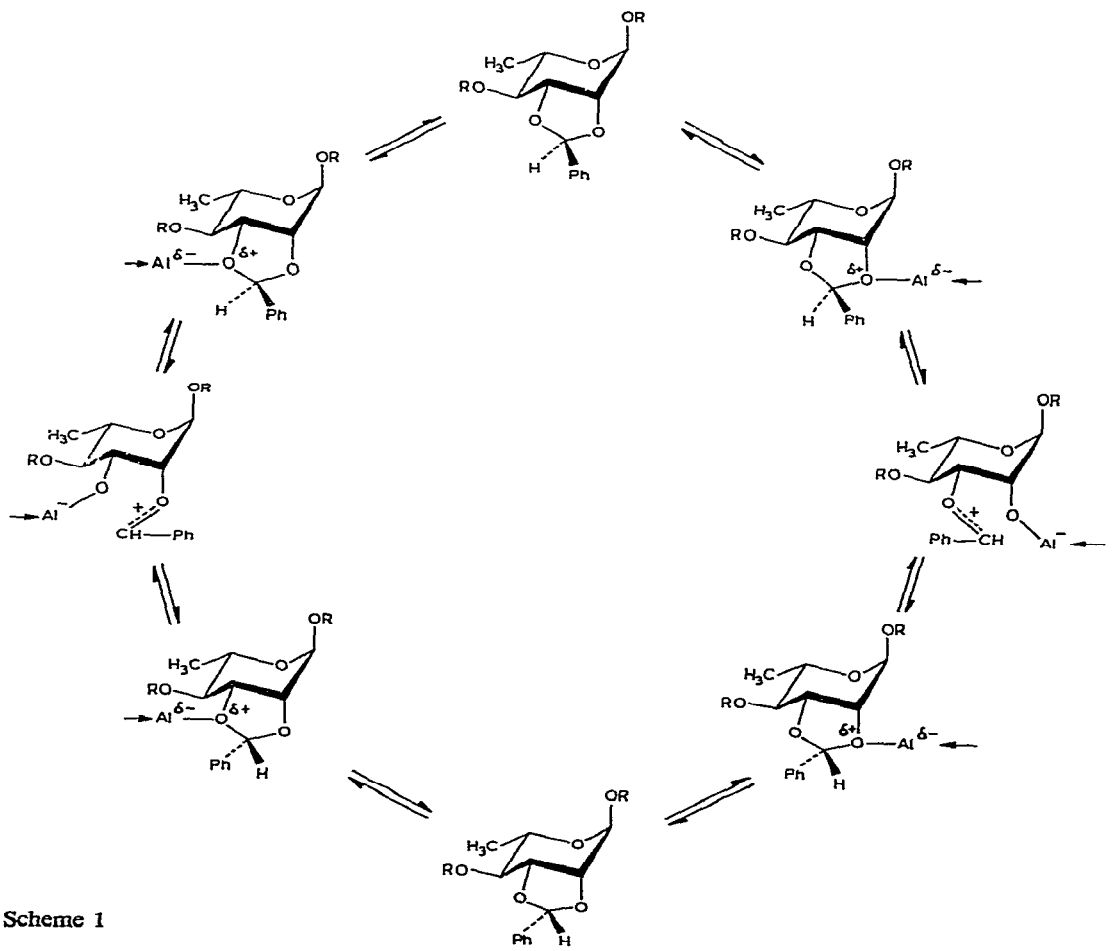
sulphonic acid has been reported[20], and the formation and simultaneous isomerisation of the 2,3-*O*-benzylidene derivative from methyl 3,4-*O*-benzylidene-β-D-ribopyranoside has been described[21]. The benzylidenation of methyl β-D-arabinopyranoside by the Gerhardt method[22] gave the *endo*-phenyl analogue which, in the presence of toluene-*p*-sulphonic acid, equilibrated with the *exo*-phenyl derivative to give a 1:1 mixture[23].

DISCUSSION

Under the conditions of the ring-cleavage reaction, the $LiAlH_4$–$AlCl_3$ reagent furnishes a Lewis-acid-type chloroalane[24], the Lewis-acid character of which is weaker[25] than that of $AlCl_3$. Therefore, $AlCl_3$ is a suitable catalyst for investigating isomerisation without cleavage of the acetal ring.



Scheme 1

TABLE I

ISOMERISATION OF METHYL 2,3-*O*-BENZYLIDENE-α-L-RHAMNOPYRANOSIDE DERIVATIVES

Derivative	$t_{1/2}$ *(min)*		*Isomer ratio (%)*	
	exo	endo	exo	endo
4-*O*-Bzl	18	27	52.0	48.0
4-*O*-Ac	4.5	12	60.5	39.5
4-*O*-Me	16.5	21	53.0	47.0
4-OH	2	4	53.5	46.5

TABLE II

ISOMERISATION OF METHYL 3,4-*O*-BENZYLIDENE-β-L-ARABINOPYRANOSIDE DERIVATIVES

Derivative	$t_{1/2}$ *(min)*		*Isomer ratio (%)*	
	exo	endo	exo	endo
2-*O*-Bzl	117	138	42.5	57.5
2-*O*-Ac	70	53	53.0	47.0
2-*O*-Me	32	41	48.0	52.0
2-OH	7	9	46.5	53.5

The initial phase of the isomerisation and ring cleavage is the interaction of a lone pair of electrons of the ring-oxygens with the aluminium atom which results in the polarisation and splitting of the C–O bond to form an oxo-carbonium cation[26]. Regeneration of the ring may afford either of the two isomers and may involve the cycle shown in Scheme 1.

The $t_{1/2}$ values for the isomerisation were obtained under standard conditions, using catalytic amounts of $AlCl_3$ (see Experimental), and they reflect the tendency to isomerise. The equilibrium ratio of the isomers was determined with both isomers.

The isomer equilibrium ratio was 1 : 1 for most of the dioxolane-type benzylidene acetals investigated, and thus there is only a small difference in energy between the *exo* and *endo* isomers.

Tables I and II show the equilibrium ratios and $t_{1/2}$ values obtained for methyl *exo*- (**1**) and *endo*-2,3-*O*-benzylidene-α-L-rhamnopyranoside[28–32] (**2**), their 4-*O*-acetyl[29] (**3** and **4**), 4-*O*-benzyl[29] (**5** and **6**), and 4-*O*-methyl[28,30,31] (**7** and **8**) derivatives, methyl *exo*- (**9**) and *endo*-3,4-*O*-benzylidene-β-L-arabinopyranoside[23,33,34] (**10**), and their 2-*O*-acetyl (**11** and **12**), 2-*O*-benzyl (**13** and **14**), and 2-*O*-methyl (**15** and **16**) derivatives.

The results show that substitution of the hydroxyl group vicinal to the benzylidene ring significantly increases the $t_{1/2}$ value, especially for the benzyl derivatives. The *exo* isomers isomerise more rapidly than the *endo* isomers and, in general, the rate

of isomerisation of the rhamnopyranoside analogues is higher than that of the arabinosides.

For the reactions with chloroalane or dichloroalane, the rate of isomerisation is comparable to that of the reductive ring-cleavage, and thus, the by-product is formed to an extent of 1–25%.

In order to detect isomerisation during the ring-cleavage reaction, the reaction of methyl *endo*-3,4-*O*-benzylidene-β-L-arabinopyranoside with 1:1 $LiAlH_4$–$AlCl_3$ was frozen after 10 min, and the *endo*,*exo*-ratio was determined by g.l.c. The initial ratio of 98.6:1.4 had changed to 85.6:14.4, thereby establishing that isomerisation occurred under the conditions of the ring-cleavage reaction.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. T.l.c. and column chromatography were performed on Kieselgel G (Merck) with: *A*, benzene–ethyl acetate (9:1); *B*, chloroform–acetone (95:5); *C*, light petroleum (b.p. 60–70°)–ethyl acetate (7:3); *D*, light petroleum–ethyl acetate (9:1). Detection was made possible by charring with sulphuric acid.

Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter. ^{1}H-N.m.r. spectra (Tables III and IV) were recorded at 100 MHz with a Jeol MH-100 instrument for solutions in $CDCl_3$ (internal Me_4Si).

The isomerisation reactions were carried out in n.m.r. tubes. To a 0.5M solution (0.5 ml) of the substrate in $CDCl_3$ was added a 0.1M solution of $AlCl_3$ in ether (0.1 ml), and the intensities of the signals for benzylidene protons were monitored. G.l.c. was performed using a Hewlett–Packard 5840A instrument fitted with a nickel column (1.2 m × 2 mm i.d.) packed with 10% of UCW 982 on Gas Chrom Q (80–100 mesh). Nitrogen was used as carrier gas at 20 ml/min. The temperature of the injector was 200°. The temperature programme was 170° for 1 min and then 3°/min up to 215°. A flame-ionisation detector was used with a temperature of 300°.

Methyl exo-*2,3*-O-*benzylidene-4*-O-*methyl*-α-L-*rhamnopyranoside* (**7**). — A solution of methyl *exo*-2,3-*O*-benzylidene-α-L-rhamnopyranoside[29] (**1**, 2 g) in *N*,*N*-dimethylformamide (30 ml) was methylated with methyl iodide (2.34 ml) in the presence of silver oxide (2.4 g). After 24 h, the reaction mixture was worked-up, to give syrupy **7** (1.96 g, 93%), $[\alpha]_D$ −42° (*c* 1, chloroform), R_F 0.68 (solvent *D*).

Anal. Calc. for $C_{15}H_{20}O_5$: C, 64.26; H, 7.21. Found: C, 64.15; H, 7.30.

Methyl endo-*2,3*-O-*benzylidene-4*-O-*methyl*-α-L-*rhamnopyranoside* (**8**). — Methyl *endo*-2,3-*O*-benzylidene-α-L-rhamnopyranoside[29] (**2**, 0.9 g) in *N*,*N*-dimethylformamide (10 ml) was treated with methyl iodide (1.1 ml) in the presence of silver oxide (1.1 g). The syrupy product was purified on a column of Kieselgel G (30 g), with solvent *D*, to give **8** (0.82 g, 87%), $[\alpha]_D$ −28° (*c* 1.5, chloroform), R_F 0.72 (solvent *D*).

Anal. Calc. for $C_{15}H_{20}O_5$: C, 64.26; H, 7.21. Found: C, 64.31; H, 7.18.

Methyl 2-O-*acetyl*-exo- (**11**) *and* -endo-*3,4*-O-*benzylidene*-β-L-*arabinopyranoside*

TABLE III

^{1}H-N.M.R. DATA FOR METHYL 2,3-*O*-BENZYLIDENE-α-L-RHAMNOPYRANOSIDE DERIVATIVES

Compound	*Coupling constants (Hz)*					*Chemical shifts, δ*								*Other signals*
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	H_3-*6*	*MeO-1*	=*CH-Ph*	
1	0.6	5.5	6.6	9.5	6.0	4.90	4.08	4.38	3.48	3.69	1.31	3.34	6.12	
2	<1.0			9.0	6.1	4.95				3.66	1.25	3.37	5.85	
3	<1.0	5.2	7.7	10.0	6.3	4.95	4.13	4.47	5.01	3.78	1.22	3.37	6.19	2.10 (AcO-4)
4	<1.0	6.1	6.9	10.0	6.3	4.99	4.20	4.34	4.94	3.78	1.18	3.38	5.88	2.07 (AcO-4)
5	<1.0	5.4	6.9	9.7	6.1	4.89	4.11	4.59	3.33	3.74	1.34	3.36	6.05	4.96, 4.71 ($J_{H,H}$ 11.8 Hz) (BzlO-4)
6	<1.0	6.3	6.6	9.8	6.2	4.98	4.20	4.40	3.24	3.73	1.26	3.36	5.90	4.83, 4.52 ($J_{H,H}$ 11.7 Hz) (BzlO-4)
7	<1.0	5.5	7.0	9.5	6.2	4.87	4.05	4.44	3.06	3.68	1.35	3.33	6.13	3.64 (MeO-4)
8	0.6	6.7	5.9	9.7	6.1	4.97	4.17	4.28	3.00	3.64	1.27	3.36	5.88	3.46 (MeO-4)

TABLE IV

^{1}H-N.M.R. DATA FOR METHYL 3,4-*O*-BENZYLIDENE-β-L-ARABINOPYRANOSIDE DERIVATIVES

Compound	*Coupling constants (Hz)*						*Chemical shifts, δ*								*Other signals*
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-5'*	*MeO-1*	=*CH-Ph*	
9	3.6	7.1	5.5	1.9	1.9		4.79	3.93	4.42	4.19	3.95	3.95	3.46	6.21	
10	3.7	5.6	6.2	1.6	1.6		4.70	3.83	4.32	4.24	3.99	3.99	3.42	5.88	
11	3.6	8.0	5.5	0.8	2.2	13.0	4.95	5.13	4.65	4.28	4.13	3.91	3.45	6.24	2.18 (AcO-2)
12	3.4	7.4	6.1	0.9	2.4	13.7	4.86	4.98	4.46	4.30	4.15	3.95	3.39	5.89	2.11 (AcO-2)
13	3.4	8.0	5.4	1.0	2.2	13.2	4.72	3.63	4.64	4.17	3.99	3.82	3.39	5.98	4.90, 4.77 ($J_{H,H}$ 12.3 Hz) (BzlO-2)
14	3.4	7.3	6.0	1.4	2.9	12.0	4.62	3.56	4.47	4.25	4.07	3.92	3.38	5.89	4.77, 4.58 ($J_{H,H}$ 12.6 Hz) (BzlO-2)
15	3.4	7.7	5.5	0.8	2.2	12.0	4.89	3.52	4.54	4.16	4.03	3.86	3.44	6.22	3.59 (MeO-2)
16	3.3	6.9	6.1	1.0	1.9	12.5	4.79	3.54	4.39	4.26	4.10	3.94	3.43	5.91	3.48 (MeO-2)

(**12**). — To a solution of methyl β-L-arabinopyranoside[33] (13.5 g) in *N,N*-dimethylformamide (84 ml) were added α,α-dimethoxytoluene (14 ml) and toluene-*p*-sulphonic acid (210 mg). The mixture was kept *in vacuo* for 40 min at 80°, and then cooled, diluted with chloroform (600 ml), washed with aqueous 5% $NaHCO_3$ (50 ml) and water (3 × 50 ml), dried (Na_2SO_4), and concentrated. The syrupy mixture (20 g, 96%) of **9** and **10** was treated with acetic anhydride (50 ml) in pyridine (50 ml), in the usual manner, and the product (23 g, 98%) was fractionated by column chromatography (solvent *A*), to give, first, methyl 2-*O*-acetyl-*endo*-3,4-*O*-benzylidene-β-L-arabinopyranoside (**12**, 7.5 g), m.p. 72–74°, $[\alpha]_D$ + 201° (*c* 0.9, chloroform), R_F 0.38.

Anal. Calc. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.18. Found: C, 61.32; H, 6.08.

Eluted second was methyl 2-*O*-acetyl-*exo*-3,4-*O*-benzylidene-β-L-arabinopyranoside (**11**, 5.0 g) as a syrup, $[\alpha]_D$ +211° (*c* 0.9, chloroform), R_F 0.32.

Anal. Calc. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.18. Found: C, 61.15; H, 6.29.

Methyl exo- (**9**) *and* endo-*3,4*-O-*benzylidene-β-*L-*arabinopyranoside* (**10**). — Zemplén deacetylation of **11** (4 g) gave **9** (3.1 g, 90.5%), m.p. 72–74°, $[\alpha]_D$ +207° (*c* 0.5, methanol), +175° (*c* 0.9, chloroform), R_F 0.54 (solvent *B*); lit.[23] $[\alpha]_D$ +173° (*c* 0.6, chloroform).

Anal. Calc. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.41. Found: C, 61.95; H, 6.33.

Likewise, **12** yielded **10**, m.p. 80–82°, $[\alpha]_D$ +183° (*c* 0.65, methanol), +159° (*c* 0.8, chloroform), R_F 0.58 (solvent *B*); lit.[23] $[\alpha]_D$ +162° (*c* 1, chloroform).

Anal. Calc. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.41. Found: C, 61.80; H, 6.52.

*Methyl 2-*O-*benzyl*-exo- (**13**) *and*-endo-*3,4*-O-*benzylidene-β-*L-*arabinopyranoside* (**14**). — A mixture of **9** (0.4 g), powdered potassium hydroxide (0.63 g), and benzyl chloride (5 ml) was stirred for 12 h at 100° and then cooled; unreacted benzyl chloride was removed by steam distillation. The residue was diluted with chloroform (200 ml), washed with water (3 × 50 ml), dried (Na_2SO_4), and concentrated, to give syrupy **13** (0.28 g, 51%), $[\alpha]_D$ +115° (*c* 0.9, chloroform), R_F 0.61 (solvent *B*).

Anal. Calc. for $C_{20}H_{22}O_5$: C, 70.15; H, 6.49. Found: C, 70.04; H, 6.57.

Similar benzylation of **10** (0.4 g) gave **14** (0.24 g, 44%), m.p. 58–60°, $[\alpha]_D$ +96° (*c* 0.8, chloroform), R_F 0.65 (solvent *B*).

Anal. Calc. for $C_{20}H_{22}O_5$: C, 70.15; H, 6.49. Found: C, 70.23; H, 6.36.

Methyl exo- (**15**) *and* endo-*3,4*-O-*benzylidene-2*-O-*methyl-β-*L-*arabinopyranoside* (**16**). — A mixture of **9** (0.4 g), methyl iodide (0.5 ml), and silver oxide (0.5 g) in anhydrous *N,N*-dimethylformamide (6 ml) was stirred overnight. Work-up in the usual manner gave syrupy **15** (0.4 g, 95%), $[\alpha]_D$ +164° (*c* 0.7, chloroform), R_F 0.33 (solvent *C*).

Anal. Calc. for $C_{14}H_{18}O_5$: C, 63.13; H, 6.83. Found: C, 63.21; H, 6.95.

Likewise, methylation of **10** (0.4 g) gave syrupy **16** (0.35 g, 83%), $[\alpha]_D$ +133° (*c* 1.3, chloroform), R_F 0.35 (solvent *C*).

Anal. Calc. for $C_{14}H_{18}O_5$: C, 63.13; H, 6.83. Found: C, 63.07; H, 6.71.

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