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Note

Hydrogenolysis of dioxolane-type benzylidene derivatives: a convenient preparation of methyl 2-*O*-benzyl- and 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside

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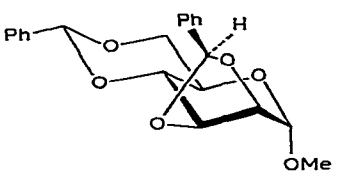
Srivastava and Srivastava[1,2] reported that benzylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside afforded methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside and that treatment of the tosylate with potassium *tert*-butoxide gave methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hex-2-enopyranoside. The m.p. and $[\alpha]_D$ value given[1] for the 3-*O*-benzyl derivative differed significantly from those reported earlier[3–5], and the selectivity of the benzylation reaction contrasts with that observed with methyl[6], benzyl[7], and *p*-nitrophenyl[8] 4,6-*O*-benzylidene-α-D-mannopyranosides. The reported ^{1}H-n.m r. data also differ from the (unpublished) data that we have obtained for methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside and for the 2-*O*-methyl analogue. We have now re-examined the reactions described by the Indian authors.

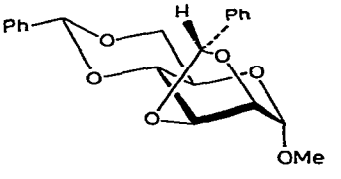
Methyl *exo*- and *endo*-2,3:4,6-di-*O*-benzylidene-α-D-mannopyranosides (**1** and **2**), first synthesised by Robertson[9] and characterised by Baggett *et al.*[10], were prepared according to the procedure of Horton[11]. Hydrogenolysis of the *exo*-isomer **1** with one mole of the $LiAlH_4$–$AlCl_3$ reagent at room temperature gave methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside[3–5] (**3**), whereas, under similar conditions, the *endo*-isomer **2** gave methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside[6] (**4**).

The observed direction of the ring-cleavage of **1** and **2** agreed with earlier findings for dioxolane-type benzylidene derivatives of L-rhamno-[13,16], D-arabino-[12,15], D-fuco[12], D-galacto-[12], and D-manno-pyranosides[13,14]. Our compound **3** was identical with the methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside severally described[3–5], but differed from the product of the Indian authors[1]. Also, our compound **4** was identical with the methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside characterised by Borén *et al.*[6].

The structures of **3** and **4** were unequivocally established by the ^{1}H-n m.r. data for the respective 2- (**5**) and 3-acetates (**6**). Of the ring-proton signals for **5**, only the signal for H-2 is shifted downfield (δ 5.39), and the low *J* values (1–3 Hz) indicate a gauche–gauche configuration of H-1,2,3. For **6**, H-3 is deshielded (δ 5.28) and the



1



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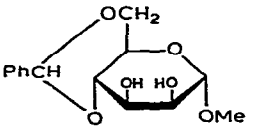
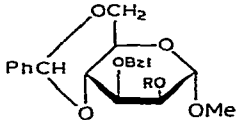
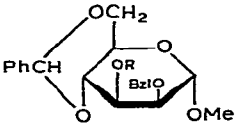


11

7 + 8





3	R = H	4
5	R = Ac	6
7	R = Me	8
9	R = Ts	10

$J_{2,3}$ and $J_{3,4}$ values (4 and 10 Hz, respectively) indicated H-2,3 to be *cis* and H-3,4 to be *trans*.

Methylation[17] of **3** and **4** gave chromatographically (g.l.c. and t.l.c.) homogeneous, syrupy **7** and **8**, respectively. The $[\alpha]_D$ value and ^{1}H-n.m.r. data for **7** were in good agreement with those reported by Nashed[5] for methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-methyl-α-D-mannopyranoside, but differed from those reported by the Indian authors[1]. The $[\alpha]_D$ value of **8** nearly corresponds to that reported[1] for methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-methyl-α-D-mannopyranoside, but the reported ^{1}H-n.m.r. data differed significantly from those obtained for our sample. The ^{13}C-n.m.r. data also supported the structures of **3** and **7**. Methylation of **3** caused shifts[18] (+10.5 and −0.5 p.p.m., respectively) in the signals for C-2 and C-1.

Tosylation of **3** gave a product (**9**), m.p. 124–126°, for which the only downfield shift in the ^{1}H-n.m.r. spectrum could be assigned to H-2. The physical constants [m.p. 97–98°, $[\alpha]_D$ +16° (*c* 1, chloroform)] of **10**, obtained by the tosylation of **4**, were consistent with those of the compound prepared by Srivastava and Srivastava[2]. However, this compound proved to be methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-toluene-*p*-sulphonyl-α-D-mannopyranoside (**10**), and not the 2-tosylate as reported[1]. The structure of **10** was established by the $J_{2,3}$ and $J_{3,4}$ values (3.5 and 10 Hz, respectively).

Benzylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**11**), under the conditions recorded by the Indian authors[1], gave (g.l.c.) a 1:1.86 mixture of **3** and **4**, from which the latter was isolated crystalline. The mobility of **4** in t.l.c., using the solvent system described by the Indian authors[1], is higher than the reported value; therefore, the compound that they isolated was the 2-*O*-benzyl derivative **4** and not the 3-*O*-benzyl isomer **3**.

TABLE I

P.M.R. CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (J)[a]

Compound	*H-1*	*H-2*	*H-3*	*H-4,5,6*	*H-6e*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	*PhCH₂O*	*PhCH*	*OMe*	*OAc*	*OH*
1	4 99	4.10	4.59	3.90–3.70	4.31	1.0	5.0			6.26 5.60	3.36		
2	5.06	— 4.50–3.60 ———				1.0				5.94 5.49	3 38		
3	4.68	— 4.30–3.60 ———				1 0			4.70	5.56	3.26		3.18
4	4.72	— 4.30–3.70 ———				1 0			4.70	5.52	3.32		2.52
5	4.66	5.39 —		4.30–3.70 ———		1.0	3.0		4.66	5.60	3.31	2.11	
6	4.72	—	5.28	4.30–3.75 ———		1.5	4 0	10 0	4.62	5.55	3.34	1.99	
7	4.70	— 4.30–3.50 ———				1.0			4.74	5.58	3.30 3.51		
8	4 70	— 4.30–3.55 ———				1.7			4.75	5.58	3.31 3 44		
9	4.93	4.76	— 4.30–3.65 ———			1.7	2.8		4.42	5.59	3.35	2.36 (tosyl)	
10	4.63	4.09	4.81	4.30–3.60 ———		2.1	3.5	10.0	4.81	5.42	3.29	2.31 (tosyl)	

[a]100 MHz, $CDCl_3$, internal Me_4Si.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. ^{1}H- and ^{13}C-n.m.r. spectra were obtained by using JEOL MH-100 (100 MHz) or VARIAN XL-100-15 F.T. instruments with Me_4Si as the internal standard. T.l.c. was performed on Kieselgel G (Merck) with chloroform–acetone (95:5).

G.l.c. was performed with a Hewlett–Packard 5830 A instrument and a column (4 ft × 2.16 mm) of stainless steel coated with 10% of UCW 982 on Gas Chrom Q (80–100 mesh); the following conditions were used: injection port, 275°; flame-ionisation detector, 300°; nitrogen flow-rate, 20 ml/min; temperature programme, 5°/min starting at 225° after a 1-min isothermal period.

Methyl 3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (**3**). — To a solution of methyl *exo*-2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside[10] (**1**, 3.7 g) in 1:1 ether–dichloromethane (50 ml) was added, with stirring, a solution of $LiAlH_4$ (0.38 g) and $AlCl_3$ (1.33 g) in ether (5 ml), and the stirring was continued for an additional 10 min. The excess of the reagent was decomposed with ethyl acetate (5 ml), and aluminium hydroxide was precipitated with water (10 ml). The salts were collected and washed with ether. The organic layer was dried (Na_2SO_4) and concentrated to obtain a syrupy mixture of two products [g.l.c., *T* 5.94 (96.3%) and 6.90 min (3.7%)]. The mixture was eluted from Kieselgel G (120 g) with 95:5 chloroform–acetone to give syrupy **3** (2.48 g, 67%), $[\alpha]_D$ +33° (*c* 2, ethanol), +47° (*c* 1.1, chloroform); lit.[3] $[\alpha]_D$ +38° (*c* 1, ethanol), lit.[4] $[\alpha]_D$ +38.3° (ethanol); *cf.* lit.[1] m.p. 68–69°, $[\alpha]_D$ +6.7° (chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ C-1 100.8, C-2 69.2, C-3 75.2, C-4 78.2, C-5 62.8, C-6 68.2, MeO-1 54.0, Ph-CH_2 72.2, and Ph-CH 101.1.

The 2-acetate (**5**) of **3** was a syrup, $[\alpha]_D$ +10.5° (*c* 2, chloroform).

Anal. Calc. for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 67.15; H, 6.46.

The 2-tosylate (**9**) of **3** had m.p. 124–126° (from 1-butanol), $[\alpha]_D$ −32° (*c* 0.9, chloroform); *cf.* lit.[2] m.p. 100°, $[\alpha]_D$ +22.8° (*c* 1, chloroform).

Anal. Calc. For $C_{28}H_{30}O_8S$: C, 63.86; H, 5.74; S, 6.09. Found: C, 63.98; H, 5.88; S, 6.21.

Methyl 2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (**4**). — Treatment of methyl *endo*-2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (**2**, 0.74 g) with $LiAlH_4$–$AlCl_3$, as described for **3**, gave (g.l.c.) a mixture of **3** and **4** in the ratio 22:78. Crystallisation of the mixture from ethanol (3 ml) gave **4** (340 mg, 45.8%), m.p. 41–42°, $[\alpha]_D$ +3.5° (*c* 1.8, chloroform); lit.[6] m.p. 42–44°, $[\alpha]_D$ +2° (*c* 1, chloroform).

The 3-acetate (**6**) of **4** was a syrup, $[\alpha]_D$ −15° (*c*. 1.8, chloroform).

Anal. Calc. for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.79; H, 6.47.

The 3-tosylate (**10**) of **4** had m.p. 97–98° (from 1-butanol), $[\alpha]_D$ +16° (*c* 1.1, chloroform).

Anal. Calc. for $C_{28}H_{30}O_8S$: C, 63.86; H, 5.74; S, 6.09. Found: C, 64.05; H, 5.81; S, 6.26.

Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl-α-D-mannopyranoside (**7**). —

A solution of **3** (3.74 g) in *N,N*-dimethylformamide (40 ml) and methyl iodide (2 72 g) was stirred for 18 h with silver oxide (2.72 g), and then diluted with chloroform (200 ml) and filtered. The filtrate was washed with 5% aqueous KCN (2 × 50 ml) and water (5 × 100 ml), dried (Na_2SO_4), and concentrated to give chromatographically homogeneous, syrupy **7** (3.49 g, 90.4%), $[\alpha]_D$ +60.5° (*c* 3, chloroform); lit.[5] $[\alpha]_D$ +65.4° (*c* 1.7, chloroform); *cf.* lit.[1] $[\alpha]_D$ +24.6° (chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ C-1 100.2, C-2 79.6, C-3 76.6, C-4 79.3, C-5 64.3, C-6 68.9, MeO-1 54.6, MeO-2 60.1, Ph-CH_2 73.0, and Ph-*C*H 101.6.

Methyl 2-O-benzyl-4,6-O-benzylidene-3-O-methyl-α-D-mannopyranoside (**8**). — Methylation of **4** (140 mg), as described for **3**, gave **7** as a syrup (136 mg, 93.8%), $[\alpha]_D$ +28° (*c* 0.9, chloroform).

Anal. Calc. for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.78: H, 6.56.

Benzylation of methyl 4,6-O-benzylidene-α-D-mannopyranoside. — A solution of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (0.3 g) in methyl sulphoxide (1.5 ml) was treated[1] for 2 h with a mixture of sodium hydride (300 mg), benzyl bromide (155 mg), and methyl sulphoxide (1 ml) under nitrogen. G.l.c. of the product revealed three components with *T* 5.94 (3-*O*-benzyl isomer), 6.90 (2-*O*-benzyl isomer), and 10 95 min (2,3-di-*O*-benzyl isomer). The ratio of the 3- and 2-*O*-benzyl isomers was 1 : 1.86.

Crystallisation of the mixture from ethanol (5 ml) gave a product (48 mg, 12 1%) whose m.p. was not depressed on admixture with **4**, and which had the same mobilities as **4** in t.l.c. and g.l.c.

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