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## Note

# Reaction pathway in the base transformation of 2,4-*O*-benzylidene-1,6-di-*O*-*p*-tolylsulfonyl-D-glucitol into 1,3-anhydro-2,4-*O*-benzylidene-D-glucitol

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A need for 2,4-*O*-benzylidene-1-*O*-*p*-tolylsulfonyl-D-glucitol (**1**) (or a derivative) arose, and examination of the literature indicated that a modification of the reaction sequence used by Haslam and Radford[1] seemed well suited for its production. Haslam and Radford, who clarified earlier work of Vargha[2], established that treatment of 2,4-*O*-benzylidene-1,6-di-*O*-*p*-tolylsulfonyl-D-glucitol (**2**) with base transformed **2** into the epoxide **3**, which was converted by further treatment into the oxetane **4**. This transformation was postulated by Haslam and Radford[1] to proceed by the pathway **2**→**3**→**1**→**4**. As the base treatment (5 h at 80°) reported was reasonably long and at a moderate temperature, there appeared a good chance that, by suitable variation, the reaction sequence could be controlled to give chiefly **1**.

Treatment of **2** with a mixture of dilute aqueous sodium hydroxide–1,4-dioxane 30° readily gave[1,2] **3** in >95% yield. When a solution of the epoxide **4** in aqueous 1,4-dioxane was heated to boiling and sodium hydroxide solution was added, t.l.c. (toluene–ethyl acetate, 1 : 1 v/v) revealed in 15–30 min the disappearance of epoxide **3** ($R_F$ 0.57) and the appearance of a spot having $R_F$ 0.45, in addition to a minor spot near the origin. Isolation gave a syrup, chromatography of which readily separated the crystalline compound ($R_F$ 0.45) from the minor spot. As this compound was expected to be **1**, its $^1$H-n.m.r. spectrum should have shown exchangeable protons and an aromatic methyl group, but neither were present. The $^1$H-n.m.r. spectrum supported structure **5** for this compound. Integration revealed 14 protons; 6 were assigned readily to a benzylidene group, the multiplets near $\delta$ 2.8 and 3.36 (2 and 1 proton, respectively) were assigned from their chemical shifts the 5,6,6′ protons in **5** on the basis that similarly located multiplets occur in **3**, and the other 5 protons were probably methine and methylene protons. The analysis was consistent with the formula $C_{13}H_{14}O_4$, a dianhydrobenzylidenehexitol.

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Structure **5** was proved correct by boiling compound **5** in sodium hydroxide–1,4-dioxane. Acetylation of the product yielded the oxetane **6**, identical in all respects with the reported compound[1]. In view of these findings, the pathway from the disulfonate **2** to the oxetane **4** requires modification as follows, **2**→**3**→**5**→**4**.

A one-proton, exchangeable doublet, $\delta$ 2.3, $J$ 10.0 Hz, was present in the $^1$H-n.m.r. spectrum of **3**, and it was assigned to HO-3. The large coupling-constant observed is unusual and indicates that the dihedral angle between H-3 and Ha in H-3–C-3–O–Ha must be fixed near 180°, suggestive of a hydrogen bond. Inspection of molecular models suggested an explanation for this hydrogen bond. In formula **7** three groups (A, B, and Ph) are equatorially disposed on the 1,3-dioxane ring. If the alternative chair form of the 1,3-dioxane ring is considered, the A, B, and Ph groups would be axially disposed in a conformation generally regarded as unfavorable because of 1,3-diaxial interactions. With structure **7** as shown, D-glucitol would require HO-3 to be axially disposed, thus placing the OH group in proximity to O-1 and O-3 of the 1,3-dioxane ring, these obviously being the source of the hydrogen bonding[3].

Formation of the oxetane ring so alters the glucitol chain that preparation of **1** by this approach seemed unlikely. A second approach appeared probable as models of **8** revealed the steric relationship of the 1-*O*-*p*-tolylsulfonyl group and the 3-*O*-acetyl group to be similar to that at C-4 and C-6 in galactopyranosides. It is well known that nucleophilic displacement of 6-*O*-sulfonyl derivatives of galactopyranosides[4a] and of similarly arranged sulfonyl derivatives[4b] occurs much less readily. Thus, the 6-*O*-*p*-tolylsulfonyl group of **8** was expected to undergo preferential displacement.

Treatment of **8** with lithium benzoate in *N*,*N*-dimethylformamide at elevated temperature gave a mixture that eventually yielded a compound whose analysis and $^1$H-n.m.r. spectrum were consistent with structure **9**.

## EXPERIMENTAL

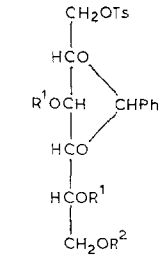
*General methods.* — For general methods, see ref. 5. Some $^1$H-n.m.r. spectra were recorded with a Bruker WH-90 instrument. Microanalyses were performed by Galbreath Laboratories, Inc., Knoxville, Tennessee.

*2,4-O-Benzylidene-D-glucitol.* — This compound was prepared according to Ness[6].

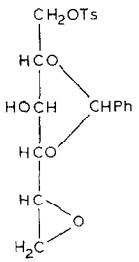
*2,4-O-Benzylidene-1,6-di-O-p-tolylsulfonyl-D-glucitol* (**2**). — The compound was prepared according to Vargha[2]; m.p. 125–126°, as reported by Haslam and Radford[1].

*3,5-Di-O-acetyl-2,4-O-benzylidene-1,6-di-O-p-tolylsulfonyl-D-glucitol* (**8**). — The compound was prepared according to Vargha[2].

*5,6-Anhydro-2,4-O-benzylidene-1-O-p-tolylsulfonyl-D-glucitol* (**3**). — Compound **1** (10.0 g) was dissolved in 1,4-dioxane (400 mL) and the solution was warmed to 30 ± 1°. Sodium hydroxide (200 mL, 0.1M) was added dropwise during 15–20 min.



1 $R^1 = R^2 = H$
2 $R^1 = H, R^2 = Ts$
8 $R^1 = Ac, R^2 = Ts$
9 $R^1 = Ac, R^2 = Bz$



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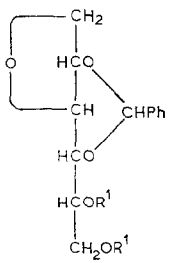
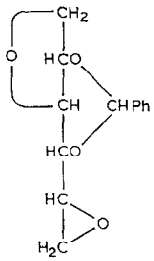


4 $R^1 = H$
6 $R^1 = Ac$



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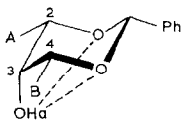

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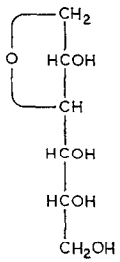

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After 1.5 h at 30 $\pm 1°$, carbon dioxide was bubbled through the solution until the pH reached ~8 (paper). During vacuum concentration of the solution, compound **3** separated as a granular solid. To remove the 1,4-dioxane, water was added and the solution was reconcentrated 2–3 times. Water was added again, and the solution was chilled overnight at 3–5°. Filtration and air drying of the solid gave between 6.7–6.9 g of **3**, m.p. 135–137° (lit.[2] m.p. 137°). This product was suitable for further reactions.

*1,3:5,6-Dianhydro-2,4-*O*-benzylidene-*D*-glucitol* (**5**). — Compound **3** (5.0 g) was dissolved in 1,4-dioxane–water (230:90 mL) and the solution was heated to boiling. Sodium hydroxide (30 mL, 0.5M) was added dropwise (~3 mL/min). After 15–30 min of boiling, the solution was cooled in an ice bath and carbon dioxide was bubbled through the solution until the pH reached ~8 (paper). Vacuum concentration gave a syrup that was transferred with water to an extractor and continuously extracted with ethyl acetate for 18 h. Removal of the solvent left a syrup that was placed on a column (3.4 × 49 cm) of dry silica gel, and the column was developed with toluene–ethyl acetate (400:200, and 200:200 mL, v/v) and ethyl acetate (400 mL). Each fraction was monitored by t.l.c. and appropriate fractions were pooled. On monitoring the fractions by t.l.c., many trace compounds appeared, and if the original boiling was not long enough, unaltered **3** would overlap **5** on elution. If this did occur,

the fractions were combined, evaporated, and reheated with sodium hydroxide in aqueous 1,4-dioxane. Concentrating the pooled fractions gave a syrup that slowly crystallized; m.p. 82–89°, yield 10–40%. Recrystallization from 95% ethanol gave an analytical sample of **5**: m.p. 94–95°, $[\alpha]_D^{21}$ +23.9 (*c* 1.31, 1,4-dioxane); n.m.r. ($CDCl_3$): $\delta$ 7.5–7.3 (m, 5 H, aryl), 5.45 (s, 1 H, PhCH), 4.9–4.8 (m, 3 H, unassigned), 4.5–4.4 (m, 1 H, unassigned), 3.7–3.6 (m, 1 H, unassigned), 3.5–3.3 (m, 1 H, H-5), and 2.9–2.8 (m, 2 H, H-6,6').

*Anal.* Calc. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.63; H, 6.09

*5,6-Di-O-acetyl-1,3-anhydro-2,4-O-benzylidene-*D*-glucitol* (**6**). — A solution consisting of 1,4-dioxane (15 mL), sodium hydroxide (8 mL, 0.5M), and **5** (404 mg) was heated to boiling for 3.5–4 h. Carbon dioxide was bubbled through the cooled solution until the pH reached ~8 (paper), and the solution was then transferred to an extractor. Continuous extraction with ethyl acetate (overnight) and removal of solvent left a gum that was acetylated by dissolving it in pyridine (5 mL) and acetic anhydride (5 mL). After being kept overnight, the mixture was poured into ice–water and the solution was extracted with five 10-mL portions of dichloromethane. Evaporation of the dichloromethane left a syrup that was placed on a column (2.5 × 49 cm) of dry silica gel and developed with toluene–ethyl acetate [125:75, 100:100, and 75:125 mL (v/v)]. The appropriate fractions were pooled and concentrated to give crystals. Recrystallization from 50% ethanol (~25 mL/g) gave pure **6**: yield 40–60%, m.p. 83–84°, $[\alpha]_D^{21}$ +12.2 (*c* 1.25, 1,4-dioxane) [lit.[1] m.p. 81–82°, $[\alpha]_D^{21}$ +11 (*c* 3.0, 1,4-dioxane)]. The $^1$H-n.m.r. spectrum nearly matched the published spectrum[1] for **6**.

*1,3-Anhydro-*D*-glucitol* (**10**). — A solution consisting of **5** (0.61 g), 1,4-dioxane (10 mL), and sodium hydroxide (50 mL, 0.1M) was boiled and extracted with ethyl acetate as just reported for the preparation of **6**. The residue left after removal of solvent was covered with 1,4-dioxane (20 mL) and hydrochloric acid (20 mL, 0.1M), boiled for 2.5 h, and cooled, and the pH was adjusted to 7.0 with dilute sodium hydroxide. Evaporation left a residue that was transferred with water to an extractor, and the solution was continuously extracted with ethyl acetate overnight. The aqueous portion was removed from the chamber and concentrated to a tacky solid. Placing this solid on a column (1.5 × 17 cm) of dry silica gel and developing with ethyl acetate–methanol (100:10, 80:20, 50:50, and 20:80 mL, v/v) gave a solid on pooling and concentrating the appropriate fractions. Recrystallization by dissolution in ethanol (~15 mL/g), cooling to room temperature, adding an equal volume of ether, and storing at 3–5° gave pure **10**: yield 40–60%; m.p. 86–86.5°, $[\alpha]_D^{21}$ −47.9 (*c* 1.5, water) [lit.[1] m.p. 98–99°, $[\alpha]_D^{20}$ −1° (*c* 6.0, water)].

*Anal.* Calc. for $C_6H_{12}O_5$: C, 43.90; H, 7.36. Found: C, 44.11; H, 7.54

Acetylation of **10** (45.3 mg) according to Haslam and Radford[1], except that a column of silica gel was used in the chromatographic step, resulting in a syrup (67 mg) whose $^1$H-n.m.r. spectrum gave a ratio of acetyl to (methine + methylene) protons of 1.4:1 (theory 1.5:1).

*3,5-Di-O-acetyl-6-O-benzoyl-2,4-O-benzylidene-1-O-p-tolylsulfonyl-*D*-glucitol*

(**9**). — A mixture of **8** (5.0 g) and lithium benzoate (3.0 g) in *N*,*N*-dimethylformamide (100 mL) was heated for 5 days at 63 ±1°, cooled, and the mixture poured into ice–water (~300 mL). A tacky solid separated. After decanting the aqueous portion, the solid was dissolved in dichloromethane (50 mL) and the solvent was washed with two 50-mL portions of water, dried, and concentrated to a syrup. The syrup was placed on a column (2.5 × 52 cm) of dry silica gel that was developed with toluene–ethyl acetate (200:10, 200:20, 160:40, 140:60 mL v/v). Monitoring each fraction by t.l.c. established that at least four compounds were eluted, but there was overlapping between components. Fractions giving single spots in t.l.c. were pooled and concentrated. Progressively eluted were: (*1*) a compound, m.p. 123–124°, whose $^1$H-n.m.r. spectrum indicated a di-*O*-acetyl-*O*-benzoyl-*O*-benzylidenehexitol; it was not further investigated; (*2*) 3,5-di-*O*-acetyl-1,6-di-*O*-benzoyl-2,4-*O*-benzylidene-D-glucitol; and (*3*) compound **9**, m.p. 128–134°, yield 1.9 g. Two recrystallizations from ethanol gave **9**; m.p. 133–134°, $[\alpha]_D^{21}$ −4.9° (*c* 1.62, acetone); n.m.r. ($CDCl_3$): δ 8.1–7.2 (m, 14 H, aryl), 5.64 (s, 1 H, PhCH), 5.4–5.1 (m, 2 H, H-3,5), 4.7–4.5 (dd, 2 H, H-6,6′), 4.45–4.2 (m, 2 H, H-2,4), 4.1 (d, 2 H, H-1,1′), and 2.40, 2.06 (s, 9 H, $CH_3$).

*Anal.* Calc. for $C_{31}H_{32}O_{11}S$: C, 60.77; H, 5.26; S, 5.23. Found: C, 60.85; H, 5.28; S, 5.20.

ACKNOWLEDGMENT

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