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Note

Synthesis of carbohydrate epoxides under phase-transfer conditions

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Intramolecular nucleophilic displacement by a vicinal α-oxyanion is a general method for the synthesis of epoxides[1] and has been applied widely in the carbohydrate field[2]. Diols are transformed into epoxides usually by sulfonylation and then treatment with a base[3]. The phase-transfer (p.t.) technique[4] is a simple method for the regioselective monotosylation of gluco- and manno-pyranosides having HO-2,3 unsubstituted under catalysis by the tetrabutylammonium ion and using dilute sodium hydroxide[5]. The alkoxide formed from the diol in the aqueous phase forms an ion-pair with the catalyst cation which is transferred into the organic phase and reacts to produce a monotosylate. The monotosylate tends to remain in the organic phase and does not undergo further tosylation or intramolecular elimination. Under p.t. conditions in the presence of conc. aqueous sodium hydroxide, the ionisation of a weak, poorly water-soluble C–H acid takes place at the interphase[6]. Under these conditions, ionisation of the hydroxyl group in the monotosylate formed would be expected with subsequent formation of the epoxide. Thus, treatment of cycloalkane-1,2-diols with 1 mol of tosyl or mesyl chloride under p.t. conditions, using conc. aqueous sodium hydroxide, gave the epoxides in good yields[7] and we now report some applications of this procedure in the carbohydrate series.

On treatment of 1,2-*O*-isopropylidene-6-*O*-toluene-*p*-sulfonyl-α-D-glucofuranose[3] (**1**) under p.t. conditions with aqueous sodium hydroxide at room temperature, in the presence, severally, of the p.t. catalysts benzyltriethylammonium chloride (TEBA), tetrabutylammonium chloride or bromide or hydrogen sulfate, and polyethylene glycol 400, the rate of the reaction depended on the concentration of the base. With saturated aqueous sodium hydroxide, **1** reacted rapidly and t.l.c. showed that the ester was converted into the 5,6-epoxide within a few minutes, whereas, in the presence of aqueous 20% sodium hydroxide, 2 days were required for completion of the reaction. When 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**4**) was treated under p.t. conditions with 1 mol of tosyl chloride in the presence of aqueous 20% sodium hydroxide, the 6-tosylate was the main product after 30 min together with the 5,6-ditosylate and a small proportion of the 5,6-epoxide **6**. On using saturated aqueous sodium hydroxide, the reaction was com-

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plete within a few minutes, and a good yield of **6** was obtained accompanied by the 5,6-ditosylate. In order to minimise this side-reaction, the solution of tosyl chloride in the organic solvent was added dropwise into the reaction mixture. In a similar manner, 1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-D-glucofuranose (**5**) and 1,2-*O*-isopropylidene-α-D-glucofuranose (**3**) were converted into the respective 5,6-epoxides **1** and **8**, and 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**9**) was converted into the 3,4-anhydro-D-altritol derivative **10**.

When methyl 4,6-benzylidene-2-*O*-toluene-*p*-sulfonyl-α-D-glucopyranoside (**12**) was treated under p.t. conditions in the presence of aqueous 5% or 20% sodium hydroxide and tetrabutylammonium bromide, no epoxide was formed, but, with saturated aqueous sodium hydroxide, 25% of the 2-tosylate was converted into the 2,3-anhydro-D-mannopyranoside derivative **13**. However, when the reaction was conducted at 80°, a good yield of **13** was obtained within 20 min. An almost theoretical yield of **13** was obtained when polyethylene glycol 400 was used as the catalyst. The 2-tosylate **12** failed to react in the absence of a p.t. catalyst.

Treatment of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**11**) with 1 mol of tosyl chloride under p.t. conditions gave **13** together with substantial amounts of the 2,3-ditosylate. The selectivity of the reaction could be improved by reacting **11** with tosyl chloride in the two-phase system benzene–conc. aqueous sodium hydroxide in the absence of the catalyst. Under these conditions, **11** can come into contact with the base only at the interphase and the resulting anion is insoluble in the aqueous phase due to the strong salt effect. Moreover, the ion-pair cannot pass into the organic phase. Consequently, the anions are unreactive and only the 2-tosylate **12** was formed. The preferential formation of **12** reflects the higher acidity of HO-2 and also[8] the sodium ion, whilst being associated with the alkoxide ion on C-2, may interact with methoxide. The use of a stable p.t. catalyst, polyethylene glycol 400, results in the formation of a very reactive ion-pair, well soluble in the organic phase, and the epoxide **13** is formed rapidly. The rapid tosylation of **11** in a two-phase system followed by the addition of a p.t. catalyst that effects epoxide formation is a more convenient one-pot synthesis of **13** than that which utilises sodium hydride under anhydrous conditions[9].

EXPERIMENTAL

General. — Optical rotations were determined for solutions in chloroform (*c* 1). T.l.c. was performed on Kieselgel G (Merck) with benzene–ethyl acetate (8:1) and detection by charring with sulfuric acid. Column chromatography was performed on Silica Gel 60 (Merck, 63–200 μm), using benzene–ether (20:1). Organic solutions were dried with $MgSO_4$ and concentrated under diminished pressure. I.r. spectra were recorded with a Specord IR spectrometer (Zeiss-Jena) for solutions in carbon tetrachloride. ^{1}H-N.m.r. spectra were recorded with a Tesla spectrometer for solutions in $CDCl_3$ (internal Me_4Si). P.t. catalysts were commercial products. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose[10], 1,2-*O*-isopropylidene-α-D-glu-

cofuranose[10] (**3**), 1,2-*O*-isopropylidene-6-*O*-toluene-*p*-sulfonyl-α-D-glucofuranose[3] (**1**), 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[11] (**4**), 1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-D-glucofuranose[12] (**5**), 1,2:5,6-di-*O*-isopropylidene-D-mannitol[13] (**9**), and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside[14] (**11**) were prepared by literature methods.

Methyl 4,6-O-benzylidene-2-O-toluene-p-sulfonyl-α-D-glucopyranoside (**12**). — A solution of **11** (2.8 g, 10 mmol) and tosyl chloride (1.9 g, 10 mmol) in benzene (20 mL) was stirred under reflux with aqueous 40% sodium hydroxide (10 mL) for 5 min. The mixture was then poured into ice–water, and the organic layer was separated, washed with water (3 × 20 mL), dried, and concentrated. The residue was recrystallised from ethanol, to yield **12** (3.3 g, 76%), m.p. 153–154°; lit.[3] m.p. 153–154°.

5,6-Anhydro-1,2-O-isopropylidene-α-D-glucofuranose (**2**). — A solution of **1** (0.274 g, 1 mmol) and TEBA (0.023 g, 0.1 mmol) in chloroform (5 mL) was stirred with saturated aqueous sodium hydroxide (1 mL) for 5 min. Ether (20 mL) was then added, and the organic layer was separated, washed with water (3 × 10 mL), dried, and concentrated. The solid residue was recrystallised from benzene, to yield **2** (0.18 g, 89%), m.p. 132–133°; lit.[3] m.p. 133.5°.

Preparation of epoxides from acyclic diols. — A solution of the diol (1 mmol) and TEBA (0.023 g, 0.1 mmol) in dichloromethane (5 mL) was stirred with saturated aqueous sodium hydroxide (2 mL) at room temperature. A solution of tosyl chloride (0.19 g, 1 mmol) in dichloromethane (5 mL) was added dropwise during 20 min, and stirring was continued for 10 min. The organic layer was separated, washed with water (3 × 10 mL), dried, and concentrated. The syrupy residue (**6–8**) was subjected to column chromatography. The structure of each epoxide was proved by comparison of the ^{1}H-n.m.r. and i.r. spectra with those of the authentic compounds.

The following compounds were prepared by the above procedure.

5,6-Anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**6** from **4**; 0.26 g, 91%), $[\alpha]_D^{20}$ −50°; lit.[15] $[\alpha]_D^{19}$ −51.2°.

5,6-Anhydro-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-D-glucofuranose (**7** from **5**; 0.24 g, 86%), $[\alpha]_D^{20}$ −58°; lit.[12] m.p. 80°, $[\alpha]_D^{24}$ −60°.

5,6-Anhydro-3-*O*-toluene-*p*-sulfonyl-α-D-glucofuranose (**8** from **3** and 2 mol of tosyl chloride; 0.32 g, 90%), $[\alpha]_D^{20}$ −49°; lit.[12] $[\alpha]_D^{26}$ −50.9°.

3,4-Anhydro-1,2:5,6-di-*O*-isopropylidene-D-altritol (**10** from **9**; 0.22 g, 89%), m.p. 53–54° (from ether–light petroleum), $[\alpha]_D^{20}$ −16°; lit.[16] m.p. 54–56°, $[\alpha]_D^{20}$ −16.2°.

Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (**13**). — A solution of **12** (0.44 g, 1 mmol) and polyethylene glycol 400 (0.04 g) in benzene (5 mL) was stirred under reflux with saturated aqueous sodium hydroxide (1 mL) for 30 min. The mixture was then cooled, and the organic layer was separated, washed with water (3 × 5 mL), dried, and concentrated. The residue was recrystallised from methanol, to yield **13** (0.24 g, 91%), m.p. 147–148°; lit.[3] m.p. 145–147°.

A mixture of **11** (2.82 g, 10 mmol) and tosyl chloride (1.90 g, 10 mmol) in benzene (25 mL) was stirred with aqueous 40% sodium hydroxide (10 mL) under reflux for 5 min. Polyethylene glycol 400 (0.40 g, 1 mmol) and sodium hydroxide (5 g) were then added. Heating was continued for 30 min and the reaction mixture was worked-up as described above, to give **13** (1.91 g, 72%), m.p. 147–148°.

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