

595 *The Preparation of Some Esters of Methyl 4 : 6-O-Benzylidene- $\alpha$ -D-altroside.\**

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Several nitrate and toluene-*p*-sulphonate esters of methyl 4 : 6-*O*-benzylidene- $\alpha$ -D-altroside have been prepared and characterized. Attention is drawn to the extreme sensitivity to alkali of the 2-toluene-*p*-sulphonate ester, which is converted into methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene- $\alpha$ -D-alloside even on being chromatographed on acid-washed alumina.

NITRATION of methyl 4 : 6-*O*-benzylidene- $\alpha$ -D-altroside (I) with excess of fuming nitric acid in acetic anhydride gives the 2 : 3-dinitrate (III), but use of one molecular proportion of acid leads to the 3-mononitrate (II). This is similar to the unimolar nitrations of methyl 4 : 6-*O*-benzylidene- $\alpha$ -D-glucoside<sup>1</sup> and methyl 4 : 6-*O*-ethylidene- $\alpha$ -D-mannoside<sup>2</sup> which also give the corresponding 3-nitrates. Methyl 4 : 6-*O*-benzylidene- $\alpha$ -D-altroside 3-nitrate has been prepared by the action of sodium nitrite in boiling aqueous ethanol on the corresponding 2 : 3-dinitrate. Again this is similar to the 2 : 3-dinitrates of methyl 4 : 6-*O*-benzylidene- $\alpha$ -D-glucoside<sup>3</sup> and methyl 4 : 6-*O*-ethylidene- $\alpha$ -D-mannoside<sup>4</sup> which preferentially lose the nitrate group from C<sub>(2)</sub>. The 3-nitrate (II) has been characterized by nitration to the 2 : 3-dinitrate and conversion, through methylation, denitration, and toluene-*p*-sulphonylation, into known methyl 4 : 6-*O*-benzylidene-2-*O*-methyl- $\alpha$ -D-altroside 3-toluene-*p*-sulphonate<sup>5</sup> (IV).

Two methods have been employed for reducing nitrates of methyl 4 : 6-*O*-benzylidene- $\alpha$ -D-altroside. Hydrazine hydrate converts both the 2 : 3-dinitrate (III) and the 3-nitrate (II) into the parent alcohol (I) in good yield, but the 3-nitrate 2-toluene-*p*-sulphonate (V) gives a mixture of methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene- $\alpha$ -D-alloside (VII) (24%) and methyl 4 : 6-*O*-benzylidene- $\alpha$ -D-altroside 2-toluene-*p*-sulphonate (VI) (66%). The latter is very sensitive to alkaline media and is wholly or partly converted into the anhydro-compound (VII) merely on being chromatographed on ordinary or acid-washed alumina.

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<sup>1</sup> Honeyman and Stening, *J.*, 1958, 537.

<sup>2</sup> Aspinal and Zweifel, *J.*, 1957, 2271.

<sup>3</sup> Honeyman and Morgan, *J.*, 1955, 3660.

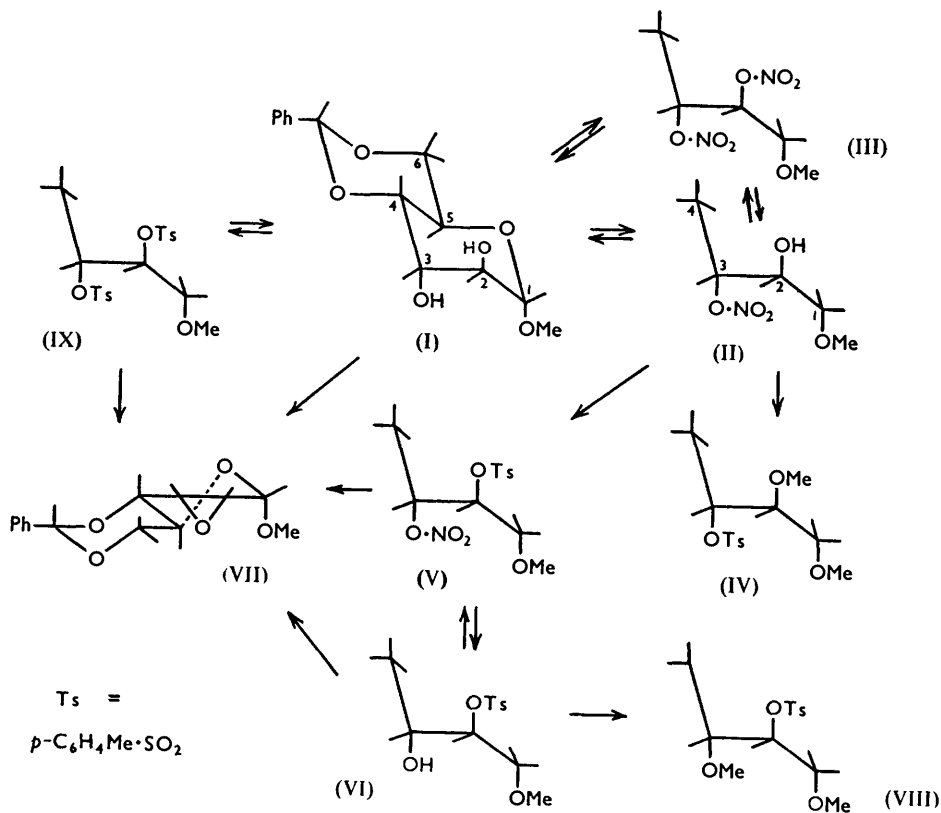
<sup>4</sup> Honeyman and Stening, *J.*, 1957, 2278.

<sup>5</sup> Robertson and Griffith, *J.*, 1935, 1193.

Although hydrazine is only a weak base, the reaction medium is sufficiently alkaline to bring about elimination of the toluene-*p*-sulphonate group with inversion of the configuration at C<sub>(2)</sub>. The diaxial system of 2-toluene-*p*-sulphonyloxy- and 3-hydroxyl groups gives a planar system which is most favourable for a base-catalysed intramolecular S<sub>N</sub>2 reaction leading to the 2:3- $\alpha$ -D-*allo*-epoxide.<sup>6</sup> In marked contrast to the 2-toluene-*p*-sulphonate, the 2:3-ditoluene-*p*-sulphonate of methyl 4:6-*O*-benzylidene- $\alpha$ -D-altroside is unaffected by hydrazine hydrate and is much more stable to alkali: it can, for example, be chromatographed on ordinary alumina without change.

In the second method catalytic hydrogenation of methyl 4:6-*O*-benzylidene- $\alpha$ -D-altroside 3-nitrate 2-toluene-*p*-sulphonate at room temperature under pressure, with palladium-charcoal, gives an almost quantitative yield of methyl 4:6-*O*-benzylidene- $\alpha$ -D-altroside 2-toluene-*p*-sulphonate. Under these neutral conditions, conversion of the 2-toluene-*p*-sulphonate into the 2:3-*allo*-epoxide is prevented. The amorphous product was characterized by nitration to the 3-nitrate 2-toluene-*p*-sulphonate and by methylation to the 3-*O*-methyl 2-toluene-*p*-sulphonate<sup>7</sup> (VIII).

Attempts to prepare methyl 4:6-*O*-benzylidene- $\alpha$ -D-altroside 2-toluene-*p*-sulphonate by selective sulphonylation of methyl 4:6-*O*-benzylidene- $\alpha$ -D-altroside all failed. When



one mole of toluene-*p*-sulphonyl chloride is used at 0° for 16 hr., only the 2:3-ditoluene-*p*-sulphonate (IX) and unchanged compound (I) were isolated. Similar experiments at -15° with a shorter reaction time gave methyl 2:3-anhydro-4:6-*O*-benzylidene- $\alpha$ -D-alloside (VII) in addition to (IX) and (I). It appears probable that any

<sup>6</sup> Newth, J., 1956, 441.

<sup>7</sup> Gut and Prins, *Helv. Chim. Acta*, 1946, 29, 1555.

2-toluene-*p*-sulphonate ester formed during these sulphonylation experiments is converted into methyl 2 : 3-anhydro-4 : 6-O-benzylidene- $\alpha$ -D-alloside on the alumina column.

#### EXPERIMENTAL

Unless otherwise stated, specific rotations were determined for  $\text{CHCl}_3$  solutions, the light petroleum used had b. p. 60—80°, solutions in chloroform or benzene were dried over sodium sulphate, and solvents were evaporated at reduced pressure.

"Alumina" refers to activated alumina, Type H, 100/200 S mesh, supplied by Messrs. Peter Spence & Sons, Ltd. Acid-washed alumina, "WOELM," is supplied by Messrs. L. Light & Co., Ltd. Hydrazine hydrate was 100% B.D.H. Laboratory Reagent.

Where appropriate, mixed m. p. were determined to help to establish identities.

*Methyl 4 : 6-O-Benzylidene- $\alpha$ -D-altroside 2 : 3-Dinitrate.*—An ice-cold solution of fuming nitric acid (*d* 1.5; 4 ml., 0.09 mole) in acetic anhydride (10 ml.) was added slowly to a suspension of methyl 4 : 6-O-benzylidene- $\alpha$ -D-altroside (5 g., 0.018 mole) in acetic anhydride (10 ml.) at 0°. After 20 min. at room temperature, the mixture was poured into ice-water containing potassium carbonate. The crude syrup was chromatographed in benzene solution on alumina, and the syrup obtained by elution with benzene was dissolved in warm methanol and reprecipitated in ice-water. After several weeks the syrup solidified to give *methyl 4 : 6-O-benzylidene- $\alpha$ -D-altroside 2 : 3-dinitrate* (70%), m. p. 48—49° (Found: C, 45.6; H, 4.5; N, 7.3.  $\text{C}_{14}\text{H}_{16}\text{O}_{10}\text{N}_2$  requires C, 45.2; H, 4.3; N, 7.5%).

Similar preparations were carried out with different reaction times, but the syrups solidified with difficulty only after long storage under water.

*Methyl 4 : 6-O-Benzylidene- $\alpha$ -D-altroside 3-Nitrate.*—(a) A solution of the 2 : 3-dinitrate (4.5 g.) in 80% aqueous ethanol (50 ml.) containing sodium nitrite (2.5 g.) was boiled under reflux for 16 hr. Evaporation left a white solid which was extracted twice with chloroform. On evaporation, the chloroform extracts yielded a solid which, recrystallized from light petroleum-ethanol, was *methyl 4 : 6-O-benzylidene- $\alpha$ -D-altroside 3-nitrate* (2.18 g., 55%), m. p. 156—157°,  $[\alpha]_D^{20} + 118^\circ$  (Found: C, 51.6; H, 5.4; N, 4.3.  $\text{C}_{14}\text{H}_{17}\text{O}_8\text{N}$  requires C, 51.4; H, 5.2; N, 4.3%).

(b) Fuming nitric acid (*d* 1.5; 0.85 ml., 0.019 mole) in acetic anhydride (5 ml.) was dropped into an ice-cold solution of methyl 4 : 6-O-benzylidene- $\alpha$ -D-altroside (4.2 g., 0.015 mole) in chloroform (20 ml.) and acetic anhydride (10 ml.). After 1 hr., the mixture was shaken with dilute potassium carbonate solution. The chloroform layer was washed twice with water before being evaporated. The resulting syrup was dissolved in benzene and chromatographed on alumina. Elution with benzene yielded a syrup (0.5 g.) which has not crystallized. The chloroform eluant gave a white solid which, recrystallized from ethanol-light petroleum, was the 3-nitrate (25%), m. p. 156—157°.

(c) Fuming nitric acid (*d* 1.5; 8 ml.) in acetic anhydride (20 ml.) was added slowly to methyl 4 : 6-O-benzylidene- $\alpha$ -D-altroside (10 g.) suspended in acetic anhydride (20 ml.) at 0°. After 10 min. at room temperature, the resulting solution was poured into ice-water containing potassium carbonate. The precipitated syrup was separated and the aqueous solution was extracted twice with chloroform. The combined product and the chloroform solutions were washed with aqueous potassium carbonate, then with water. Evaporation of the chloroform yielded a syrup (11.7 g.) which was boiled under reflux for 16 hr. with sodium nitrite (6.4 g.) in 80% ethanol (130 ml.). The solution was evaporated and the residue was extracted with chloroform. Evaporation left a solid which, recrystallized from ethanol-light petroleum, was the 3-nitrate (30%), m. p. 155—156°.

*Characterization of Methyl 4 : 6-O-Benzylidene- $\alpha$ -D-altroside 3-Nitrate.*—(a) Silver oxide (1.5 g.) was added during 5 hr. to methyl 4 : 6-O-benzylidene- $\alpha$ -D-altroside 3-nitrate (0.47 g.) suspended in boiling methyl iodide (10 ml.). Boiling was continued for a further 19 hr., then the mixture was cooled, filtered, and evaporated to a syrup which was extracted several times with chloroform. The evaporated extracts although purified by chromatography on alumina in benzene did not yield a crystalline product. A solution of the product and sodium sulphide (0.8 g.) in ethanol (50 ml.) was left at room temperature for 24 hr. The solution was filtered, and water was added to the filtrate, which was then concentrated. The residue was extracted with chloroform. Evaporation of the chloroform yielded a syrup, which was dissolved in pyridine (5 ml.), and to this was added a solution of toluene-*p*-sulphonyl chloride (0.5 g.) in pyridine (5 ml.) at 0°. After 4 days at 0°, the solution was poured into ice-water, and the

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solidified product, recrystallized from methanol, was methyl 4 : 6-*O*-benzylidene-2-*O*-methyl- $\alpha$ -*D*-altroside 3-toluene-*p*-sulphonate (0.31 g.), m. p. 165—166°.

(b) Fuming nitric acid (*d* 1.5; 0.3 ml.) in acetic anhydride (1 ml.) was added slowly at 0° to a suspension of the 3-nitrate (0.3 g.) in acetic anhydride (2 ml.). After 15 min. at 0°, the mixture was poured into ice-water. The resulting syrup solidified, to afford 4 : 6-*O*-benzylidene- $\alpha$ -*D*-altroside 2 : 3-dinitrate (0.3 g., 88%), m. p. 48—49°.

*Reduction of Methyl 4 : 6-O-Benzylidene- $\alpha$ -D-altroside 2 : 3-Dinitrate and 3-Nitrate with Hydrazine.*—A solution of methyl 4 : 6-*O*-benzylidene- $\alpha$ -*D*-altroside 2 : 3-dinitrate (1.49 g., 0.004 mole) and hydrazine hydrate (1.20 g., 0.024 mole) in ethanol (15 ml.) was boiled under reflux for 90 min. After excess of hydrazine had been decomposed by boiling the solution with Raney nickel, the solution was filtered and evaporated. The solid residue, recrystallized from methanol, was methyl 4 : 6-*O*-benzylidene- $\alpha$ -*D*-altroside (74%), m. p. 170°,  $[\alpha]_D^{18} + 116^\circ$  (*c* 0.6).

The above method when applied to the 3-nitrate gave a solution, which after evaporation yielded methyl 4 : 6-*O*-benzylidene- $\alpha$ -*D*-altroside (98%), m. p. 169—170°.

*Preparation of the Methanesulphonate and Toluene-p-sulphonate of Methyl 4 : 6-O-Benzylidene- $\alpha$ -D-altroside 3-Nitrate.*—A solution of the 3-nitrate (0.85 g.) and methanesulphonyl chloride (0.37 g.) in pyridine (2.5 ml.) was left at room temperature for 3 days, then poured into ice-water, and the resulting solid (1.0 g.) was washed with water, dried, and recrystallized from methanol to give needles of methyl 4 : 6-*O*-benzylidene- $\alpha$ -*D*-altroside 2-methanesulphonate 3-nitrate (0.87 g., 83%), m. p. 157—158°,  $[\alpha]_D^{21} + 52.6^\circ$  (*c* 2.5) (Found: C, 44.6; H, 4.7; S, 8.1.  $C_{15}H_{19}O_{10}NS$  requires C, 44.4; H, 4.7; S, 7.9%).

Similar treatment of the 3-nitrate (0.95 g.) and toluene-*p*-sulphonyl chloride (0.95 g.) in pyridine (4 ml.) at room temperature for 4 days gave methyl 4 : 6-*O*-benzylidene- $\alpha$ -*D*-altroside 3-nitrate 2-toluene-*p*-sulphonate (1.1 g., 79%), m. p. 147°,  $[\alpha]_D^{19} + 39.6^\circ$  (*c* 1.3) (Found: C, 52.2; H, 5.0.  $C_{21}H_{23}O_{10}NS$  requires C, 52.4; H, 4.8%).

*Preparation and Characterization of Methyl 4 : 6-O-Benzylidene- $\alpha$ -D-altroside 2-Toluene-p-sulphonate.*—Reduction of the 3-nitrate 2-toluene-*p*-sulphonate (1.20 g., 0.0025 mole) with hydrazine hydrate (0.37 g., 0.0075 mole) in ethanol (12 ml.) was carried out as described for the 2 : 3-dinitrate. The cooled, filtered reaction solution deposited needles which, recrystallized from ethanol, were methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene- $\alpha$ -*D*-alloside (0.10 g., 15%), m. p. 196—197°,  $[\alpha]_D^{18} + 141^\circ$  (*c* 0.8). The remaining reaction solution was evaporated to a syrup which was chromatographed in benzene on acid-washed alumina. After benzene had failed as eluant, elution with benzene-chloroform yielded, in the early fractions, the anhydro- $\alpha$ -*D*-alloside (0.06 g., 9%), m. p. 196—197°. Further elution with benzene-chloroform gave methyl 4 : 6-*O*-benzylidene- $\alpha$ -*D*-altroside 2-toluene-*p*-sulphonate (0.72 g., 66%), an amorphous solid even after repeated separation from ethanol,  $[\alpha]_D^{20} + 44.5^\circ$  (*c* 3.0) (Found: C, 57.4; H, 5.6; S, 7.1.  $C_{21}H_{24}O_8S$  requires C, 57.8; H, 5.5; S, 7.3%).

A solution of the 3-nitrate 2-toluene-*p*-sulphonate (2.50 g.) in methanol (150 ml.) was shaken with palladium-charcoal (2.5 g.) under hydrogen (20 atm.) at room temperature during 30 min. The catalyst was filtered off and washed with warm methanol, and the combined filtrate and washings were evaporated to give the amorphous 2-toluene-*p*-sulphonate (2.20 g., 97%).

Fuming nitric acid (*d* 1.5; 0.06 ml.) in acetic anhydride (0.2 ml.) was added slowly to a solution of the 2-toluene-*p*-sulphonate (0.40 g.) in acetic anhydride (0.3 ml.) at 0°. After 10 min. at room temperature, the solution was poured into ice-water containing potassium carbonate. The resulting solid, recrystallized from methanol, was methyl 4 : 6-*O*-benzylidene- $\alpha$ -*D*-altroside 3-nitrate 2-toluene-*p*-sulphonate (0.29 g., 66%), m. p. 144—145°,  $[\alpha]_D^{25} + 39.7^\circ$  (*c* 1.2).

Silver oxide (1 g.) was added in portions to a suspension of the 2-toluene-*p*-sulphonate (0.50 g.) in boiling methyl iodide (3 ml.) during 2 hr. The mixture was boiled for 4 hr. more before the silver residue was filtered off and washed with acetone, and the combined filtrate and washings were evaporated to a solid. This was chromatographed in benzene on acid-washed alumina. Elution with benzene yielded a solid which, recrystallized from methanol, was methyl 4 : 6-*O*-benzylidene-3-*O*-methyl- $\alpha$ -*D*-altroside 2-toluene-*p*-sulphonate (0.38 g., 74%), m. p. 140—141°,  $[\alpha]_D^{23} + 53.0^\circ$  (*c* 1.4) (Found: C, 58.7; H, 5.9. Calc. for  $C_{22}H_{26}O_8S$ : C, 58.7; H, 5.8%).

*Effect of Alumina on Methyl 4 : 6-O-Benzylidene- $\alpha$ -D-altroside 2-Toluene-p-sulphonate.*—The 2-toluene-*p*-sulphonate (0.20 g.) was chromatographed on alumina in benzene. Washing

the column with benzene yielded methyl 2 : 3-anhydro-4 : 6-O-benzylidene- $\alpha$ -D-alloside (0.12 g., 99%), m. p. 200—201°,  $[\alpha]_D^{23} + 139^\circ$  (*c* 0.6).

The 2-toluene-*p*-sulphonate (0.052 g.) was chromatographed in benzene (10 ml.) on acid-washed alumina. Elution with benzene-chloroform removed methyl 2 : 3-anhydro-4 : 6-O-benzylidene- $\alpha$ -D-alloside (90%), m. p. 195—196° (from methanol-chloroform).

*Reaction of Methyl 4 : 6-O-Benzylidene- $\alpha$ -D-altroside 2 : 3-Ditoluene-*p*-sulphonate with Sodium Iodide in Acetone and with Hydrazine.*—(a) A sealed tube containing the 2 : 3-ditoluene-*p*-sulphonate (1.18 g., 0.002 mole) and sodium iodide (0.90 g., 0.006 mole) dissolved in acetone (20 ml.) was heated at 100° for 46 hr. The colourless solution was evaporated and the residue was extracted with chloroform which, on evaporation, yielded unchanged starting compound (1.15 g., 97%), m. p. 178°,  $[\alpha]_D^{20} + 46.0^\circ$  (*c* 2.1).

(b) A solution of the 2 : 3-ditoluene-*p*-sulphonate (1.18 g., 0.002 mole) and hydrazine hydrate (0.6 g., 0.012 mole) in ethanol (5 ml.) and chloroform (5 ml.) was boiled under reflux for 1.5 hr. The solution was boiled with Raney nickel for 15 min., filtered, and evaporated. The residual solid, recrystallized from ethanol-acetone, was unchanged starting compound (1.06 g., 90%), m. p. 178°,  $[\alpha]_D^{20} + 46.6^\circ$  (*c* 1.3).

*Attempted Selective Sulphonylation of Methyl 4 : 6-O-Benzylidene- $\alpha$ -D-altroside.*—(a) This altroside (5.0 g., 0.018 mole) was dissolved in pyridine (14 ml.) and cooled to 0°. A cold solution of toluene-*p*-sulphonyl chloride (3.8 g., 0.020 mole) in pyridine (14 ml.) was added slowly, and the mixture kept at room temperature for 16 hr. Water (1 ml.) was added, and after 2 hr. the mixture was diluted with water and extracted with chloroform. The chloroform extract was washed successively with 2*N*-hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, then evaporated to a yellow syrup. On the addition of ether and light petroleum, a white solid was formed which, recrystallized from methanol-chloroform, was methyl 4 : 6-O-benzylidene- $\alpha$ -D-altroside 2 : 3-ditoluene-*p*-sulphonate (1.9 g., 18%), m. p. 176—178°,  $[\alpha]_D^{21} + 45.0^\circ$  (*c* 1.0). The remaining syrup (4.1 g.) was chromatographed in benzene on alumina. Elution with benzene and benzene-ether gave a white solid (1.6 g.), which recrystallized from methanol-chloroform was also 2 : 3-ditoluene-*p*-sulphonate (15%). Elution with chloroform and methanol gave white crystals which, recrystallized from methanol-chloroform, were unchanged methyl 4 : 6-O-benzylidene- $\alpha$ -D-altroside (1.3 g., 26%), m. p. 169—170°,  $[\alpha]_D^{20} + 121^\circ$  (*c* 1.0).

(b) The above esterification was repeated at  $-15^\circ$  for 6 hr. The resulting syrup, which did not yield crystals on addition of ether, was chromatographed in benzene on alumina. Elution with benzene gave methyl 4 : 6-O-benzylidene- $\alpha$ -D-altroside 2 : 3-ditoluene-*p*-sulphonate (0.15 g., 2%). Elution with benzene-ether (9 : 1) gave a white solid (0.85 g., 17%) which, recrystallized from methanol-chloroform, was methyl 2 : 3-anhydro-4 : 6-O-benzylidene- $\alpha$ -D-alloside, m. p. 195—196°,  $[\alpha]_D^{21} + 138^\circ$  (*c* 1.9). Successive elutions with benzene-ether, ether, and ether-chloroform gave small amounts of unidentified syrups (0.35 g.). Elution with chloroform, chloroform-methanol (2 : 1), and methanol gave a white solid (1.53 g., 36%), which, recrystallized from methanol-ether, was unchanged methyl 4 : 6-O-benzylidene- $\alpha$ -D-altroside, m. p. 169—171°.

(c) A third experiment was carried out at  $-16^\circ$  for 4 hr. The mixture was examined as above except that the chromatography was done on acid-washed alumina. No product was eluted with benzene or benzene-ether (9 : 1). Benzene-ether (1 : 1), ether, and ether-chloroform (9 : 1) removed methyl 4 : 6-O-benzylidene- $\alpha$ -D-altroside 2 : 3-ditoluene-*p*-sulphonate (1.1 g., 13%). Elution with ether-chloroform (1 : 1, and 1 : 4) gave methyl 2 : 3-anhydro-4 : 6-O-benzylidene- $\alpha$ -D-alloside (0.6 g., 16%). Chloroform-methanol (2 : 1) and methanol gave unchanged starting compound (0.9 g., 14%).

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