349. *Methyl 2,3-Anhydro-α-D-mannoside and 3,4-Anhydro-α-D-altroside and their Derivatives. Part II.*[1]

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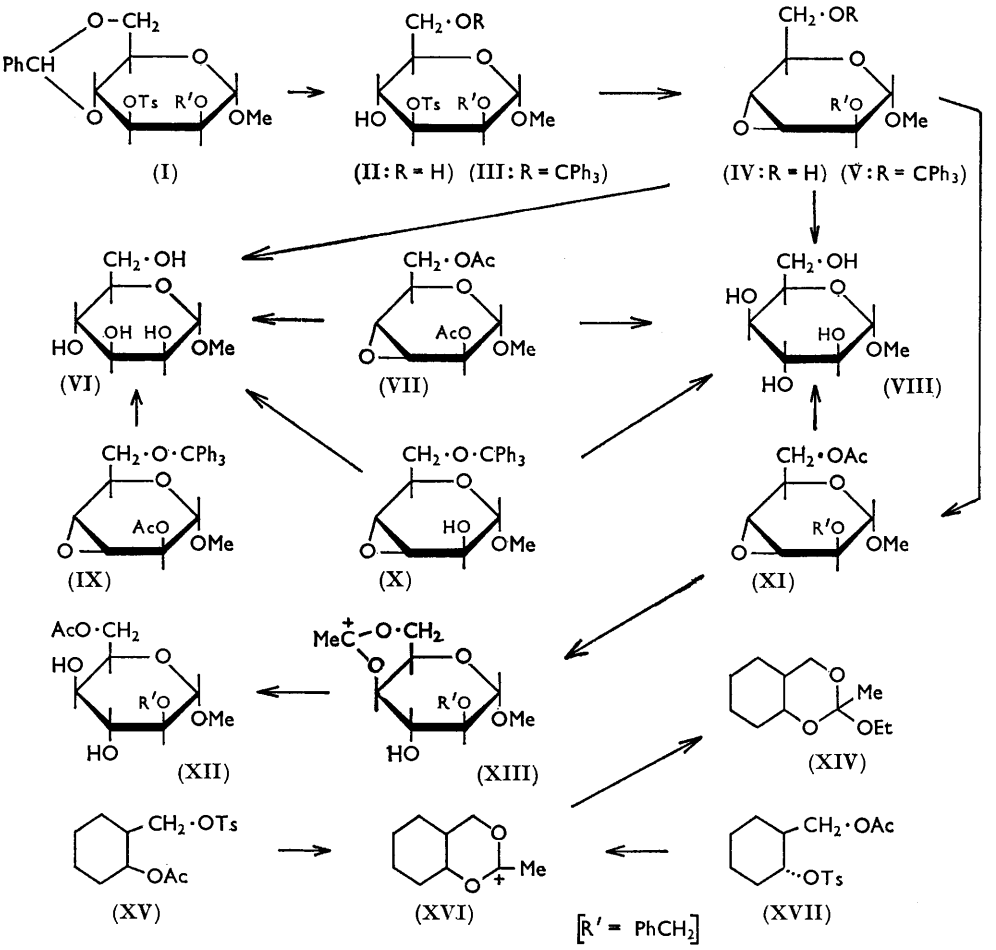
The presence of a 6-*O*-acetyl group in derivatives of methyl 3,4-anhydro-α-D-altroside has been shown to lead to formation of D-idose derivatives on acid hydrolysis. An acetoxonium ion having a six-membered ring is postulated as an intermediate.

The preparation and properties of methyl 3,4-anhydro-α-D-altroside and some of its derivatives were described in Part I.[1] When the anhydroaltroside (X) was treated with 80% acetic acid, methyl α-D-mannoside (VI) and methyl α-D-idoside (VIII) were produced, the latter in greater amount. When a neighbouring *trans*-acetoxyl group was present, as in (IX), a monoacetate of methyl α-D-mannoside was formed and the reaction rate was considerably increased. It has now been found that the diacetate (VII), when heated with 80% acetic acid, yields both mannoside and idoside derivatives in comparable amounts.

[1] Buchanan and Schwarz, *J.*, 1962, 4770.

Since the rate of disappearance of the anhydro-compound was comparable with that of the acetate (IX), it was reasonable to suppose that the 6-acetoxyl group was participating in the reaction leading to the idoside. To settle this point we have prepared the 6-acetate (XI) and examined its behaviour under acidic conditions.

Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-toluene-*p*-sulphonyl-α-D-mannoside (I) was prepared by benzylation of the hydroxy-compound [1] with benzyl bromide and silver oxide in dimethylformamide.[2,3] Acid hydrolysis gave the glycoside (II) which yielded the crystalline trityl ether (III). Treatment of the sulphonate (II) with sodium methoxide gave syrupy methyl 3,4-anhydro-2-*O*-benzyl-α-D-altroside (IV); no epoxide migration is possible in this compound [1] because of the benzyl ether group. The anhydroaltroside gave



the crystalline trityl ether (V) and the acetate (XI); the trityl ether (V) was also obtained by alkali treatment of the sulphonate (III).

The behaviour of the four anhydroaltrosides (V), (IX), (X), and (XI) towards 80% acetic acid was then studied. Under these conditions a trityl group is removed very rapidly, and disappearance of vicinal epoxide could be followed chromatographically using

[2] Dr. J. C. P. Schwarz, personal communication.
[3] Croon and Lindberg, *Acta Chem. Scand.*, 1959, **13**, 593.

the sodium iodide–Methyl Red reagent.[1] Under comparable conditions the acetates (IX) and (XI) were hydrolysed at about the same rate, both more rapidly than the compounds (V) and (X) which lack the acetyl group. When the hydrolysis of the acetate (XI) was carried out on a preparative scale and the benzyl group in the product was hydrogenolysed, the resulting syrup, on acetylation, gave methyl α-D-idoside tetra-acetate, the acetate of (VIII), in 53% yield. Deacetylation of the mother-liquors, and paper chromatography of the products, showed methyl idoside to be the main component, with a trace of methyl mannoside. Hydrolysis with dilute sulphuric acid in aqueous dioxan gave a similar result.

When the products of acid treatment of the anhydroaltroside (V) were examined chromatographically after hydrogenolysis of the benzyl group, comparable amounts of methyl mannoside and methyl idoside were present. This is in agreement with the behaviour of methyl 3,4-anhydro-6-*O*-trityl-α-D-altroside described in Part I,[1] and shows that the benzyl group does not exert any major influence on the rate or direction of ring cleavage of the 3,4-epoxide.

The participation of the acetyl group in the hydrolysis of the epoxide ring in the anhydro-compound (XI) probably involves the formation of the acetoxonium ion (XIII), leading to the 6-acetate (XII). Six-membered acetoxonium ions have been postulated by Plattner and Lang [4] and by Burke, Turnbull, and Wilson [5] as intermediates in the solvolysis of some steroid sulphonates bearing a neighbouring acetoxyl group. The closest analogy is the ethanolysis of *cis*-2-toluene-*p*-sulphonyloxymethylcyclohexyl acetate (XV) and *trans*-2-toluene-*p*-sulphonyloxycyclohexylmethyl acetate (XVII) in the presence of potassium acetate to give 2-ethoxy-2-methyl-1,3-dioxa-*cis*-decalin (XIV), presumably by way of the common intermediate (XVI).[6]

Experimental

The general methods employed were described in Part I.[1] The following solvent systems were used for paper chromatography: (A) butan-1-ol–water (86 : 14, v/v); (B) butan-2-one saturated with water, the chromatograms being pre-equilibrated for a few hours before running. Reducing sugars were detected by using aniline phthalate,[7] α-glycols with periodate and Schiff's reagent,[8] and vicinal epoxides with sodium iodide and Methyl Red.[1]

Methyl 2,6-Di-O-acetyl-3,4-anhydro-α-D-altroside and its Hydrolysis.—Methyl 3,4-anhydro-α-D-altroside [1] (0·24 g.) was treated with acetic anhydride (2 c.c.) in pyridine (5 c.c.) for 44 hr. The acetate was isolated using chloroform, giving a syrup (0·31 g., 87%). The acetate (0·15 g.) in 80% acetic acid (v/v), 5 c.c. was heated at 100° for 1 hr. The solution was evaporated to dryness, dissolved in methanol (10 c.c.), and sufficient methanolic sodium methoxide added to make the solution just alkaline. After 48 hr., solid carbon dioxide was added, the solution evaporated to a syrup, dissolved in water, and passed through a short column of Dowex 50 (NH_4^+) resin. Evaporation gave a syrup which was examined by chromatography in solvent B. No vicinal epoxide was present and methyl α-mannoside and methyl α-idoside, in approximately equal quantities, were the sole glycosidic products. Treatment of the mixture with ethanol, and nucleation, gave methyl α-D-mannoside, m. p. 190—192°, identical with an authentic sample. The mother-liquors were evaporated to a syrup, treated with acetic anhydride (2 c.c.) and pyridine (5 c.c.), and left for 22 hr. The tetra-acetates were isolated, using chloroform, as a syrup (0·13 g.) which crystallised when treated with light petroleum and nucleated with methyl α-D-idoside tetra-acetate. The acetate (0·1 g.) had m. p. 90—94°, raised to 108° (0·05 g.) by recrystallisation from water, and was identical with an authentic sample of methyl α-D-idoside tetra-acetate.[1]

Methyl 2-O-Benzyl-4,6-O-benzylidene-3-O-toluene-p-sulphonyl-α-D-mannoside.—Methyl

[4] Plattner and Lang, *Helv. Chim. Acta*, 1944, **27**, 1872; Shoppee, *Ann. Reports*, 1946, **43**, 212.
[5] Burke, Turnbull, and Wilson, *J.*, 1953, 3237.
[6] Kovacs, Schneider, and Lang, XIXth Internat. Cong. Pure and App. Chem., 1963, Abstracts A, p. 144; *Proc. Chem. Soc.*, 1963, 374.
[7] Partridge, *Nature*, 1949, **164**, 443.
[8] Baddiley, Buchanan, Handschumacher, and Prescott, *J.*, 1956, 2818.

4,6-*O*-benzylidene-3-*O*-toluene-*p*-sulphonyl-α-D-mannoside [1] (1·0 g.) was dissolved in dimethylformamide (20 c.c.), and benzyl bromide (5·0 g.) was added. Silver oxide (2·8 g.) was added during 1 hr. at 50°, and the mixture stirred at room temperature for 20 hr. in the dark. Pyridine (4 c.c.) was added, and the mixture set aside for 20 hr. and poured into an excess of water. Solids were filtered off and the filtrate was extracted with chloroform. The chloroform solution was washed with aqueous sulphuric acid, aqueous sodium carbonate, and finally with water; it was dried ($MgSO_4$) and evaporated to a syrup which was dissolved in benzene–chloroform (4 : 1) and filtered through a short column of neutral alumina. The *benzyl ether* crystallised from methanol as needles (0·74 g., 61%), m. p. 93—94°, $[\alpha]_D^{19}$ +18·0° (*c* 2·6 in chloroform) (Found: C, 64·1; H, 5·9. $C_{28}H_{30}O_8S$ requires C, 63·8; H, 5·9%).

Methyl 2-O-*Benzyl*-3-O-*toluene*-p-*sulphonyl*-α-D-*mannoside*.—The above benzylidene compound (1·0 g.) was heated with methanol (70 c.c.) and 0·1N-sulphuric acid (40 c.c.) under reflux for 3½ hr. The solution was neutralised with barium carbonate, filtered, and the filtrate evaporated to a syrup (0·81 g., 96%), $[\alpha]_D^{22}$ +26·1° (*c* 1·41 in chloroform) (Found: S, 7·5. $C_{21}H_{26}O_8S$ requires S, 7·3%).

Methyl 2-O-*Benzyl*-3-O-*toluene*-p-*sulphonyl*-6-O-*trityl*-α-D-*mannoside*.—Methyl 2-*O*-benzyl-3-*O*-toluene-*p*-sulphonyl-α-D-mannoside (1·96 g.), in pyridine (10 c.c.), was treated with trityl chloride (1·3 g., 1·1 mol.) at room temperature for 4 days. The product was isolated using chloroform, to give a syrup which was dissolved in benzene and chromatographed on neutral silica.[1] Benzene–ether (4 : 1) eluted the *trityl ether*, which crystallised from methanol as prisms (1·33 g., 43%), m. p. 78—84°, $[\alpha]_D^{22}$ +6·6° (*c* 3·62 in chloroform) (Found: C, 70·0; H, 6·6; OMe, 6·3. $C_{40}H_{40}O_8S,\frac{1}{2}MeOH$ requires C, 69·8; H, 6·1; OMe, 6·7%). The trityl ether crystallised only from methanol (Found, for the syrupy compound: C, 70·4; H, 6·3. $C_{40}H_{40}O_8S$ requires C, 70·6; H, 5·9%).

Methyl 3,4-*Anhydro*-2-O-*benzyl*-α-D-*altroside*.—Methyl 2-*O*-benzyl-3-*O*-toluene-*p*-sulphonyl-α-D-mannoside (1·96 g.) was dissolved in methanol (40 c.c.) containing sodium methoxide [from sodium (0·23 g.)] and left at room temperature for 20 hr. Solid carbon dioxide was added and the solution was evaporated to dryness. The residue was extracted with chloroform and the solution was washed with water, dried ($MgSO_4$), and evaporated, to give the anhydro-compound as a syrup (0·83 g., 70%), $[\alpha]_D^{22}$ +39·0° (*c* 3·68 in chloroform).

Methyl 6-O-*Acetyl*-3,4-*anhydro*-2-O-*benzyl*-α-D-*altroside*.—Methyl 3,4-anhydro-2-*O*-benzyl-α-D-altroside (0·83 g.) was treated with pyridine (15 c.c.) and acetic anhydride (3·6 c.c.) for 20 hr. at room temperature. The product was isolated with chloroform, giving a syrup (0·89 g., 93%), $[\alpha]_D^{21}$ +23·6° (*c* 2·65 in chloroform) (Found: C, 61·8; H, 6·6. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·5%).

Treatment of Methyl 6-O-*Acetyl*-3,4-*anhydro*-2-O-*benzyl*-α-D-*altroside with Acids*.—(*a*) *With sulphuric acid*. The anhydro-sugar (1·03 g.) was dissolved in dioxan (27 c.c.) and 2N-sulphuric acid (1·44 c.c.), and heated under reflux. Samples were removed at intervals and examined by paper chromatography; no vicinal epoxide was detectable after 10—15 min. After 20 min. the solution was neutralised ($BaCO_3$), filtered, and evaporated to dryness. The residue was dissolved in ethanol (20 c.c.) and hydrogenated over palladium [from palladium oxide (1·0 g.)] for 20 hr. After filtration, the solution was evaporated to a syrup which was acetylated with acetic anhydride (10 c.c.) in pyridine (30 c.c.) for 20 hr. at room temperature. The acetates were isolated, using chloroform, as a syrup which crystallised from ether–light petroleum to give methyl α-D-idoside tetra-acetate as needles (0·6 g., 62%), m. p. 107—108°, identical with an authentic sample.[1] The evaporated mother-liquors were deacetylated with sodium methoxide in methanol, and the products examined by paper chromatography in solvent B. The major product was methyl α-D-idoside with traces of methyl α-D-mannoside and idose.

(*b*) *With acetic acid*. The anhydro-sugar (0·23 g.) was dissolved in acetic acid (80% v/v; 8 c.c.) and heated under reflux. Paper chromatography of samples withdrawn at intervals showed no vicinal epoxide after 20—30 min. After 1 hr., the solution was evaporated to dryness and treated as in (*a*). Methyl α-D-idoside tetra-acetate (0·13 g., 53%), m. p. 107—108°, was isolated; when the mother-liquors were evaporated, deacetylated, and examined by paper chromatography in solvent B, methyl α-D-idoside was the major product together with traces of methyl α-D-mannoside and idose.

Methyl 3,4-*Anhydro*-2-O-*benzyl*-6-O-*trityl*-α-D-*altroside*.—(*a*) Methyl 2-*O*-benzyl-3-*O*-toluene-*p*-sulphonyl-6-*O*-trityl-α-D-mannoside (1 g.) was dissolved in methanol (35 c.c.) containing sodium methoxide [from sodium (0·16 g.)] and left at room temperature for 20 hr. The

anhydro-compound separated as fine needles. Water (20 c.c.) was added and the anhydro-compound filtered off (0·47 g., 63%), m. p. 94—95°, $[\alpha]_D^{22}$ +13·7° (*c* 2·9 in chloroform) (Found: C, 77·8; H, 6·6. $C_{33}H_{32}O_5$ requires C, 77·9; H, 6·3%).

(*b*) Methyl 3,4-anhydro-2-*O*-benzyl-α-D-altroside (0·18 g.), in pyridine (5 c.c.), was treated with trityl chloride (0·32 g., 1·9 mol.) at room temperature for 4 days. After addition of water, the product was isolated with chloroform; the final syrup was dissolved in benzene, and chromatographed on neutral silica. Benzene–ether (4 : 1) eluted the trityl ether, needles (0·09 g., 26%), m. p. 94—95° (from methanol), identical with that in (*a*).

Treatment of Methyl 3,4-*Anhydro*-2-O-*benzyl*-6-O-*trityl*-α-D-*altroside with Acids.*—(*a*) *With sulphuric acid.* The anhydro-compound (0·16 g.) was dissolved in dioxan (5·35 c.c.) and 2N-sulphuric acid (0·28 c.c.), and heated under reflux. Samples were removed at intervals and examined by paper chromatography in solvent A. The trityl group was hydrolysed almost immediately and no vicinal epoxide was detectable after 20—30 min. After 30 min., the solution was neutralised ($BaCO_3$), filtered, and evaporated to dryness. The residue was dissolved in ethanol (10 c.c.), and hydrogenated over palladium black [from palladium oxide (0·16 g.)] for 20 hr. After filtration, the solution was concentrated and examined by paper chromatography in solvent B. Methyl α-D-idoside and methyl α-D-mannoside were present in approximately equal amounts; traces of idose and mannose were also present.

(*b*) *With acetic acid.* The anhydro-compound (0·06 g.) was dissolved in acetic acid (80% v/v, 1·5 c.c.) and heated under reflux for 140 min. Samples were removed at intervals and examined by paper chromatography in solvent A. The trityl group was hydrolysed in 5 min., but vicinal epoxide remained after 140 min. The solution was evaporated to dryness, and the residue was dissolved in ethanol (10 c.c.) and hydrogenolysed over palladium [from palladium oxide (0·1 g.)] for 20 hr. After filtration, the solution was concentrated and examined by paper chromatography in solvent B. Methyl α-D-idoside and methyl α-D-mannoside were present in approximately equal amounts; a trace of idose was present.

Comparison of Hydrolysis of Anhydro-sugars by 80% *Acetic Acid.*—The anhydro-sugars named in the Table were each dissolved in 80% acetic acid (v/v) to give approximately 0·1M-solutions. Samples were heated at 100° for different periods and examined chromatographically in solvent A, using the sodium iodide–Methyl Red spray.[1]

Anhydro-sugar	(V)	(VII)	(IX)	(X)	(XI)
Time of loss of CPh_3 group * (min.)	<10	—	<10	<10	—
Time (hr.) of disappearance of epoxide *	⩾3	<1 †	<0·5	⩾3	<0·5

* Extent of reaction greater than 95%. † Maximum figure derived from preparative experiment quoted above.

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