208. *The Action of Acidic Reagents on Ethylene Oxide Anhydrosugars. Part III.* Methyl 3 : 4-Anhydro-α-D-galactoside.†*

By V. Y. Labaton and F. H. Newth.

The reaction of methyl 2-*O*-acetyl-3 : 4-anhydro-6-*O*-trityl-α-D-galactoside with hydrogen chloride in acetone has been re-examined (Oldham and Robertson, *J.*, 1935, 685). The presence of galactose in the product is confirmed and a mechanism proposed which accounts for the formation of methyl 3 : 4-*O*-*iso*propylidene-α-D-galactoside and methyl 4 : 6-*O*-*iso*propylidene-α-D-guloside. With aqueous hydrochloric acid the products are methyl 3-chloro-3-deoxy-α-D-guloside and methyl 4-chloro-4-deoxy-α-D-glucoside. The alcoholysis of a carbohydrate trityl ether has been observed.

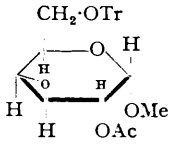
Sugar epoxides undergo fission with alkaline and acidic reagents to form two isomers in which the configuration is *trans*, inversion having occurred at the point of substitution (Peat, *Adv. Carbohydrate Chem.*, 1948, **2**, 38; Newth, Overend, and Wiggins, *J.*, 1947, 10; Mukherjee and Srivastava, *Proc. Indian Acad. Sci.*, 1952, **35**, 178). There is one example however in which this general rule would appear to be contradicted. Oldham and Robertson (*J.*, 1935, 685) claimed to have isolated a derivative of galactose from the reaction of methyl 2-*O*-acetyl-3 : 4-anhydro-6-*O*-trityl-α-D-galactoside (I) with hydrogen chloride in acetone. Müller (*Ber.*, 1935, **68**, 1094) showed that the products of hydrolysis of methyl 3 : 4-anhydro-β-D-galactoside with sulphuric acid were gulose and glucose. In view of this and also the absence of sugar chlorohydrins in Oldham and Robertson's reaction product the reaction of (I) with hydrogen chloride was investigated.

The anhydro-compound was prepared from methyl 2 : 3-*O*-dibenzoyl-4-*O*-tosyl-6-*O*-trityl-α-D-glucoside (II) by treatment with warm sodium hydroxide in aqueous acetone (Oldham and Robertson, *loc. cit.*) or sodium methoxide solution in chloroform. The latter was preferred since the reaction is milder and less likely to cause fission of the epoxide ring. The product was a syrup which neither crystallised nor gave a crystalline derivative. Methyl 2-*O*-acetyl-3 : 4-anhydro-6-*O*-trityl-α-D-galactoside was treated with acetone containing hydrogen chloride in the manner described by Oldham and Robertson and, after removal of triphenylmethanol, a portion of the reaction mixture was deacetylated and

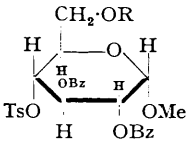
* Part II, preceding paper. † For details of the carbohydrate nomenclature used see *J.*, 1952, 5108.

hydrolysed. Examination of the product by paper partition chromatography demonstrated the presence of galactose and gulose but glucose was absent. From the remainder of the mixture methyl 2-acetyl-*O*-*iso*propylidene-α-D-guloside and methyl 2-acetyl-*O*-*iso*propylidene-α-D-galactoside were isolated. These had the same physical constants as those given by the earlier workers, who established the identity of the sugar components but provided no evidence for the constitution of the *iso*propylidene derivatives. The methyl *O*-*iso*propylidene-α-D-galactoside which they obtained by deacetylation is obviously methyl 3 : 4-*O*-*iso*propylidene-α-D-galactoside (III), previously formed by condensing methyl α-D-galactoside with acetone (Ault, Haworth, and Hirst, *J.*, 1935, 1012; Wiggins, *J.*, 1944, 522). The gulose derivative was shown to be methyl 2-*O*-acetyl-4 : 6-*O*-*iso*propylidene-α-D-guloside (IV) by the formation of the toluene-*p*-sulphonate (V) and heating this with sodium iodide in acetone. No exchange of anions had occurred after 30 hours at 110°, a clear indication that the toluene-*p*-sulphonyl group is not attached to a primary hydroxyl. It must be at $C_{(3)}$ with the *iso*propylidene group at $C_{(4)}$ and $C_{(6)}$ since a 3 : 6-derivative would be sterically impossible in the gulose series.

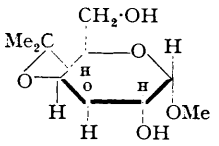
When methyl 3 : 4-anhydro-6-*O*-trityl-α-D-galactoside was treated with hydrochloric acid in acetone, the trityl group was eliminated and a mixture of chlorohydrins obtained. The two expected isomers would be methyl 3-chloro-3-deoxy-α-D-guloside (VI) and methyl 4-chloro-4-deoxy-α-D-glucoside (VII). The syrupy product consumed 0·4 mol. of lead tetra-acetate, indicating the presence of 40% of the oxidizable glucose isomer. The syrup was condensed with benzaldehyde, whereupon a crystalline benzylidene derivative was formed and the remaining methyl chlorodeoxy-α-D-hexoside crystallised (m. p. 113—114°; $[\alpha]_D$ +138°). It was expected that it would be the gulose isomer which would condense with benzaldehyde at positions 4 and 6 rather than the glucose isomer in which position 4 is not available, but when the benzylidene derivative was hydrolysed the product (m. p. 124—126°; $[\alpha]_D$ +84°) reacted with one mol. of periodate. This isomer therefore must be methyl 4-chloro-4-deoxy-α-D-glucoside (VII) and the benzylidene derivative the 3 : 6-compound (VIII). The fraction (m. p. 113—114°) which did not condense with benzaldehyde was not susceptible to periodate oxidation and must be methyl 3-chloro-3-deoxy-α-D-



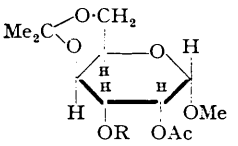
(I)



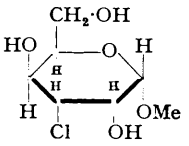
(II; R = Tr)
(IX; R = H)
(X; R = Ts)



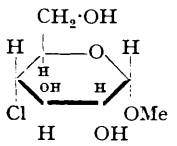
(III)



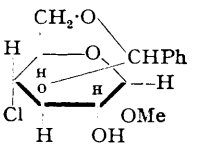
(IV; R = H)
(V; R = Ts)



(VI)



(VII)

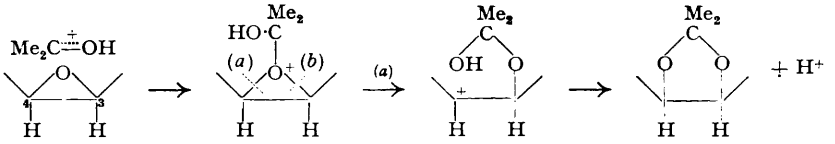


(VIII)

guloside (VI). Both (VI) and (VII) with sodium methoxide gave the same halogen-free product, presumably methyl 3 : 4-anhydro-α-D-galactoside, showing that each isomer has the *trans*-configuration at positions 3 and 4.

The reaction of the anhydro-sugar with aqueous hydrochloric acid needs no further comment; it follows the normal course of epoxide fission resulting in the formation of the two isomeric methyl chlorodeoxyhexosides. With hydrogen chloride in acetone however no chlorohydrins are produced and the chief products are the *iso*propylidene derivatives of methyl α-D-guloside and methyl α-D-galactoside. The acid-catalysed formation of cyclic acetals and ketals from alkylene oxides and aldehydes and ketones has been described (Bogert and Roblin, *J. Amer. Chem. Soc.*, 1933, **55**, 3741; Petrov, *J. Gen. Chem., U.S.S.R.*, 1941, **10**, 981), and the same reaction would account for the production of the *iso*propylidene derivatives but with stereochemical consequences which are not apparent in the case

of the alkylene oxides. The formation of methyl 3 : 4-*O*-*iso*propylidene-α-D-galactoside may be represented by the following sequence :



The formation of the 4 : 6-*O*-*iso*propylidenegulose derivative (IV) can be explained by fission of the cyclic intermediate at (*b*) followed by ring closure at $C_{(6)}$ to give the dioxan with simultaneous nucleophilic *trans* attack at $C_{(3)}$ by H_2O. The formation of a 2 : 2-dimethyl-1 : 3-dioxan ring as in (IV) is unusual and its preponderance over the galactose isomer is probably accounted for by the more positive nature of $C_{(3)}$ owing to the neighbouring $C_{(2)}$-acetyl. The absence of glucose among the reaction products is significant and is possibly due to the fact that an *iso*propylidene residue cannot be accommodated in the methyl α-D-glucopyranoside molecule. This reaction merits further investigation and possibly provides a general route to *cis*-glycols from epoxides.

During recrystallisation of methyl 2 : 3-*O*-dibenzoyl-4-*O*-tosyl-6-*O*-trityl-α-D-glucoside (II) from alcohol, in which the compound is only sparingly soluble, it was found that considerable alcoholysis of the trityl group apparently occurred and in addition to (II), ethyl triphenylmethyl ether and methyl 2 : 3-*O*-dibenzoyl-4-*O*-tosyl-α-D-glucoside (IX) were obtained. The latter compound, identical with that described by Bell (*J.*, 1934, 1177), was converted into the 4 : 6-di-*O*-toluene-*p*-sulphonate (X) also described by that author, and with triphenylmethyl chloride (II) could be regained. That the alcoholysis was not fortuitous was shown by boiling (II) with highly purified ethanol and after 19 hours, 80% of the trityl group had been removed. As far as the authors are aware this is the first example of the cleavage of a carbohydrate trityl ether by alcohol alone.

Experimental

Methyl 2 : 3-O-*Dibenzoyl*-4-O-*tosyl*-6-O-*trityl*-α-D-*glucoside*.—This compound was prepared from methyl 2 : 3-di-*O*-benzoyl-α-D-glucoside (29 g.) (Mathers and Robertson, *J.*, 1933, 1097) by Oldham and Robertson's method (*loc. cit.*). Recrystallised from alcohol the glycoside (16 g.) had m. p. 163—164°, $[\alpha]_D^{17}$ +66·3° (*c*, 2·13 in $CHCl_3$) (Found : C, 70·7; H, 5·6; S, 3·9. Calc. for $C_{47}H_{42}O_{10}S$: C, 70·7; H, 5·3; S, 4·0%).

Evaporation of the mother liquors provided methyl 2 : 3-di-*O*-benzoyl-4-*O*-tosyl-α-D-glucoside, m. p. 179°, $[\alpha]_D^{18}$ +97·5° (*c*, 4·70 in $CHCl_3$) (Found : C, 60·3; H, 5·0; S, 6·1. Calc. for $C_{28}H_{28}O_{10}S$: C, 60·4; H, 5·0; S, 5·8%) {Bell (*loc. cit.*) gives m. p. 179—180°, $[\alpha]_D$ +106·3° (in $CHCl_3$)}. Treatment of this compound with trityl chloride in pyridine afforded the above derivative and with toluene-*p*-sulphonyl chloride there was formed methyl 2 : 3-di-*O*-benzoyl-4 : 6-di-*O*-tosyl-α-D-glucoside, m. p. 135—136°, $[\alpha]_D^{18}$ +102° (*c*, 1·76 in $CHCl_3$) (Found : C, 59·1; H, 4·4; S, 8·9. Calc. for $C_{35}H_{34}O_{12}S_2$: C, 59·1; H, 4·8; S, 9·0%) {Bell (*loc. cit.*) gives m. p. 122—124°, $[\alpha]_D$ +94·6° (in $CHCl_3$)}. Further concentration of the alcoholic mother liquors gave ethyl triphenylmethyl ether, m. p. 83° (Gomberg, *Ber.*, 1902, **35**, 1834, gives m. p. 82—83°) (Found : C, 87·2; H, 6·4. Calc. for $C_{21}H_{20}O$: C, 87·5; H, 6·9%).

Alcoholysis of Methyl 2 : 3-*Di*-O-*benzoyl*-4-O-*tosyl*-6-O-*trityl*-α-D-*glucoside*.—The compound (1·0 g.) was boiled under reflux for 19 hours with absolute ethanol [100 ml.; purified by Smith's method (*J.*, 1927, 1288) as modified by Manske (*J. Amer. Chem. Soc.*, 1931, **53**, 1106) and fractionated through a Fenske column]. Crystals (0·4 g.) separated as the solution cooled; they had m.p. 179—180° (not depressed in admixture with methyl 2 : 3-di-*O*-benzoyl-4-*O*-tosyl-α-D-glucoside). On concentrating the filtrate, a further 0·2 g. was obtained, m. p. 143—158°, apparently a mixture of starting material and 4-*O*-toluene-*p*-sulphonate. Further concentration yielded ethyl triphenylmethyl ether (0·3 g.), m. p. 81—83°.

Methyl 3 : 4-*Anhydro*-6-O-*trityl*-α-D-*galactoside*.—(*a*) Methyl 2 : 3-di-*O*-benzoyl-4-*O*-tosyl-6-*O*-trityl-α-D-glucoside (10·5 g.) was treated with warm 2N-sodium hydroxide in aqueous acetone as described by Oldham and Robertson (*loc. cit.*). The product (5·5 g.) was a sulphur-free yellow glass, having $[\alpha]_D^{18}$ +15·8° (*c*, 2·20 in $CHCl_3$) (Found : OMe, 6·6. Calc. for $C_{26}H_{26}O_5$: OMe, 7·4%). (*b*) Methyl 2 : 3-di-*O*-benzoyl-4-*O*-tosyl-6-*O*-trityl-α-D-glucoside (8·5 g.) in chloroform (25 ml.) was treated with methanolic sodium methoxide (30 ml.; 0·6 g. of Na) for 16 hours,

and the mixture was then poured into water and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated. The product, after removal of methyl benzoate, was a sulphur-free yellow glass (5·4 g.), [α] +17·0° (*c*, 2·67 in $CHCl_3$) (Found : OMe, 6·8%). It did not crystallise after chromatography on alumina.

Methyl 2-*O*-acetyl-3 : 4-anhydro-6-*O*-trityl-α-D-galactoside was obtained as a syrup by treating the above anhydro-compound with acetic anhydride in pyridine; it had $[\alpha]_D^{18}$ +8·7° (*c*, 4·96 in $CHCl_3$). The 2-benzoate, 2-toluene-*p*-sulphonate, and 2-α-naphthylcarbamate also failed to crystallise.

Treatment of Methyl 2-O-*Acetyl*-3 : 4-*anhydro*-6-O-*trityl*-α-D-*galactoside with Hydrogen Chloride in Acetone.*—The glycoside (6·2 g.) was dissolved in acetone, and a solution of dry hydrogen chloride (1·5 g.) in acetone (20 ml.) added. After 1 hour the acid was neutralised (Na_2CO_3), and the solution filtered and concentrated. It was poured into water containing a little pyridine, and the precipitated triphenylmethanol (3·5 g.) removed.

A portion of the aqueous solution was evaporated to dryness and the residue deacetylated in methanol with a trace of sodium. The resulting product was then boiled with 0·05N-hydrochloric acid for 7 hours, the acid neutralised, the inorganic ions removed by ion-exchange resins, and the solution concentrated. This concentrate was examined by paper partition chromatography [butanol–acetic acid–water; spraying reagent : benzidene–trichloroacetic acid (Bacon and Edelman, *Biochem. J.*, 1951, **48**, 114)]. The presence of galactose was demonstrated, and also of gulose by comparison with a spot obtained from sorbose by treatment with calcium hydroxide at 35° for 6 days (Hough, Jones, and Wadman, *J.*, 1950, 1702).

The remainder of the aqueous solution was extracted with chloroform, and the extract dried (Na_2SO_4) and evaporated. The residue afforded crystalline material (0·34 g.) on treatment with ether. Recrystallised from ether this had m. p. 177—179°, $[\alpha]_D^{20}$ +78·3° (*c*, 1·66 in $CHCl_3$) (Found : C, 52·4; H, 7·5. Calc. for $C_{12}H_{20}O_7$: C, 52·2; H, 7·2%), and corresponds with the methyl monoacetyl-*iso*propylidene-α-D-guloside, m. p. 176—178°, $[\alpha]_D$ +76·8° (in $CHCl_3$), isolated by Oldham and Robertson.

After some time a second crystalline fraction (0·3 g.) was obtained, m. p. 101—102° (from ether), $[\alpha]_D^{20}$ +122·4° (*c*, 0·94 in $CHCl_3$) (Found : C, 52·6; H, 7·3. Calc. for $C_{12}H_{20}O_7$: C, 52·2; H, 7·2%), corresponding with m. p. 101—102°, $[\alpha]_D$ +127·3° (in $CHCl_3$) reported by Oldham and Robertson for methyl monoacetyl-*iso*propylidene-α-D-galactoside. No further crystalline material could be obtained from the syrupy residue (0·72 g.) by deacetylation.

The original aqueous solution after chloroform extraction was freed from traces of chloride ion, treated with hydrogen sulphide, filtered, and evaporated to dryness. The residue was extracted with hot acetone, and removal of the solvent provided a halogen-free syrup (0·5 g.) from which a small amount of crystalline material separated, m. p. 192—194°, $[\alpha]_D^{18}$ +90·8° (*c*, 0·38 in H_2O) (Found : C, 44·4; H, 6·5%).

Methyl 2-O-*Acetyl*-4 : 6-O-iso*propylidene*-3-O-*tosyl*-α-D-*guloside*.—Methyl 2-*O*-acetyl-4 : 6-*O*-*iso*propylidene-α-D-guloside (0·12 g.) was treated in pyridine solution with toluene-*p*-sulphonyl chloride. The mixture was poured into water, the aqueous solution extracted with chloroform, and the *derivative* recrystallised from alcohol; it had m. p. 122—123°, $[\alpha]_D^{20}$ +52·2° (*c*, 0·52 in $CHCl_3$) (Found : C, 53·3; H, 6·0; S, 7·5. $C_{19}H_{26}O_9S$ requires C, 53·0; H, 6·0; S, 7·4%). When it was heated at 110° in acetone solution with dry sodium iodide, no sodium toluene-*p*-sulphonate had separated after 30 hours.

Treatment of Methyl 3 : 4-*Anhydro*-6-O-*trityl*-α-D-*galactoside with Hydrochloric Acid.*—The anhydro-compound (5·3 g.) was boiled under reflux for 4 hours in acetone (400 ml.) containing hydrochloric acid (11 ml.; 2N). Excess of acid was neutralised ($PbCO_3$) and the inorganic residue removed and washed with aqueous acetone. When the acetone was evaporated, triphenylmethanol (3·3 g.; m. p. 159—160°) was precipitated. The aqueous solution was evaporated to dryness and the residue extracted with hot ethyl acetate. Evaporation of the solvent gave a pale yellow syrup (2·5 g.) containing methyl chlorodeoxyhexosides. Quantitative oxidation with lead tetra-acetate showed a consumption of 0·4 mol.

Benzylidene derivative. The syrup (2·5 g.) was shaken for 20 hours with benzaldehyde (15 ml.) and zinc chloride (3·2 g.). Zinc chloride was removed by the addition of sodium carbonate and benzaldehyde removed by distillation with steam under reduced pressure. The turbid aqueous solution which remained was extracted with chloroform, and the extract dried (Na_2SO_4) and evaporated. *Methyl* 3 : 6-O-*benzylidene*-4-*chloro*-4-*deoxy*-α-D-*glucoside*, recrystallised from alcohol, had m. p. 166°, $[\alpha]_D^{18}$ +67·2° (*c*, 0·63 in $CHCl_3$) (Found : C, 55·9; H, 5·9; Cl, 12·5. $C_{14}H_{17}O_5Cl$ requires C, 55·9; H, 5·7; Cl, 11·8%).

The aqueous solution after chloroform extraction was evaporated to dryness and the residue extracted with acetone. The syrup obtained on evaporation of the solvent crystallised slowly;

methyl 3-*chloro*-3-*deoxy*-α-D-*guloside*, recrystallised from ethyl acetate, had m. p. 113—114°, $[\alpha]_D^{18}$ +138·3° (*c*, 0·52 in H_2O) (Found : C, 39·4; H, 6·3. $C_7H_{13}O_5Cl$ requires C, 39·5; H, 6·1%). It was not oxidised by sodium metaperiodate in aqueous solution.

Hydrolysis of methyl 3 : 6-O-*benzylidene*-4-*chloro*-4-*deoxy*-α-D-*glucoside*. A solution of the compound (0·5 g.) in acetone (50 ml.) containing aqueous oxalic acid (8 ml.; 25%), was boiled under reflux for 9 hours, the acid was neutralised ($BaCO_3$), and the acetone evaporated after removal of the inorganic precipitate. After being washed with ether and filtered from unchanged benzylidene derivative (0·1 g.) the aqueous solution was evaporated to dryness. The syrupy product (0·2 g.) slowly crystallised and was recrystallised from ethyl acetate. *Methyl* 4-*chloro*-4-*deoxy*-α-D-*glucoside* had m. p. 124—126°, $[\alpha]_D^{18}$ +84° (*c*, 0·34 in H_2O) (Found : C, 39·5; H, 6·1; Cl, 16·6. $C_7H_{13}O_5Cl$ requires C, 39·5; H, 6·1; Cl, 16·7%). When treated with aqueous sodium metaperiodate, the compound consumed 1·00 mol. (22 hrs.); 1·09 mol. (46 hrs.).

Treatment of the Methyl Chlorodeoxyhexosides with Sodium Methoxide.—Methyl 4-chloro-4-deoxy-α-D-glucoside and methyl 3-chloro-3-deoxy-α-D-guloside were each treated with sodium methoxide (1·1 mol.) in methanol. In each case the product was a syrup which did not contain chlorine; $[\alpha]_D^{20}$ +53·1 and 53·5° (*c*, 2·03; 0·50 in H_2O), respectively. There was no reaction with trityl chloride in pyridine.

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