207. *The Action of Acidic Reagents on Ethylene Oxide Anhydro-sugars. Part II.* The Action of Hydrochloric Acid on Methyl* 2 : 3-*Anhydro*-4 : 6-O-*benzylidene*-α-D-*mannoside.*†

By F. H. Newth and (in part) R. F. Homer.

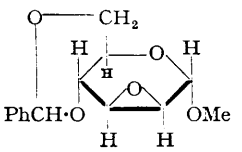
The chief product from the reaction of methyl 2 : 3-anhydro-*O*-4 : 6-benzylidene-α-D-mannoside with hydrochloric acid is methyl 3-chloro-3-deoxy-α-D-altroside.

In Part I the constitutions of the products of fission of the epoxide ring in methyl 2 : 3-anhydro-α-D-alloside with hydrochloric and hydrobromic acids were established. Methyl 2-deoxy-2-halogeno-α-D-altroside and methyl 3-deoxy-3-halogeno-α-D-glucoside were formed by substitution with inversion at positions 2 and 3 respectively with the latter predominating. The present work deals with the course of the reaction of methyl 2 : 3-anhydro-α-D-mannoside with hydrochloric acid; by analogy with the previous reaction the expected products would be methyl 2-chloro-2-deoxy-α-D-glucoside and methyl 3-chloro-3-deoxy-α-D-altroside. When methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside (I) was treated with hydrochloric acid in acetone solution the benzylidene residue was removed and the resulting product was a syrup. The consumption of periodate by this syrup was 0·08 mol. showing that 92% of the product was methyl 3-chloro-3-deoxy-α-D-altroside (II) and the remainder methyl 2-chloro-2-deoxy-α-D-glucoside (III) since, of these two isomers, only (III) contains an oxidisable 1 : 2-glycol system. When this work was almost complete, Mukherjee and Srivastava (*Proc. Indian Acad. Sci.*, 1952, **35**, 178) described the examination of the same reaction mixture with periodate and recorded an oxidant uptake of 0·56 mol., which would indicate the predominance of (III). This result is questionable since in the present work crystalline methyl 2 : 4 : 6-tri-*O*-acetyl-3-chloro-3-deoxy-α-D-altroside (IV) was isolated in 72% yield from the syrup. The Indian workers also found the ratio of altrose to glucose in the reaction product from the fission of methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside with hydrochloric acid to be 1 : 3, which

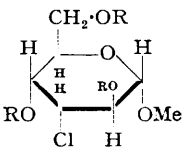
* Part I, *J.*, 1947, 10. † For details of the carbohydrate nomenclature used see *J.*, 1952, 5108.

agrees with the results obtained by Newth, Overend, and Wiggins (Part I). By the same reaction they confirmed the structures already assigned to the two methyl chlorodeoxyhexosides and this showed that periodate consumption could be used safely to evaluate the composition of such reaction mixtures.

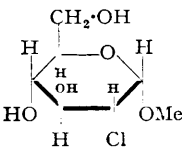
The evidence for assigning the altrose configuration to the crystalline triacetate (IV) may now be considered. Deacetylation of (IV) gave a methyl chlorodeoxy-α-D-hexoside which did not crystallise, consumed only 0·06 mol. of periodate, and did not react with lead tetra-acetate, thus indicating the absence of a 1 : 2-glycol. The benzylidene derivative (V) also failed to crystallise, but when treated with a solution of sodium methoxide it gave methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside (I). The chlorine atom must therefore be *trans* to the vicinal hydroxyl group and situated at $C_{(3)}$ since such a structure,



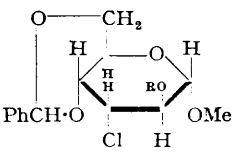
(I)



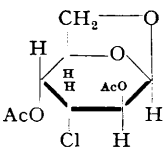
(II; R = H)
(IV; R = Ac)



(III)



(V; R = H)
(VI; R = Ac)



(VII)

methyl 3-chloro-3-deoxy-α-D-altroside (II), would not react with glycol-splitting reagents. Whereas the uptake of 0·06 mol. of periodate may be neglected in the diagnosis of structure, it should be taken into account in the estimation of the composition of the initial product; this therefore probably contains 98% of the altrose isomer. The syrupy benzylidene derivative provided a crystalline acetate with physical constants the same as those given by Mukherjee and Srivastava (*loc. cit.*) for their methyl monoacetyl-4 : 6-*O*-benzylidene-chlorodeoxy-α-D-hexoside, which may now be described as methyl 2-*O*-acetyl-4 : 6-*O*-benzylidene-3-chloro-3-deoxy-α-D-altroside (VI).

When methyl 3-chloro-3-deoxy-α-D-altroside or its triacetate was boiled with methanolic hydrogen chloride crystalline methyl 3-chloro-3-deoxy-β-D-altroside (m. p. 129°; $[\alpha]_D$ −112°) was obtained. Its physical constants clearly show it to be different from methyl 2-chloro-2-deoxy-β-D-glucoside (m. p. 159—164°; $[\alpha]_D$ −12°) (Fischer, Bergmann, and Schotte, *Ber.*, 1920, **53**, 509), the other isomer which could arise from the fission products of the anhydro-sugar by inversion of the glycosidic group. Furthermore, vigorous hydrolysis of the methyl tri-*O*-acetylchlorodeoxy-α-D-altroside with acid led to the formation of a non-reducing anhydro-compound isolated as the diacetate, 2 : 4-di-*O*-acetyl-1 : 6-anhydro-3-chloro-3-deoxy-β-D-altrose (VII). The formation of 1 : 6-anhydro-derivatives in the presence of aqueous acid is characteristic of altrose derivatives and the strong lævorotation ($[\alpha]_D$ −202°) is in accordance with that of related compounds (Newth and Wiggins, *J.*, 1950, 1734, and Part I).

Mukherjee and Srivastava (*loc. cit.*) showed that the rule put forward by Newth, Overend, and Wiggins (Part I) governing the action of alkaline and acidic reagents and hydrogen on 2 : 3-anhydro-rings was not generally applicable. This stated that if the epoxide bridge lies above the plane of the sugar ring, then with alkaline reagents it is the C–O bond farther from the glycosidic group which suffers most extensive fission, and the nearer C–O bond if the epoxide bridge is below the sugar ring. With acidic reagents methyl 2 : 3-anhydro-α-D-alloside showed a reversal of the proportion of isomers produced but this did not occur with dibenzyl hydrogen phosphate (Harvey, Michalski, and Todd, *J.*, 1951, 2271). The present investigation has revealed a further departure from the rule in that methyl 2 : 3-anhydro-α-D-mannoside with hydrochloric acid follows the same course as its alkaline fission with sodium methoxide (Robertson and Griffith, *J.*, 1935, 1193) and ammonia (Wiggins, *J.*, 1947, 18).

Added in Proof.—Mr. J. A. Mills, to whom our thanks are due, has suggested that the rule that steroid epoxides break to give a product having the two groups in polar positions (Fürst and Plattner, 12th Int. Congr. Pure and Applied Chem., 1951, Abstracts, p. 409) may also be applied to epoxides in sugar derivatives which have the conformation stabilised by a 1 : 6-anhydro-ring or a 4 : 6-*O*-benzylidene group (Reeves, *Adv. Carbohydrate Chem.*, 1951, **6**, 107; Angyal and Mills, *Rev. Pure Appl. Chem.*, 1952, **2**, 185). The behaviour, for example, of 1 : 6-2 : 3- and 1 : 6-3 : 4-dianhydro-β-talose with ammonia (James, Smith, Stacey, and Wiggins, *J.*, 1946, 625), and the predominance of methyl 4 : 6-*O*-benzylidene-D-altroside derivatives from both methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside and (I) support this. If, however, the anhydro-sugar lacks the stabilising group, or this is removed during reaction with acidic reagents, the steric course of ring opening is not so easily predicted. In the reaction of methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside with dibenzyl hydrogen phosphate in carbon tetrachloride (Harvey, Michalski, and Todd, *loc. cit.*) the benzylidene group is retained and the altrose isomer predominates. This argument will be discussed in detail elsewhere.

Experimental

Treatment of Methyl 2 : 3-Anhydro-4 : 6-O-benzylidene-α-D-mannoside with Hydrochloric Acid.—The sugar (9 g.) was dissolved in acetone (1 l.) containing hydrochloric acid (27 ml.; 2N), and the solution boiled under reflux for 4 hours. The excess of acid was neutralised with lead carbonate, and the inorganic residue filtered off and washed with aqueous acetone. After evaporation of the acetone from the combined filtrate and washings and removal of benzaldehyde by ether-extraction, the aqueous solution was evaporated to dryness under reduced pressure. The residue was extracted with hot ethyl acetate, evaporation of which gave a clear syrup (7·7 g.); $[\alpha]_D^{20}$ +51·4° (*c*, 0·89 in H_2O). When this syrup was treated with sodium metaperiodate in the standard manner the consumption of oxidant was 0·08 mol.

Methyl 2 : 4 : 6-Tri-O-acetyl-3-chloro-3-deoxy-α-D-altroside.—The syrup (4·5 g.) obtained above was dissolved in pyridine (50 ml.), acetic anhydride (25 ml.) added to the cold solution, and the mixture kept for 36 hours. The mixture was then evaporated to half the volume under reduced pressure and on its being poured into water an oil separated which crystallised rapidly. Recrystallised from alcohol the *triacetate* had m. p. 98—99°, $[\alpha]_D^{20}$ +70·3° (*c*, 1·61 in $CHCl_3$) (Found: C, 46·3; H, 5·6; Cl, 10·0; OMe, 9·6. $C_{13}H_{19}O_8Cl$ requires C, 46·2; H, 5·6; Cl, 10·4; OMe, 9·2%). The total yield of triacetate was 5·2 g. (72%). No other product could be isolated.

Methyl 3-Chloro-3-deoxy-α-D-altroside.—Methyl 2 : 4 : 6-tri-*O*-acetyl-3-chloro-3-deoxy-α-D-altroside (0·5 g.) was dissolved in dry methanol (15 ml.), and sodium methoxide solution (1 ml.; 0·1N) added. After being kept overnight the solution was evaporated and the residual syrup extracted with ethyl acetate. Evaporation of the solvent gave a hygroscopic syrup (0·32 g.), having $[\alpha]_D^{20}$ +103·5° (*c*, 1·01 in EtOH) (Found: C, 39·6; H, 6·6; OMe, 13·7. $C_7H_{13}O_5Cl$ requires C, 39·6; H, 6·1; OMe, 14·6%). It did not react with lead tetra-acetate in glacial acetic acid solution and consumed 0·06 mol. of periodate.

Condensation of Methyl 3-Chloro-3-deoxy-α-D-altroside with Benzaldehyde.—The compound (0·57 g.) obtained as above was shaken overnight with freshly distilled benzaldehyde (5 ml.) and zinc chloride (0·5 g.). The mixture was neutralised with aqueous sodium carbonate and evaporated under reduced pressure. Steam distillation under reduced pressure was then continued until no more benzaldehyde remained. The dry residue was extracted with chloroform and on evaporation of the solvent the benzylidene derivative was obtained as a syrup (0·6 g.), which showed $[\alpha]_D^{14}$ +95·7° (*c*, 6·07 in $CHCl_3$).

Acetylation of the syrup (0·1 g.) with acetic anhydride in pyridine gave methyl 2-*O*-acetyl-4 : 6-*O*-benzylidene-3-chloro-3-deoxy-α-D-altroside which, after recrystallisation from alcohol, had m. p. 126°, $[\alpha]_D^{17}$ +90·0° (*c*, 1·89 in $CHCl_3$) (Found: C, 56·3; H, 5·6. Calc. for $C_{16}H_{19}O_6Cl$: C, 56·1; H, 5·5%). Mukherjee and Srivastava (*loc. cit.*) give m. p. 126°, $[\alpha]_D^{27}$ +96·6° in $CHCl_3$.

Formation of Methyl 2 : 3-Anhydro-4 : 6-O-benzylidene-α-D-mannoside.—A solution of the syrupy benzylidene derivative (0·5 g.) in chloroform (10 ml.) was treated with sodium methoxide solution (25 ml.; 0·1N) for 24 hours at 20° and then 2 hours at 60°. The excess of alkali was neutralised (CO_2) and the solution evaporated to dryness. The residue was extracted with chloroform and evaporation of the solvent afforded methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside (0·4 g.) which, recrystallised from alcohol, had m. p. and mixed m. p. 145—146°.

Treatment of Methyl 2 : 4 : 6-Tri-O-acetyl-3-chloro-3-deoxy-α-D-altroside with Methanolic Hydrogen Chloride.—The compound (1·0 g.) was dissolved in dry methanol (25·7 ml.) containing

hydrogen chloride (0·24 g.), and the solution boiled under reflux; α_D, initially +1·49° (0·5 dm.), reached the constant value −0·05° in 5 hours. The acid was neutralised (Ag_2CO_3) and the solvent evaporated giving a syrup (0·62 g.), which crystallised when triturated with ethyl acetate. *Methyl 3-chloro-3-deoxy-β-D-altroside* was recrystallised from ethyl acetate and then had m. p. 128—129°, $[\alpha]_D^{20}$ −111·8° (*c*, 0·33 in EtOH) (Found: C, 40·1; H, 6·2. $C_7H_{13}O_5Cl$ requires C, 39·6; H, 6·1%). The residual syrup provided more crystalline material on re-treatment with methanolic hydrogen chloride. The same compound was obtained from methyl 3-chloro-3-deoxy-α-D-altroside.

Treatment of Methyl 2 : 4 : 6-Tri-O-acetyl-3-chloro-3-deoxy-α-D-altroside with Hydrochloric Acid.—The compound (0·97 g.) was added to hydrochloric acid (25 ml.; 5N), and the mixture boiled under reflux for 2 hours after solution was complete. The acid was neutralised (Ag_2CO_3) and soluble silver salts precipitated with hydrogen sulphide. The aqueous solution was evaporated under reduced pressure and the residual syrup (0·46 g.) which reduced Fehling's solution only very slightly was treated with acetic anhydride in pyridine for 2 days. *2 : 4-Di-O-acetyl-1 : 6-anhydro-3-chloro-3-deoxy-β-D-altrose* (0·18 g.) was formed which when recrystallised from alcohol had m. p. 114—115°, $[\alpha]_D^{19}$ −202° (*c*, 0·91 in $CHCl_3$) (Found: C, 45·9; H, 4·7. $C_{10}H_{13}O_6Cl$ requires C, 45·4; H, 4·9%). Concentration of the mother liquors gave a syrup (0·16 g.) showing $[\alpha]_D^{20}$ −77·7° (*c*, 0·81 in EtOH) which did not crystallise.

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