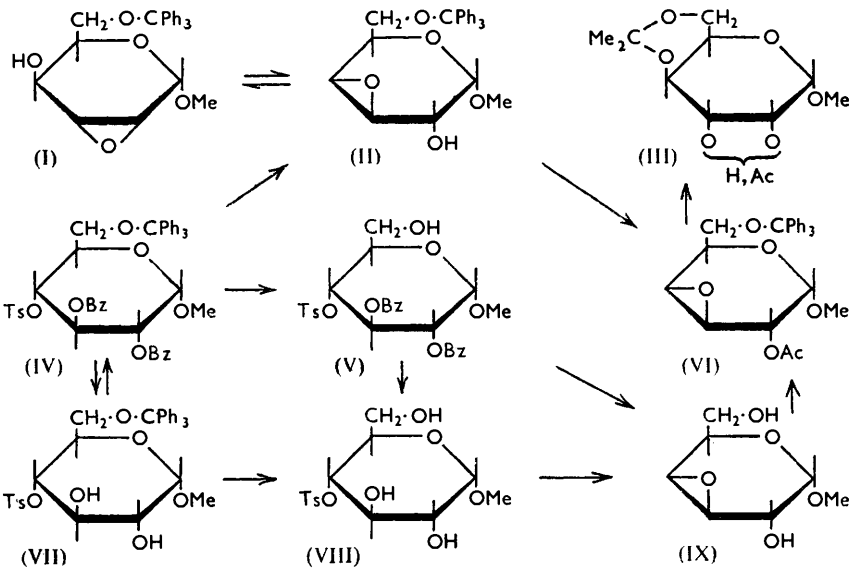
511. *The Behaviour of Derivatives of 3 : 4-Anhydrogalactose towards Acidic Reagents. Part II.*[1]

By J. G. Buchanan.

Methyl 3 : 4-anhydro-α-D-galactoside (IX) has been prepared and converted into the crystalline 2-*O*-acetyl-6-*O*-triphenylmethyl derivative (VI). The latter, with anhydrous hydrogen chloride in acetone, gives methyl *O*-acetyl-4 : 6-*O*-*iso*propylidene-α-D-guloside (III). It is shown that a neighbouring *trans*-*O*-acetyl group exerts a directive influence on the scission of an ethylene oxide by acidic reagents, and carbonium-type intermediates are suggested. The chlorohydrins resulting from the reaction of methyl 3 : 4-anhydro-α-D-galactoside with aqueous hydrochloric acid have been characterised.

Methyl 3 : 4-anhydro-β-D-galactoside was described by Helferich and Müller [2] in 1930. The 6-*O*-triphenylmethyl derivative (II) of the α-anomer was later prepared by Oldham and Robertson,[3] who examined the reaction of its 2-acetate (VI) with acetone containing dry hydrogen chloride. It has recently been shown [1,4] that this preparation of the 3 : 4-epoxide (II) contains an appreciable amount of isomeric 2 : 3-anhydroguloside (I). In order to explain the course of the reactions described by Oldham and Robertson [3] and later by Labaton and Newth [5] it was necessary to prepare the authentic 3 : 4-anhydro-compound in the α-series. This paper describes some of the results obtained.



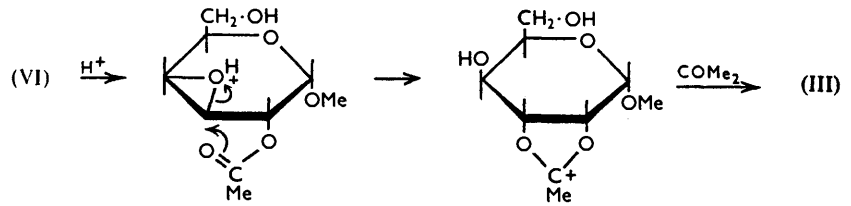
Ts = *p*-$C_6H_4Me\cdot SO_2$.

Oldham and Robertson [3] treated methyl 2 : 3-di-*O*-benzoyl-4-*O*-tosyl-6-*O*-triphenylmethyl-α-D-glucoside (IV) with alkali in hot aqueous acetone to obtain the anhydro-compound (II). Even Labaton and Newth's modified conditions [5] lead to formation of the anhydroguloside (I). The conditions used by Helferich and Müller,[2] a slight excess of sodium methoxide in methanol–chloroform at 0°, were therefore studied. A crystalline

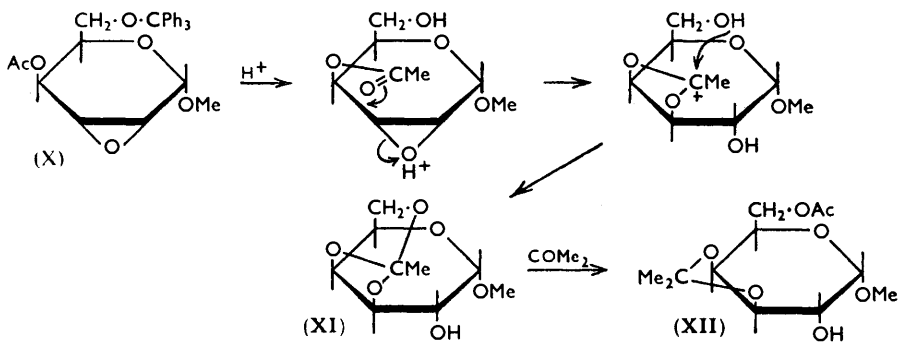
[1] Part I, Buchanan, *J.*, 1958, 995.
[2] Helferich and Müller, *Ber.*, 1930, **63**, 2142.
[3] Oldham and Robertson, *J.*, 1935, 685.
[4] Buchanan, *Chem. and Ind.*, 1954, 1484.
[5] Labaton and Newth, *J.*, 1953, 992.

compound was isolated which, however, contained sulphur and was shown to be methyl 4-*O*-tosyl-6-*O*-triphenylmethyl-α-D-glucoside (VII). On benzoylation this gave its dibenzoate (IV) and with alcoholic hydrochloric acid yielded methyl 4-*O*-tosyl-α-D-glucoside (VIII). The structure of the latter was confirmed by periodate oxidation: consumption was very slow, in agreement with the behaviour of certain other 4-substituted glucosides.[1,6]

It therefore seemed unlikely that pure 3 : 4-anhydro-6-*O*-triphenylmethyl-α-D-galactoside (II) could be made by the action of alkali on compound (IV); the use of more drastic conditions would bring about oxide migration. The relative inertness of the toluene-*p*-sulphonyl group was almost certainly due to a conformational effect of the bulky triphenylmethyl group; [7] and this was confirmed by mild treatment of methyl 2 : 3-di-*O*-benzoyl-4-*O*-tosyl-α-D-glucoside [5,8] (V) with alkali, which gave a methyl anhydrohexoside in good yield; the same compound was obtained from the 2 : 3-diol (VIII). The anhydrohexoside was shown to be the 3 : 4-anhydrogalactoside (IX) by hydrolysis with dilute sulphuric acid. As in the β-series,[9] paper chromatography showed that D-gulose and methyl α-D-guloside were the major products, together with methyl α-D-glucoside. No trace of idose or galactose derivatives was present, showing the absence of 2 : 3-anhydroguloside in the anhydro-compound.



Treatment of the anhydro-compound (IX) with a slight deficiency of triphenylmethyl chloride in pyridine [10] gave a crystalline derivative (II), acetylation of which yielded the monoacetate (VI), also crystalline. The behaviour of the pure ester (VI) towards dry hydrogen chloride in acetone could now be examined; methyl (2 or 3)-*O*-acetyl-4 : 6-*O*-*iso*propylidene-α-D-guloside (III) was isolated, identical with that described previously,[1] and no galactose derivative could be detected by paper chromatography. It appears,



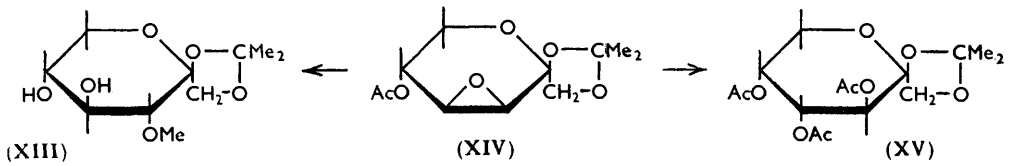
therefore, that the guloside arises from the anhydrogalactoside component of Oldham and Robertson's mixture of anhydro-sugars. In formulating a mechanism for this reaction, three facts must be considered: (*a*) the epoxide ring has suffered *trans*-scission; (*b*) no glucose derivatives were found in the products, in contrast to ring-opening of (IX) by sulphuric or by hydrochloric acid (see below); (*c*) no chlorohydrin was detected in the

[6] Harvey, Michalski, and Todd, *J.*, 1951, 2271; Baddiley, Buchanan, and Szabó, *J.*, 1954, 3826.
[7] Newth, *J.*, 1956, 441.
[8] Bell, *J.*, 1934, 1177.
[9] Müller, *Ber.*, 1935, **68**, 1094.
[10] *Idem*, *Ber.*, 1934, **67**, 421.

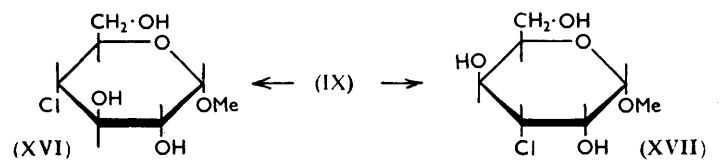
reaction mixture. This implies that the acetyl group exerts a controlling influence on the reaction, and the annexed mechanism (VI) ⟶ (III) is proposed.

Evidence in favour of this mechanism was obtained by hydrolysis of the anhydro-compound (II) and its acetate (VI) by dilute sulphuric acid in aqueous dioxan. Paper chromatography showed that the former gave gulose and methyl α-D-glucoside, but gulose was the only product of hydrolysis of the acetate (VI). Similarly, the anhydro-compound (IX) and its syrupy diacetate were treated with sulphuric acid in aqueous acetone: the former gave methyl α-D-glucoside in addition to gulose derivatives, but no glucose or glucoside was present in the diacetate hydrolysate, methyl tetra-*O*-acetyl-α-D-guloside [11] being isolated in 82% yield after acetylation.

A corollary to the experiments on the pure anhydrogalactoside was that methyl 6-*O*-acetyl-3 : 4-*O*-*iso*propylidene-α-D-galactoside [1] (XII), the other sugar originally isolated from the hydrogen chloride–acetone reaction mixture by Oldham and Robertson,[3] arises from methyl 4-*O*-acetyl-2 : 3-anhydro-6-*O*-triphenylmethyl-α-D-guloside (X). This reaction is of great interest, since none of the idose derivatives, which might be expected to preponderate,[1,12] was detected. The mechanism proposed, (X) ⟶ (XII), through the orthoacetate (XI), has an analogy [13] in the formation of 5-*O*-benzoyl-α-D-ribose 1 : 2 : 3-orthobenzoate by the action of mercuric acetate on 3 : 5-di-*O*-benzoyl-D-ribosyl chloride.



It appears that in the acid-catalysed scission of the oxide rings in both compounds (VI) and (X) the neighbouring *trans*-acetyl group is the major factor deciding the orientation of the product. The only other example in the carbohydrate field is the behaviour of 5-*O*-acetyl-3 : 4-anhydro-1 : 2-*O*-*iso*propylidene-D-tagatose (XIV): [14] with sodium methoxide the product is the D-sorbose derivative (XIII), the first step presumably being deacetylation; acetic anhydride–acetic acid containing a little pyridine gives the D-fructose derivative (XV). The application to other systems is being studied.



It was suggested in Part I [1] that one of the chlorodeoxyhexosides isolated by Labaton and Newth [5] was the 4-chloro-4-deoxyglucoside (XVI); this has now been confirmed. Methyl 3 : 4-anhydro-α-D-galactoside (IX) was treated with aqueous hydrochloric acid in acetone. The two expected chlorohydrins (XVII) and (XVI) were isolated directly by crystallisation from ethyl acetate. The first (45% yield) had m. p. 142°, $[\alpha]_D$ +114·5°, and was clearly different from either of the chlorohydrins isolated earlier.[5] Since it was stable to sodium periodate it was methyl 3-chloro-3-deoxy-α-D-guloside (XVII). The second chlorohydrin (24% yield) was identical with the methyl 4-chloro-4-deoxy-α-D-glucoside (XVI) first made by Labaton and Newth [5] (cf. Part I [1]). When the chloro-deoxyguloside (XVII) was treated with benzaldehyde and zinc chloride a chloroform-soluble *O*-benzylidene compound was formed. This did not crystallise, and its ready solubility in alcohol explains the earlier failure to detect the parent chlorohydrin.[5]

[11] Isbell, *J. Res. Nat. Bur. Stand.*, 1932, **8**, 1.
[12] Reichstein and Sorkin, *Helv. Chim. Acta*, 1945, **28**, 1.
[13] Ness and Fletcher, *J. Org. Chem.*, 1957, **22**, 1465, 1470.
[14] Ohle and Schultz, *Ber.*, 1938, **71**, 2302.

Experimental

Methyl 2 : 3-*Di*-O-*benzoyl*-4-O-*tosyl*-6-O-*triphenylmethyl*-α-D-*glucoside*.—The pure compound was prepared in 79% overall yield from methyl 4 : 6-*O*-benzylidene-α-D-glucoside by Oldham and Robertson's method,[3] with two modifications: (i) Methyl 4 : 6-*O*-benzylidene-α-D-glucoside was benzoylated with excess of benzoyl chloride in pyridine at 100° for 2 hr. The yield of product,[15] m. p. 153°, was 94%. (ii) The triphenylmethyl compound [3,5] was crystallised from chloroform–methanol and then had m. p. 169—170°, $[\alpha]_D^{21}$ +61·8° (*c* 1·66 in $CHCl_3$) (Found: C, 70·9; H, 5·7. Calc. for $C_{47}H_{42}O_{10}S$: C, 70·7; H, 5·3%). The m. p. dropped to *ca.* 160° during storage under normal conditions for several months; the reason was not investigated (cf. Labaton and Newth [5]).

Methyl 2 : 3-*Di*-O-*benzoyl*-4-O-*tosyl*-α-D-*glucoside*.—The above triphenylmethyl compound (IV) was heated for 1 hr. under reflux in ethanol (300 c.c.) containing concentrated hydrochloric acid (2 drops). The product crystallised in needles; it was filtered off and washed with methanol (yield 12·5 g., 90%), and had m. p. 185°, $[\alpha]_D^{21}$ +99·7° (*c* 1·42 in $CHCl_3$) [5,8] (Found: C, 60·6; H, 4·8; S, 5·8. Calc. for $C_{28}H_{28}O_{10}S$: C, 60·4; H, 5·0; S, 5·8%).

Methyl 4-O-*Tosyl*-6-O-*triphenylmethyl*-α-D-*glucoside*.—The triphenylmethyl compound (IV) (17·0 g.) was dissolved in chloroform (100 c.c.) and treated with sodium methoxide (0·6 g. of sodium) in methanol (100 c.c.) at 0° for 2 hr. Water was added, and the chloroform layer separated, washed with water, and dried (Na_2SO_4). The solution was evaporated to a syrup, and light petroleum (b. p. 40—60°; 1 l.) added. The solid formed was filtered off and recrystallised from chloroform–light petroleum (1 : 3), to give the *ester* as small needles (8·0 g., 64%), m. p. 146—147°, $[\alpha]_D^{20}$ +74·9° (*c* 1·33 in $CHCl_3$) (Found: C, 65·3; H, 6·1; S, 5·1. $C_{33}H_{34}O_8S$·OMe requires C, 67·1; H, 5·8; S, 5·4; OMe, 5·3%). These analytical values were confirmed in 3 independent preparations.

Benzoylation of this compound with excess of benzoyl chloride in pyridine at room temperature for 30 hr. gave the dibenzoate (IV) in good yield (mixed m. p.).

Methyl 4-O-*Tosyl*-α-D-*glucoside*.—Methyl 4-*O*-tosyl-6-*O*-triphenylmethyl-α-D-glucoside (4·0 g.), ethanol (50 c.c.), and concentrated hydrochloric acid (0·2 c.c.) were heated under reflux for ½ hr. Chloroform (50 c.c.) was added and the solution evaporated to a syrup. Trituration with ether (50 c.c.) gave the crystalline *toluene*-p-*sulphonate* (2·15 g., 91%), m. p. 147—148° raised by recrystallisation from ethyl acetate–ether to 148—149°, $[\alpha]_D^{22}$ +107·6° (*c* 1·14 in EtOH) (Found: C, 48·3; H, 6·0. $C_{14}H_{20}O_8S$ requires C, 48·3; H, 5·8%). The glycoside (0·11 g.) was treated with sodium metaperiodate (0·19 g.) in water (50 c.c.) at room temperature. Consumption was: 0·23 mol. (16 hr.); 0·40 mol. (43 hr.); 0·65 mol. (112 hr.); 0·89 mol. (211 hr.); 0·98 mol. (282 hr.); 0·98 mol. (331 hr.).

Methyl 3 : 4-*Anhydro*-α-D-*galactoside*.—(i) Methyl 2 : 3-di-*O*-benzoyl-4-*O*-tosyl-α-D-glucoside (9·40 g.) in chloroform (50 c.c.) was treated with sodium methoxide (0·5 g. of sodium) in methanol (50 c.c.) at 0° for 5 hr., with occasional shaking. Solid carbon dioxide was added and some solid was removed. The filtrate was evaporated to dryness, dissolved in water (50 c.c.), and extracted with light petroleum (b. p. 40—60°; 50 c.c.) followed by ethyl acetate (20 c.c.). The aqueous layer was evaporated to dryness, and extracted with a boiling mixture (1 : 1) of ethyl acetate and toluene. From the extract the *anhydro-compound* was isolated, by crystallisation from ethyl acetate, as fine needles (2·42 g., 81%), m. p. 118·5—119·5°, $[\alpha]_D^{19}$ +67·5° (*c* 1·11 in H_2O) (Found: C, 48·0; H, 7·1; OMe, 17·9. $C_7H_{12}O_5$ requires C, 47·7; H, 6·9; OMe, 17·6%). Shorter reaction times led to the isolation of some methyl 4-*O*-tosyl-α-D-glucoside, as well as the anhydro-compound (*e.g.*, after 2 hr., 20% of the toluene-*p*-sulphonate and 49% of the anhydro-sugar). The toluene-*p*-sulphonate is sparingly soluble in water and can be extracted from aqueous solution by ethyl acetate. (ii) Methyl 4-*O*-tosyl-α-D-glucoside (1·74 g.), suspended in chloroform (15 c.c.), was treated with sodium methoxide (0·14 g. of sodium) in methanol (15 c.c.) at 0° for 5 hr. The anhydro-compound was isolated as in (i). It crystallised from ethyl acetate–toluene in needles (0·65 g., 74%), m. p. 118—119°, undepressed by the compound prepared as in (i). A sample (*ca.* 5 mg.) was heated with 0·1N-sulphuric acid (0·2 c.c.) at 100° for 1·25 hr. Examination of the product by paper chromatography showed the presence of D-gulose, methyl α-D-guloside, and methyl α-D-glucoside; D-idose,

[15] Ohle and Spencker, *Ber.*, 1928, **61**, 2392; Ansell and Honeyman, *J.*, **1952**, 2778; Jeanloz and Jeanloz, *J. Amer. Chem. Soc.*, 1957, **79**, 2579.

D-galactose, and methyl α-D-galactoside were absent (methyl α-D-idoside would have been largely converted into D-idose in these conditions). For R_F values, see Tables.

Methyl 3 : 4-*Anhydro*-6-O-*triphenylmethyl*-α-D-*galactoside*.—The anhydrogalactoside (IX) (2·0 g.) in pyridine (10 c.c.) was treated with triphenylmethyl chloride (2·95 g., 0·93 mol.) for 40 hr. at room temperature. The *glycoside* was isolated by use of chloroform and, crystallised from aqueous methanol, had m. p. 142° (3·77 g., 85%). It recrystallised from ethyl acetate–light petroleum (b. p. 40—60°) as needles, m. p. 144·5°, $[\alpha]_D^{21}$ +8·7° (*c* 3·19 in $CHCl_3$) (Found: C, 74·5; H, 6·6. $C_{26}H_{26}O_5$ requires C, 74·6; H, 6·3%).

The glycoside (*ca.* 5 mg.) was treated with 1 : 1 dioxan–0·2N-sulphuric acid in a sealed tube at 100° for 5 hr. Paper chromatography showed the formation of D-gulose and methyl α-D-glucoside.

Methyl 2-O-*Acetyl*-3 : 4-*anhydro*-6-O-*triphenylmethyl*-α-D-*galactoside*.—The above anhydro-compound (II) (2·0 g.) was acetylated with acetic anhydride in pyridine overnight. Isolated by means of chloroform the *acetate* crystallised from light petroleum (b. p. 60—80°) as plates (2·02 g., 92%), m. p. 119·5—120°, $[\alpha]_D^{21}$ +31·0° (*c* 3·23 in $CHCl_3$) (Found: C, 73·1; H, 6·3. $C_{28}H_{28}O_6$ requires C, 73·0; H, 6·1%). The glycoside (*ca.* 5 mg.) was treated with acid in the same way as the preceding compound. D-Gulose, but no methyl α-D-glucoside, was demonstrated by paper chromatography.

Methyl O-*Acetyl*-4 : 6-O-iso*propylidene*-α-D-*guloside*.—The acetate (VI) (3·78 g.) in acetone (20 c.c.) was treated with acetone (20 c.c.) containing dry hydrogen chloride (1 g.) for 1 hr. at room temperature and the solution then neutralised with anhydrous sodium carbonate. The filtrate after removal of inorganic solid was evaporated to small volume and treated with excess of water containing a little pyridine. The crystalline triphenylmethanol (2·09 g., 98%) was removed and the filtrate extracted several times with chloroform, leaving an aqueous solution, *A*. The combined chloroform extracts were dried (Na_2SO_4) and evaporated to a crystalline mass which was treated with ether and filtered, leaving needles (0·9 g., 40%), m. p. 165—167°, undepressed in admixture with the compound prepared as in Part I.[1] Identity was confirmed by the infrared spectra. The ethereal mother-liquors, which had deposited no further crystalline material,[1,3,5] were evaporated to dryness and deacetylated catalytically.[16] The solution was evaporated, the residue was dissolved in water, and sodium ions were removed in a Dowex 50 (H^+) column. The acidic eluate (pH *ca.* 3) was kept for 48 hr. at room temperature, neutralised with Dowex 3 (OH^-) resin and examined chromatographically. Gulose (a trace) and methyl α-D-guloside were present, together with small amounts of two unidentified spots giving yellow colours with the periodate–Schiff reagent sprays.[17] No galactose or methyl α-D-galactoside was present. The solution *A* above was freed from chloride ions with Dowex 3 (OH^-) resin, concentrated, and subjected to chromatography. A compound with the properties of a methyl mono-*O*-acetyl-α-D-guloside together with a trace of methyl α-D-guloside were the only substances present. Deacetylation gave only methyl α-D-guloside. For R_F values, see Tables.

Methyl 2 : 6-*Di*-O-*acetyl*-3 : 4-*anhydro*-α-D-*galactoside*.—The anhydro-galactoside (IX) (0·5 g.) was treated with acetic anhydride (2 c.c.) in pyridine (5 c.c.) for 24 hr. at room temperature. The diacetate was isolated, by means of chloroform, as a syrup (0·72 g., 97%), $[\alpha]_D^{21}$ +57·4° (*c* 2·86 in $CHCl_3$) (Found: C, 51·2; H, 6·3. $C_{11}H_{16}O_7$ requires C, 50·8; H, 6·2%).

Methyl Tetra-O-*acetyl*-α-D-*guloside*.—The above diacetate (1·49 g.) was heated under reflux with acetone (50 c.c.) and 2N-sulphuric acid (1·5 c.c.) for 4 hr. The solution was neutralised with barium carbonate, filtered, and evaporated to dryness. The residue was deacetylated catalytically [16] and a portion examined by paper chromatography. A heavily loaded chromatogram showed methyl α-D-guloside as the main component, with a small amount of gulose and a minute amount of a fast-running compound (reacting with periodate). Methyl α-D-glucoside could not be detected. The methanol solution was evaporated to dryness and acetylated with acetic anhydride in pyridine. The acetate was isolated in orthodox fashion and crystallised from water, to give prisms (1·70 g., 82%), m. p. *ca.* 95°. Recrystallised from water it had m. p. 98°, $[\alpha]_D^{23}$ +96·5° (*c* 1·16 in $CHCl_3$) (Found: C, 50·0; H, 6·3. Calc. for $C_{15}H_{22}O_{10}$: C, 49·7; H, 6·1%). Isbell [11] gives m. p. 98° and $[\alpha]_D$ +97·3° (in $CHCl_3$).

When methyl 3 : 4-anhydro-D-galactoside was treated with acid under the same conditions, paper chromatography showed the presence of methyl α-D-glucoside in addition to gulose and

[16] Zemplén, Gerecs, and Hadácsy, *Ber.*, 1936, **69**, 1827.
[17] Buchanan, Dekker. and Long, *J.*, 1950, 3162; Baddiley, Buchanan, Handschumacher, and Prescott, *J.*, 1956, 2818.

methyl α-D-guloside. The glucoside was isolated by crystallisation from ethyl acetate and identified by mixed m. p. and infrared spectrum. For R_F values see Tables.

Paper Chromatography.—The most suitable solvent was butan-1-ol–pyridine–water (3 : 1 : 1 by vol.).[18] Whatman No. 4 paper was used; free sugars were detected by aniline phthalate [19] and glycosides by periodate–Schiff's reagent.[17]

Hexose	R_F	Methyl α-D-hexoside	R_F	Colour * [17]
Galactose	0·21	Galactoside	0·35	GP
Glucose	0·24	Glucoside	0·41	GP
Gulose	0·31	Guloside	0·46	P
Idose	0·41	*O*-Acetylguloside	0·68	P †

* G = Grey, P = purple. † Only after exposure to NH_3.[20]

Methyl 3-Chloro-3-deoxy-α-D-guloside and Methyl 4-Chloro-4-deoxy-α-D-glucoside.—Methyl 3 : 4-anhydro-α-D-galactoside (1·12 g.) in acetone (190 c.c.) containing 2N-hydrochloric acid (5 c.c.) was heated under reflux for 4 hr. The solution was neutralised with lead carbonate, filtered, and evaporated to dryness. The residue was extracted with hot ethyl acetate, and careful crystallisation gave first the pure *guloside* as prisms (0·61 g., 45%), m. p. 142° (decomp.), $[\alpha]_D^{24}$ +114·5° (*c* 1·20 in H_2O) (Found: C, 39·6; H, 6·1; Cl, 16·1. $C_7H_{13}O_5Cl$ requires C, 39·5; H, 6·1; Cl, 16·7%). The glycoside consumed no sodium metaperiodate during 3 days. On nucleation the mother-liquors deposited the glucoside as prisms (0·32 g., 24%), m. p. 114—115°, undepressed in admixture with a specimen prepared by Labaton and Newth's method.[1,5] The identity was confirmed by infrared spectra.

I thank Professor J. Baddiley for his interest and Miss S. Robinson for preparations of methyl 4 : 6-*O*-benzylidene-α-D-glucoside from methyl α-D-glucoside, a generous gift from Messrs. Brown and Polson, Ltd.

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[18] Hough, Jones, and Wadman, *J.*, 1950, 1702.
[19] Partridge, *Nature*, 1949, **164**, 443.
[20] Baddiley, Buchanan, Hodges, and Prescott, *J.*, 1957, 4769.