199. *The Behaviour of Derivatives of* 3 : 4-*Anhydrogalactose towards Acidic Reagents. Part I.*

By J. G. Buchanan.

The product arising from alkaline hydrolysis of methyl 2 : 3-di-*O*-benzoyl-4-*O*-tosyl-6-*O*-triphenylmethyl-α-D-glucoside [1] (I) is shown to be a mixture of methyl 3 : 4-anhydro-6-*O*-triphenylmethyl-α-D-galactoside (V) and methyl 2 : 3-anhydro-6-*O*-triphenylmethyl-α-D-guloside (XXI). The structures of several compounds made during earlier investigations of this problem [1, 2] have been elucidated.

The behaviour of methyl 3 : 4-anhydro-β-D-galactoside [3] towards acidic reagents was investigated by Müller.[4, 5] Dilute sulphuric acid was shown to yield a mixture of D-gulose and D-glucose,[5] in agreement with the well-known steric course of these reactions.[6] Oldham and Robertson [1] prepared methyl 3 : 4-anhydro-6-*O*-triphenylmethyl-α-D-galactoside (V) by treatment of methyl 2 : 3-di-*O*-benzoyl-4-*O*-tosyl-6-*O*-triphenylmethyl-α-D-glucoside (I) with alkali. The compound was not crystalline, nor was its 2-acetate (IV). The acetate (IV), with acetone containing dry hydrogen chloride, gave a mixture from which mono-*O*-acetyl-*O*-*iso*propylidene derivatives of methyl α-D-galactoside and methyl α-D-guloside were isolated. Reaction of a sugar epoxide with acid or alkaline reagents normally yields *trans*-products.[6] The reaction of the 3 : 4-anhydrogalactoside with acetone involved both *cis*- and *trans*-opening of the epoxide ring. It is known, moreover, that aqueous hydrochloric acid in acetone causes *trans*-opening of an epoxide ring, to give chlorohydrins.[7] These apparent inconsistencies led to a re-investigation of the problem by Labaton and Newth.[2]

These authors confirmed the earlier work and made certain other observations on the structures of the *iso*propylidene compounds. The galactoside had been deacetylated by Oldham and Robertson to a methyl *O*-*iso*propylidene-α-D-galactoside which, from its properties, was clearly the 3 : 4-cyclic acetal; Labaton and Newth therefore assigned structure (VII) to the acetate. The guloside was converted into a toluene-*p*-sulphonate in which the sulphonyloxy-group was stable to treatment with sodium iodide. The original acetate had therefore structure (VIII), giving the derivative (IX). No sugars other than galactose or gulose were present in acid hydrolysates of the total deacetylated mixture.

Labaton and Newth then examined the action of hydrochloric acid on the anhydro-sugar (V). The products to be expected [8, 9] were the chlorodeoxyglucoside (VI) and the chlorodeoxyguloside (II). The crude product consumed 0·4 mol. of lead tetra-acetate, indicating the presence of 40% of the glucoside (VI), and gave a benzylidene compound on treatment with benzaldehyde and zinc chloride. The other chlorodeoxy-sugar was isolated from the aqueous mother-liquors. It was expected that the sugar which had reacted with benzaldehyde would be the guloside (II) but it was found, after hydrolysis of the benzylidene residue, that the chlorodeoxy-sugar consumed 1 mol of periodate. It was therefore assigned the glucoside structure (VI) and the benzylidene compound the 3 : 6-structure (X). The other sugar did not react with periodate and was therefore the guloside (II). When either chlorodeoxy-sugar was treated with sodium methoxide the same halogen-free product, presumably methyl 3 : 4-anhydro-α-D-galactoside (III), was

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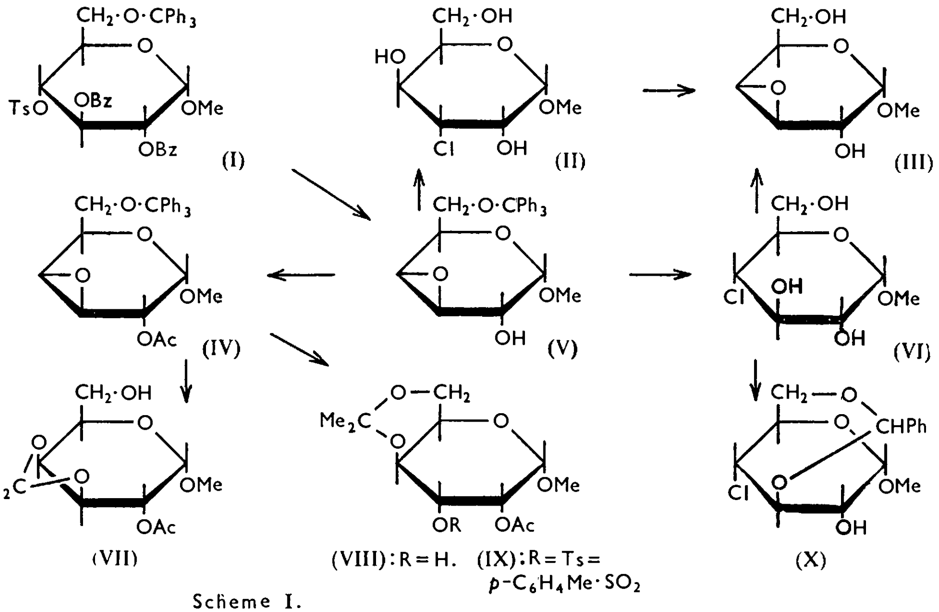
[1] Oldham and Robertson, *J.*, 1935, 685.
[2] Labaton and Newth, *J.*, 1953, 992.
[3] Helferich and Müller, *Ber.*, 1930, **63**, 2142.
[4] Müller, *Ber.*, 1934, **67**, 421.
[5] *Idem, Ber.*, 1935, **68**, 1094.
[6] Peat, *Adv. Carbohydrate Chem.*, 1946, **2**, 51.
[7] Robertson and Dunlop, *J.*, 1938, 472.
[8] Newth, Overend, and Wiggins, *J.*, 1947, 10.
[9] Newth and Homer, *J.*, 1953, 989.

obtained; it did not give a triphenylmethyl derivative. Most of this analysis is summarised in Scheme I. The more recent work, while it confirmed the earlier observations, seemed to present more difficulties. While 3 : 6-*O*-benzylidene compounds in the glucose series are sterically possible, this is the only known example. The problem of both *cis*- and *trans*-opening of the epoxide ring by acetone remained.

It appeared that Lake and Peat's results [10] on derivatives of 2 : 3-anhydromannose might have some bearing.[11] When methyl 3 : 4 : 6-tri-*O*-acetyl-2-*O*-tosyl-β-D-glucoside (XI) is treated with sodium methoxide, derivatives of both the 2 : 3-anhydromannoside (XII) and the 3 : 4-anhydroaltroside (XIII) can be isolated. The 3-hydroxyl group in the mannoside, the anhydro-sugar which is formed first, is *trans* to the epoxide ring and can yield the altroside; the reaction is probably reversible. In the 3 : 4-anhydrogalactoside (V) the situation is similar and one might expect to have some of the 2 : 3-anhydroguloside (XXI) produced. Newth,[12] Overend and Ricketts,[13] and Angyal and Gilham [14] have recently cited other examples of this phenomenon. Methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-guloside [15] (XV) was therefore treated with hydrochloric acid in acetone.[7] The benzylidene group was removed during the reaction and a methyl chlorodeoxyhexoside was isolated directly from the reaction mixture in 42% yield.[11] Since the product consumed 1 mol. of periodate, it was the 2-chloro-2-deoxyidoside (XVI). It had the same



Scheme I.

melting point as, and similar rotation to, Labaton and Newth's " chlorodeoxyglucoside; " its benzylidene compound (XIV) was identical with " methyl 3 : 6-*O*-benzylidene-4-chloro-4-deoxy-α-D-glucoside," [2] and the latter gave a quantitative yield of methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-guloside on treatment with sodium methoxide. These experiments showed clearly that the 2 : 3-anhydroguloside (XXI) was present in appreciable amounts in earlier preparations of methyl 3 : 4-anhydro-6-*O*-triphenylmethyl-α-D-galactoside. The other methyl chlorodeoxyhexoside isolated by Labaton

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[10] Lake and Peat, *J.*, 1939, 1069.

[11] Buchanan, *Chem. and Ind.*, 1954, 1484.

[12] Newth, *J.*, 1956, 441.

[13] Overend and Ricketts, *Chem. and Ind.*, 1957, 632.

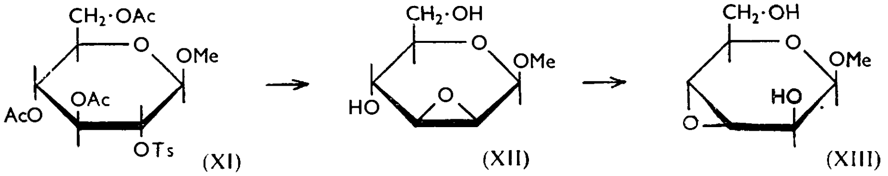
[14] Angyal and Gilham, *J.*, 1957, 3691.

[15] Reichstein and Sorkin, *Helv. Chim. Acta*, 1945, **28**, 1.

and Newth could then have one of three structures: the 3-chloro-3-deoxyguloside (II), the 4-chloro-4-deoxyglucoside (VI) (both derived from the 3 : 4-anhydrogalactoside), or a 3-chloro-3-deoxygalactoside derived from the 2 : 3-anhydroguloside. Of these, the guloside and galactoside are capable of forming 4 : 6-benzylidene derivatives and would be stable to periodate; the glucoside cannot form a cyclic 4 : 6-acetal, but contains an α-glycol system.

The chlorodeoxyhexoside was therefore isolated and found to reduce 1·03 mol. of periodate in 7 days; Labaton and Newth's " methyl 3-chloro-3-deoxy-α-D-guloside " was therefore the 4-chloro-4-deoxyglucoside (VI). The slow periodate consumption was in agreement with the results of periodate oxidation of certain other 4-substituted glucosides.[16, 17]

The *iso*propylidene compounds resulting from the reaction with dry acetone and hydrogen chloride were then studied. The galactoside was shown to be methyl 6-*O*-acetyl-3 : 4-*O*-*iso*propylidene-α-D-galactoside (XVII) by the following transformations. Toluene-*p*-sulphonylation gave a crystalline derivative (XVIII), with properties differing from those of Iselin and Reichstein's syrupy 2-*O*-acetyl-6-*O*-tosyl isomer.[18] Deacetylation yielded a crystalline ester (XIX), different from the 6-*O*-tosyl compound.[18, 19] The known 2 : 6-di-*O*-tosyl derivative [20] (XX) was formed from the ester (IX). Structure (XVII) was confirmed by acid hydrolysis of the ester (XIX) to syrupy methyl 2-*O*-tosyl-α-D-galactoside [21] (XXII) which gave the known crystalline 4 : 6-*O*-benzylidene compound [21, 22] (XXIII). Hydrolysis of the glycoside (XXIII) yielded methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-taloside (XXIV) identified by comparison with an authentic sample.



(XI) (XII) (XIII)

The guloside presented more difficulty. The methyl *O*-acetyl-*O*-*iso*propylidene-α-D-guloside, m. p. 177—179°, described by the earlier workers could not be isolated; instead, the product had m. p. 165—167°. Deacetylation gave a methyl *O*-*iso*propylidene-α-D-guloside with the same physical constants as that isolated by Oldham and Robertson; it consumed 1 mol. of periodate. The deacetylated gulose derivative must therefore be the cyclic 4 : 6-acetal (XXV). Toluene-*p*-sulphonylation of the acetyl compound gave a derivative of m. p. 128—129° and $[\alpha]_D$ +47·3°; Labaton and Newth report m. p. 122—123° and $[\alpha]_D$ +52·2° for their *O*-acetyl-*O*-tosyl derivative. It seemed likely that the *O*-acetyl compound of m. p. 177—179° previously isolated was isomeric with that described in this paper; attempts to cause acetyl migration have so far been unsuccessful. It was, however, certain that the guloside product was methyl 2(or 3)-*O*-acetyl-4 : 6-*O*-*iso*-propylidene-α-D-guloside (VIII) or (XXVI); the corresponding tosyl compounds were (IX) or (XXVII).

While much is known regarding the formation of chlorohydrins from sugar epoxides, the reaction with anhydrous acetone has received little attention. The problem remains as to the origin of each *iso*propylidene derivative in Oldham and Robertson's work.

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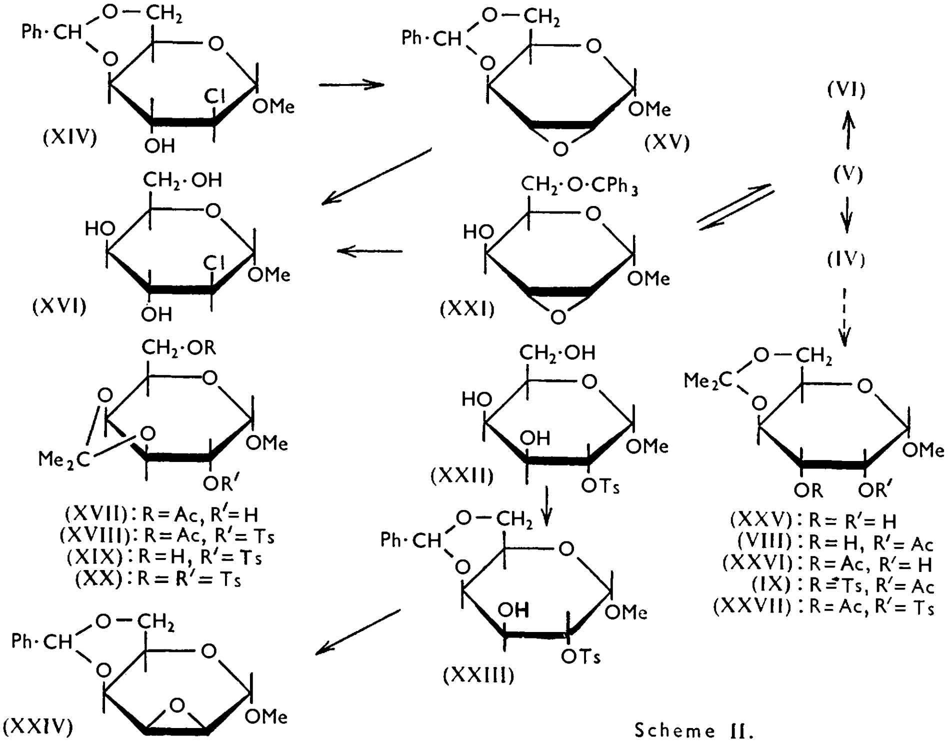
[16] Harvey, Michalski, and Todd, *J.*, 1951, 2271.
[17] Baddiley, Buchanan, and Szabó, *J.*, 1954, 3826.
[18] Iselin and Reichstein, *Helv. Chim. Acta*, 1946, **29**, 508.
[19] Ohle and Thiel, *Ber.*, 1933, **66**, 525.
[20] Rao and Smith, *J.*, 1944, 229.
[21] Wiggins, *J.*, 1944, 522.
[22] Reber and Reichstein, *Helv. Chim. Acta*, 1945, **28**, 1164.

Preliminary experiments indicate that the guloside is derived from the 3 : 4-anhydrogalactoside, and experiments on this point will be reported later.



Scheme II.

Experimental

Methyl 4 : 6-O-*Benzylidene-α-*D*-galactoside*.—This compound, required in the preparation of the 2 : 3-anhydroguloside (XV), was made by Reichstein and Sorkin's method [15] from methyl α-D-galactoside of $[\alpha]_D$ +195° which had been purified through the tetra-acetate. It had m. p. 168—170° and $[\alpha]_D^{22}$ +141·3° (c 3·11 in $CHCl_3$), in agreement with Bell and Greville [23] who give m. p. 169—170° and $[\alpha]_D$ +144° (in $CHCl_3$).

Methyl 2-*Chloro*-2-*deoxy-α-*D*-idoside*.—Methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-guloside (m. p. 175—175·5°; 1·5 g.) was heated under reflux in acetone (170 c.c.) containing 2N-hydrochloric acid (4·5 c.c.) for 4 hr. The solution was neutralised with lead carbonate, filtered, and evaporated to dryness. Extraction of the solid residue with hot ethyl acetate followed by evaporation left a syrup which crystallised. Recrystallised from ethyl acetate the chlorodeoxy-idoside (0·5 g., 42%) had m. p. 124—126°, $[\alpha]_D^{22}$ +86·8° (c 0·34 in H_2O) {Labaton and Newth give m. p. 124—126°, $[\alpha]_D^{18}$ +84° (in H_2O)} (Found: C, 39·4; H, 6·2; Cl, 16·8; OMe, 14·9. Calc. for $C_7H_{13}O_5Cl$: C, 39·5; H, 6·1; Cl, 16·7; OMe, 14·6%). When treated with aqueous sodium metaperiodate, the glycoside consumed 0·92 mol. (3 hr.); 0·97 mol. (5 hr.); 1·22 mol. (24 hr.). The initial preparation of this compound had m. p. 111—112°, but yielded the material of m. p. 124—126° by inoculation of the melt at 120°.

Methyl 4 : 6-O-*Benzylidene*-2-*chloro*-2-*deoxy-α-*D*-idoside*.—(i) Prepared by Labaton and Newth's method,[2] the compound had m. p. 166°, $[\alpha]_D^{20}$ +64·8° (c 1·80 in $CHCl_3$) (Found: C, 56·3; H, 6·1; OMe, 10·8. Calc. for $C_{14}H_{17}O_5Cl$: C, 55·9; H, 5·7; OMe, 10·3%). Labaton and Newth give m. p. 166°, $[\alpha]_D^{18}$ +67·2° (in $CHCl_3$). (ii) Prepared (85% yield) by treatment of methyl 2-chloro-2-deoxy-α-D-idoside (from the anhydroguloside above) with benzaldehyde and zinc chloride, and crystallised from ethanol, it had m. p. and mixed m. p. 166° and $[\alpha]_D^{20}$ +65·6° (c 1·85 in $CHCl_3$) (Found: C, 56·0; H, 5·9; OMe, 9·8%).

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[23] Bell and Greville, *J.*, 1955, 1136.

Action of Sodium Methoxide on Methyl 4 : 6-O-*Benzylidene*-2-*chloro*-2-*deoxy*-α-D-*idoside*.—The glycoside (0·25 g.) was dissolved in methanol (5 c.c.) containing sodium methoxide (from 0·05 g. of sodium) by gentle heating. Within a few minutes the anhydro-sugar separated as fine needles. After 10 hr., water (5 c.c.) was added; the anhydro-sugar was filtered off and washed with water. The product (yield quantitative) had m. p. 175—175·5°, $[\alpha]_D^{20}$ −6·5° (*c* 1·14 in $CHCl_3$) (Found: C, 63·6; H, 6·2; OMe, 12·3. Calc. for $C_{14}H_{16}O_5$: C, 63·6; H, 6·1; OMe, 11·7%). Reichstein and Sorkin [15] give m. p. 178—179° (corr.) and $[\alpha]_D^{14}$ −7·4° (in $CHCl_3$) for methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-guloside. The m. p. was not depressed on admixture with an authentic sample, m. p. 175—175·5°.

Methyl 4-*Chloro*-4-*deoxy*-α-D-*glucoside*.—Prepared according to directions of Labaton and Newth,[2] the glycoside had m. p. 114—115°, $[\alpha]_D^{21}$ +130·9° (*c* 1·03 in H_2O) (Found: C, 39·3; H, 6·2. Calc. for $C_7H_{13}O_5Cl$: C, 39·5; H, 6·1%). Labaton and Newth give m. p. 113—114°, $[\alpha]_D^{18}$ +138·3° (in H_2O). It consumed 0·42 mol. of sodium periodate after 20 hr.; 0·58 (40 hr.); 1·03 (170 hr.); 1·06 (212 hr.).

Treatment of the Methyl O-*Acetylanhydro*-6-O-*triphenylmethyl*-α-D-*hexoside Mixture with Hydrogen Chloride in Acetone*.—The mixture of anhydro-sugars was prepared from methyl 2 : 3-di-*O*-benzoyl-4-*O*-tosyl-6-*O*-triphenylmethyl-α-D-glucoside (18·5 g.) by Oldham and Robertson's method.[1] A solution of dry hydrogen chloride (3 g.) in acetone (50 c.c.) was added to a solution of the anhydro-sugar in acetone (50 c.c.), and the mixture left for 1 hr. at room temperature. Anhydrous sodium carbonate (40 g.) was added and after a few minutes' shaking the solid was filtered off. The filtrate was evaporated to small volume and then poured into an excess of water containing a little pyridine. When the triphenylmethanol had crystallised it was removed and the filtrate extracted several times with chloroform. The combined extracts were washed with dilute sulphuric acid and water, dried (Na_2SO_4), and evaporated to dryness. On treatment with ether *methyl* O-*acetyl*-4 : 6-O-iso*propylidene*-α-D-*guloside* (0·95 g.), m. p. 164—166°, separated. Recrystallised from ethanol or ethyl acetate this had m. p. 165—167°, $[\alpha]_D^{21}$ +75·6° (*c* 0·73 in $CHCl_3$) (Found: C, 52·5; H, 7·6. $C_{12}H_{20}O_7$ requires C, 52·2; H, 7·2%). The same product was obtained, in slightly higher yield, when the acetone solutions were mixed at 0°, or when the chloroform solution was not shaken with acid. Contact with the sodium carbonate overnight merely lowered the yield slightly.

To the ethereal mother-liquor light petroleum (b. p. 60—80°; 2 vols.) was added and the solution left for 24 hr. The crystalline solid, m. p. 95—99°, was recrystallised from ether–light petroleum (b. p. 60—80°), to give methyl 6-*O*-acetyl-3 : 4-*O*-*iso*propylidene-α-D-galactoside (0·7 g.), m. p. 101—102°, $[\alpha]_D^{17}$ +126·0° (*c* 1·51 in $CHCl_3$) (Found: C, 52·1; H, 7·4. Calc. for $C_{12}H_{20}O_7$: C, 52·5; H, 7·2%). Oldham and Robertson [1] give m. p. 101—102° and $[\alpha]_D$ +127·3° (in $CHCl_3$); Labaton and Newth [2] give m. p. 101—102° and $[\alpha]_D$ +122·4° (in $CHCl_3$).

The aqueous liquor was freed from halide ion by silver carbonate, followed by hydrogen sulphide, and evaporated to dryness. Paper chromatography showed the presence of methyl mono-*O*-acetyl-guloside and -galactoside.

Methyl 6-O-*Acetyl*-3 : 4-iso*propylidene*-2-O-*tosyl*-α-D-*galactoside*.—Methyl 6-*O*-acetyl-3 : 4-*iso*propylidene-α-D-galactoside (0·50 g.) was treated with toluene-*p*-sulphonyl chloride (1 g.) in pyridine (5 c.c.) for 24 hr. After destruction of the excess of acid chloride the mixture was poured into water, and the *product* filtered off and washed with water. Recrystallisation from light petroleum (b. p. 60—80°) gave needles (0·50 g.), m. p. 107—107·5°, $[\alpha]_D^{17}$ +146·9° (*c* 1·22 in $CHCl_3$) (Found: C, 53·0; H, 6·3; S, 7·7. $C_{19}H_{26}O_9S$ requires C, 53·0; H, 6·0; S, 7·4%).

Methyl 3 : 4-O-iso*Propylidene*-2-O-*tosyl*-α-D-*galactoside*.—The above sugar (0·39 g.) was deacetylated with sodium methoxide in methanol. Solid carbon dioxide was added, the solution evaporated to dryness, and the solid extracted with hot benzene. The extract was evaporated to dryness. The *product*, crystallised from benzene–light petroleum (b. p. 60—80°), gave needles (0·31 g.), m. p. 162°, $[\alpha]_D^{19}$ +153·1° (*c* 1·53 in $CHCl_3$) (Found: C, 52·4; H, 6·4; S, 8·4. $C_{17}H_{24}O_8S$ requires C, 52·6; H, 6·2; S, 8·3%).

Methyl 3 : 4-O-iso*Propylidene*-2 : 6-*di*-O-*tosyl*-α-D-*galactoside*.—The above sugar (0·2 g.) was treated with toluene-*p*-sulphonyl chloride (1 g.) in pyridine (5 c.c.). The product, isolated in the usual way and crystallised from chloroform–light petroleum (b. p. 40—60°) (0·2 g.), had m. p. 151°, $[\alpha]_D^{21}$ +115·3° (*c* 1·32 in $CHCl_3$). Iselin and Reichstein [18] give m. p. 149—150°, $[\alpha]_D$ +113·5° (in $CHCl_3$). An authentic sample (m. p. 151°) gave no m. p. depression on admixture, and had an identical infrared spectrum (KBr disc) (Found: C, 52·8; H, 5·7. Calc. for $C_{24}H_{30}O_{10}S_2$: C, 53·1; H, 5·5%).

Methyl 4 : 6-O-*Benzylidene*-2-O-*tosyl*-α-D-*galactoside*.—Methyl 3 : 4-*O*-*iso*propylidene-2-*O*-tosyl-α-D-galactoside (0·7 g.) was heated with 2N-acetic acid (30 c.c.) under reflux for 1 hr. The solution was evaporated to dryness and the syrupy residue shaken with benzaldehyde (15 c.c.) and powdered zinc chloride (2 g.) at room temperature for 20 hr. Water and chloroform were added and the chloroform layer was steam-distilled until benzaldehyde had been removed. Sodium hydrogen carbonate was added and the solution extracted with chloroform. Evaporation of the chloroform layer left a solid which crystallised when triturated with ether and light petroleum. Recrystallised from acetone–ether–light petroleum (b. p. 60—80°) the product (0·52 g., 66%) had m. p. 134—134·5°, $[\alpha]_{\mathrm{D}}^{21}$ +121·6° (*c* 1·66 in $CHCl_3$) (Found: C, 58·1; H, 5·9. Calc. for $C_{21}H_{24}O_8S$: C, 57·8; H, 5·5%). Reber and Reichstein [22] gave m. p. 137—138° and 187—188° and $[\alpha]_{\mathrm{D}}^{13}$ +116·6° (in $CHCl_3$); Wiggins [21] gave m. p. 179—180° and $[\alpha]_{\mathrm{D}}^{18}$ +117·8° (in $CHCl_3$).

Methyl 2 : 3-*Anhydro*-4 : 6-O-*benzylidene*-α-D-*taloside*.—The above sugar was treated with sodium methoxide in methanol (cf. Reber and Reichstein [22]). The product had m. p. 234—236° alone or in admixture with an authentic sample (m. p. 234—236°); Reichstein and Sorkin [15] give m. p. 241—242° (corr.). The infrared spectra were also identical.

Methyl 4 : 6-O-iso*Propylidene*-α-D-*guloside*.—The preceding monoacetyl derivative was deacetylated with sodium methoxide in methanol. The product crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as needles, m. p. 132—134°, $[\alpha]_{\mathrm{D}}^{20}$ +88·9° (*c* 1·77 in $CHCl_3$) (Found: C, 51·1; H, 7·6. Calc. for $C_{10}H_{18}O_6$: C, 51·3; H, 7·7%). Oldham and Robertson [1] give m. p. 132—133°, $[\alpha]_{\mathrm{D}}$ +88·5° (in $CHCl_3$). The glycoside consumed 1·00 mol. of sodium periodate in 2 hr. (constant value).

Methyl O-*Acetyl*-4 : 6-O-iso*propylidene*-O-*tosyl*-α-D-*guloside*.—The preceding acetyl derivative (0·88 g.) was treated in pyridine (10 c.c.) with toluene-*p*-sulphonyl chloride (1 g.) for 36 hr. Isolation in the usual way gave the *derivative* (1·10 g., 80%), m. p. 124—126°. Recrystallisation from ethanol gave prisms, m. p. 128—129°, $[\alpha]_{\mathrm{D}}^{21}$ +47·3° (*c* 2·08 in $CHCl_3$) (Found: C, 52·9; H, 6·3. $C_{19}H_{26}O_9S$ requires C, 53·0; H, 6·0%).

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