OXETANS

PART I. 3,5-ANHYDRO-1,2-*O*-ISOPROPYLIDENE-α-D-GLUCOFURANOSE AND -β-L-IDOFURANOSE

J. G. BUCHANAN AND E. M. OAKES
Department of Organic Chemistry, University of Newcastle-upon-Tyne (Great Britain)
(Received April 7th, 1965)

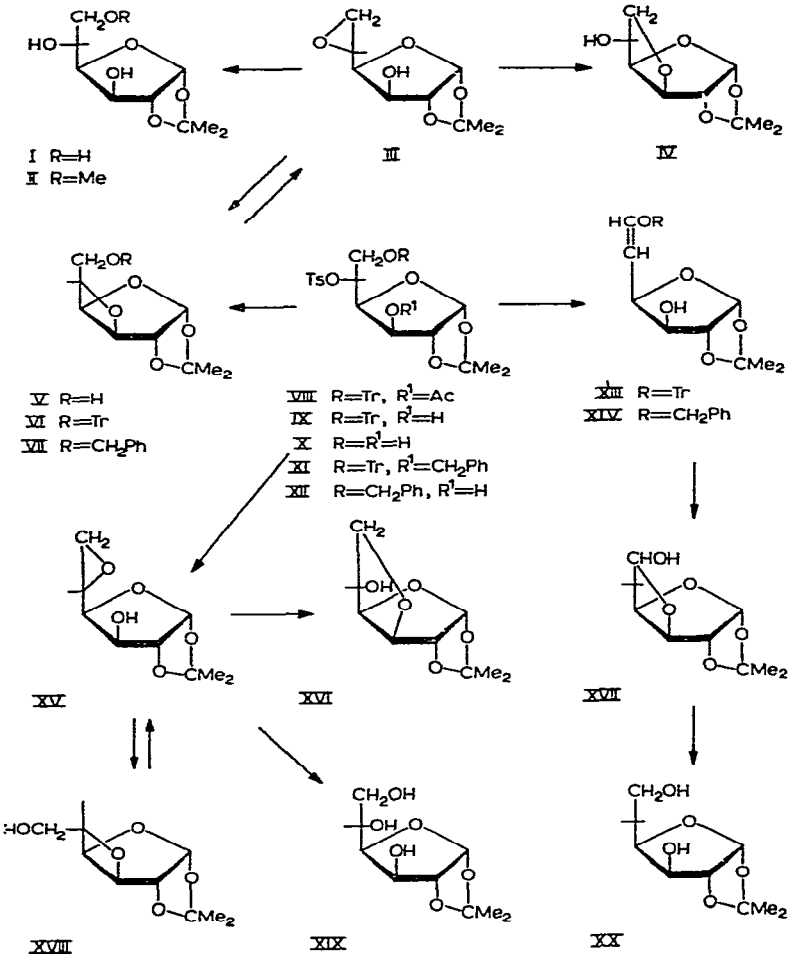
INTRODUCTION

Vicinal epoxides derived from sugars can undergo a number of reactions in which ring opening is caused by intramolecular, nucleophilic attack[1,2]. We have previously studied several of these reactions which occur under either acidic[3–5] or alkaline conditions[5,6]. Seebeck *et al.*[7] have shown that 3,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (IV) is one of the products when the 5,6-anhydro-compound (III) is treated with aqueous alkali. In this laboratory Dr. J. Conn[8] attempted to carry out the analogous reaction on the L-*ido*-epoxide (XV)[9], in order to obtain 3,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose (XVI), required in another study[3]. He concluded that another anhydride was produced, but was unable to pursue the matter at that time. We have examined the reaction in some detail, and a preliminary account has already been published[10].

RESULTS AND DISCUSSION

When the action of aqueous alkali on the 5,6-epoxide (XV) was studied by thin-layer chromatography, several products were observed. Meyer and Reichstein[9] had shown that 1,2-*O*-isopropylidene-β-L-idofuranose (XIX) was the major product, and this was confirmed. In addition, there was a small amount of the 3,6-anhydride (XVI), together with a product of low R_F value, which may be a bimolecular compound[7], and an unknown compound whose R_F value resembled that of the 5,6-anhydride. On a preparative scale, the unknown compound (m.p. 68–69°, $[\alpha]_D$ +38.4°) crystallised in 12% yield after chromatography on silica gel, and gave correct analyses for an isopropylidenehexose anhydride. Since it differed from the two known anhydrides (XV)[9] and (XVI)[11], it probably contained a 3,5-anhydro-ring, such as that existing in 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose (XXI)[12]. The behaviour on hydrolysis with N sulphuric acid at 100° was consistent with such a structure. Initially, a reducing sugar of high R_F value was formed (presumably a 3,5-anhydrohexose), and this was further hydrolysed to L-idose (identified chromatographically); 1,6-anhydro-β-L-idopyranose triacetate was isolated after acetylation of the hydrolysis products. When 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose (XXI) was hydrolysed under the same conditions, the reaction

followed a similar course, yielding finally xylose; the rate of hydrolysis was greater than in the previous case. The assignment of the D-*gluco*-configuration (XVIII) to the 3,5-anhydride is based on the reasonable assumption that formation and opening of the 3,5-anhydro-ring are each accompanied by inversion at the carbon atom involved. It is interesting that D-allose, which would have arisen by inversion at C-3, was not detected in the acid hydrolysate.



The behaviour of the 3,5-anhydro-compound (XVIII) towards N sodium hydroxide has proved particularly interesting. Thin-layer chromatography of the products showed them to be the same as those formed by similar treatment of the 5,6-epoxide (XV); 1,2-*O*-isopropylidene-β-L-idofuranose (XIX) and its 3,6-anhydride (XVI) were isolated from the mixture, after chromatography. It appears, therefore, that the oxides (XV) and (XVIII) are interconvertible under alkaline conditions, and that it is the more reactive 5,6-epoxide (XV) which undergoes ultimate

irreversible ring scission. In agreement with this idea, it was found that 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose (XXI) reacted with N sodium hydroxide more slowly, despite the presence of a primary carbon at C-5, giving 1,2-*O*-isopropylidene-α-D-xylofuranose.

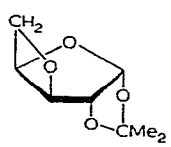
In the light of these observations, we reinvestigated the action of aqueous alkali on 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (III), in the hope of detecting the 3,5-anhydride (V). Under the conditions used by the Swiss workers[7], the sole product having a high R_F value in thin-layer chromatography was the 3,6-anhydride (IV). When shorter reaction times were used, however, a new anhydro-compound could be detected. After extensive chromatography, 3,5-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose (V) (m.p. 49°) was isolated in low yield. It was subsequently prepared in larger amounts by a different route, as described below, and its properties resembled those of the D-*gluco*-anhydride (XVIII). Acid hydrolysis with N sulphuric acid at 100° yielded D-glucose as the sole hexose, again indicating specific attack at C-5. As expected, N sodium hydroxide converted it into the same mixture of products as obtained from the 5,6-epoxide (III). 1,2-*O*-Isopropylidene-α-D-glucofuranose (I) and its 3,6-anhydride (IV) were identified chromatographically. From the reaction of the 3,5-anhydride with sodium methoxide, 1,2-*O*-isopropylidene-6-*O*-methyl-α-D-glucofuranose (II) was isolated.

We believe that these are the first cases to be reported of a reversible "oxide migration" involving a 3- and a 4-membered ring. It is not possible with these compounds to study an equilibration of the two ring-systems, because of the reactivity of the 5,6-epoxides. It is hoped to study such an equilibrated system by suitable choice of compounds.

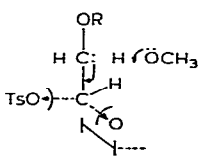
In order to obtain a larger quantity of the 3,5-anhydro-L-*ido*-compound (V) than was available from oxide migration, the action of sodium methoxide on the 5-toluene-*p*-sulphonate (VIII) was investigated. Under the reaction conditions, deacetylation occurs first to give the alcohol (IX), and the method is analogous to that used for the preparation of the 3,5-anhydro-D-xylose derivative (XXI)[12]. The major product when the sulphonate was heated with methanolic sodium methoxide was the enol ether (XIII)[10], which was obtained independently by Gramera *et al.*[13]. The chemistry of this reaction will be discussed below. A product having a higher R_F value in thin-layer chromatography was also noted, and was purified by chromatography on silica gel, after removal of most of the enol ether (XIII) by crystallisation. It was the triphenylmethyl ether (VI), and was characterised when hydrolysis with acetic acid gave 3,5-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose (V), identical to the 3,5-anhydride prepared from the 5,6-anhydro-compound (III) by oxide migration. The overall yield was 6%. The formation of this compound from the 5-sulphonate of a D-glucose derivative gives further support to the configurational assignments at C-5 in (V) and (XVIII).

The enol ether (XIII) crystallises with solvent of crystallisation from chloroform or benzene–light petroleum. Analytical samples were carefully dried to constant weight (see Experimental). Gramera *et al.*[13,14] do not comment on this

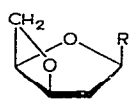
property, but, in one paper[13], their quoted yield is in excess of 100%. The structure of the enol ether was proved by acid hydrolysis to give the syrupy 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexodialdo-1,4:6,3-difuranose (XVII), which was characterised as its 2,4-dinitrophenylhydrazone. The same dialdohexofuranose (XVII) resulted as a minor product from the action of sodium methoxide on 1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose (X), and its structure was proved by borohydride reduction to give 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (XX)[15,16]. Gramera *et al.*[13] have examined the action of sodium methoxide on several pairs of 5-toluene-*p*-sulphonates, one in each pair having an alkali-stable group on the 3-hydroxyl group, *e.g.* (VIII) and (XI). They conclude, from a study of four such pairs of sulphonates, that a free hydroxyl group at C-3 is essential for the β-elimination reaction leading to an enol ether. These workers[13,17] have been unable to isolate a 3,5-anhydride from any of their reactions, but have postulated that formation of the 3,5-L-*ido*-anhydride (VI) is in some way linked to the formation of the enol ether (XIII). Two mechanisms are discussed, the first of which involves the sequence shown in (XXII). The authors omit the negative charges in the region of C-5 and on the methoxide ion, which would certainly repel each other; we shall not discuss this mechanism further. In the second mechanism, the 3,5-anhydride is the actual intermediate, and we have investigated this possibility. The crystalline 3,5-anhydride (V) was converted into its triphenylmethyl ether (VI), and heated with sodium methoxide under conditions more drastic than those used to prepare the enol ether. No reaction was observed, and the anhydride (V) was recovered in high yield after removal of the triphenylmethyl group by acid hydrolysis. We conclude that the 3,5-anhydride (VI) is not an intermediate in the conversion of the 5-sulphonate (IX) into the enol ether (XIII) by sodium methoxide. Horwitz *et al.*[18] have recently described an elimination reaction of the nucleoside oxetans (XXIII), using potassium *t*-butoxide in dimethyl sulphoxide, to give the olefins (XXIV). An attempted elimination using sodium methoxide was unsuccessful[18].



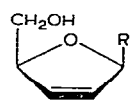
XXI



XXII



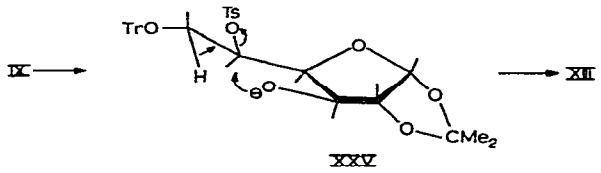
XXIII R=uracil or thymine



XXIV R=uracil or thymine

The observations of Gramera *et al.*[13] can be explained if the alkoxy anion resulting from removal of the proton from the 3-hydroxyl group in the sulphonate (IX) acts as the base for removal of the proton on C-6. If this is so, one can form a six-membered, cyclic transition-state (XXV), in which the large groups are equatorial, leading specifically to the *trans*-enol ether (XIII). It is assumed that the triphenylmethyl enol ether (XIII) has a trans arrangement of hydrogen atoms at C-5 and C-6 by analogy with the benzyl compound (XIV)[17]; the infrared spectrum

of the triphenylmethyl ether is too complex for unambiguous interpretation. The same alkoxy-anion is, of course, the intermediate for the formation of the 3,5-anhydride and it is difficult to see how one could prevent the two reactions



XXV

occurring side by side. Gramera *et al.*[13] quote unpublished work of Gramera and Whistler which indicates that the 3,5-anhydride (VII) is formed during hydrazinolysis of the benzyl ether (XII) and undergoes nucleophilic attack by hydrazine at both C-3 and C-5. The major product is still the enol ether (XIV)[17]. Whistler and his colleagues clearly believe that by using hydrazine they have "trapped" the oxetan (VII), which would otherwise have been converted into the enol ether (XIV). This interpretation is contrary to our findings in the triphenylmethyl ether series.

EXPERIMENTAL

Evaporations were carried out under reduced pressure with a bath temperature below 40°. Melting points are uncorrected. Infrared spectra were measured for potassium bromide discs. Light petroleum refers to the fraction of b.p. 60–80°. Comparison of materials with authentic substances was made, unless stated otherwise, by mixed m.p. determination, infrared spectra, and thin-layer chromatography (t.l.c.).

Chromatographic methods. Adsorption chromatography was carried out on silica gel (Hopkin and Williams) and neutral alumina (Woelm). T.l.c. on Kieselgel G (Merck) was used in preliminary investigations, and also to monitor the fractions from chromatography columns. Carbohydrates were detected by anisaldehyde–sulphuric acid[19]; triphenylmethyl ethers appeared as yellow spots with this reagent on gentle heating. Toluene-*p*-sulphonates were detected by the diphenylamine method[20]; a number of non-sulphonates gave a very weak positive reaction. Paper chromatography was carried out on Whatman No. 1 paper using butan-1-ol–pyridine–water (3:1:1, v/v), and aniline phthalate[21] to detect reducing sugars.

*3-O-Acetyl-1,2-O-isopropylidene-5-O-toluene-*p*-sulphonyl-6-O-triphenylmethyl-α-D-glucose (VIII)*

This was prepared by triphenylmethylation and subsequent toluene-*p*-sulphonylation of 3-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (*cf.* refs. 13, 14). The product contained triphenylmethanol, and in t.l.c. had the same R_F value as the latter (anisaldehyde spray).

1,2-O-Isopropylidene-5-O-toluene-p-sulphonyl-α-D-glucofuranose (X)

(*a*) 3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-6-*O*-triphenylmethyl-α-D-glucofuranose[22] (5.68 g) in glacial acetic acid (50 ml) was hydrogenated over palladium black (1.3 g) at atmospheric pressure for 16 h. After removal of the palladium by filtration, the solution was heated at 100° for 5 min and evaporated to dryness. The product crystallised from benzene–light petroleum to give the 5-sulphonate (2.34 g, 78%), m.p. 122°, $[\alpha]_D^{23}$ +5.2° (*c* 2.4, chloroform). Gramera *et al.*[17] give m.p. 124°, $[\alpha]_D$ +8.0° (chloroform). (Found: C, 51.3; H, 6.1; S, 8.4. $C_{16}H_{22}O_8S$ calc.: C, 51.3; H, 5.9; S, 8.6%).

(*b*) The above 3-acetate (VIII) (0.78 g) was treated with methanol (50 ml) containing sodium methoxide [from sodium (10 mg)], at 20° for 4 h. The solution was neutralised (CO_2) and evaporated to dryness, and the residue extracted with chloroform. After removal of the chloroform, the residue was dissolved in glacial acetic acid (4.8 ml), ethanol (1.5 ml), and water (1.2 ml), and heated for 12 min under reflux. The solution was evaporated to dryness, and extracted with hot benzene. After cooling and addition of light petroleum, the 5-sulphonate (0.28 g, 64%) m.p. 122°, crystallised; the infrared spectrum was identical to that of the compound in (*a*) above.

5,6-Anhydro-1,2-O-isopropylidene-β-L-idofuranose[9] *(XV)*

(*a*) 6-*O*-Benzoyl-1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose[23] (0.42 g) was dissolved in chloroform (1.5 ml) and cooled to −15°. Sodium methoxide [from Na (0.05 g)] in methanol (0.6 ml) was added, and the mixture kept at −15° for 0.5 h, and 0° for a further 2 h. 5% Aqueous sodium hydrogen carbonate (4 ml) was added and the solvent evaporated at 0°. The residue was extracted with chloroform, dried (sodium sulphate), and evaporated to a syrup (0.17 g). A benzene solution was chromatographed on silica gel. Ether eluted the 5,6-anhydro-compound (0.14 g, 79%), m.p. 69–71° (lit.[9], m.p. 73–75°).

(*b*) 1,2-*O*-Isopropylidene-5-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose (4.2 g) was dissolved in chloroform and cooled to 0°. Sodium methoxide [from sodium (0.3 g)] in cold methanol (5 ml) was added, and the mixture kept for 0.5 h in an ice bath. 25% Aqueous potassium hydrogen carbonate (4 ml) was added and the solution concentrated; the product was extracted and chromatographed as above. Benzene–ether (3:1) eluted 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexodialdo-1,4:6,3-difuranose (XVII) (0.13 g, 6%), $[\alpha]_D^{23}$ +34.9° (*c* 1.75, chloroform). Ether eluted the 5,6-anhydrocompound (2.02 g, 89%), m.p. 72–74°.

5-Deoxy-1,2-O-isopropylidene-α-D-xylo-hexodialdo-1,4-furanose 2,4-dinitrophenylhydrazone

(*a*) The above sugar (33 mg) was dissolved in methanol (1 ml) and 2,4-dinitrophenylhydrazine (33 mg) in methanol (1 ml) added, followed by acetic acid (0.2 ml). The mixture was left at room temperature overnight, when yellow crystals were precipitated. Recrystallised from methanol, the hydrazone (42 mg,

64%) had m.p. 184–185°, $[\alpha]_D^{23}$ −17.4° (*c* 1.35, dioxan). (Found: C, 47.1; H, 4.9; N, 14.7. $C_{15}H_{18}N_4O_8$ calc.: C, 47.2; H, 4.7; N, 14.65%).

(*b*) 5-Deoxy-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-*xylo*-hexofuran-5-enose (XIII) (see below) (98 mg) was heated with 80% acetic acid (v/v, 1 ml) containing sodium acetate (2 mg) for 5 min at 100°. The cooled solution was evaporated to dryness, dissolved in benzene, and chromatographed on silica gel. Benzene–ether (1:1) eluted the hexodialdo-sugar (22 mg, 48%) which was treated with 2,4-dinitrophenylhydrazine as in (*a*). The hydrazone (24 mg) had m.p. 183°, and was identical to that in (*a*) above.

*5-Deoxy-1,2-*O*-isopropylidene-α-*D*-xylo-hexofuranose (XX)*

5-Deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexodialdo-1,4-furanose (18 mg) was dissolved in ethanol (0.5 ml), and sodium borohydride (6 mg) added. The mixture was kept at room temperature for 16 h. Acetic acid (1 drop) was added and sodium ions were removed by passage through Dowex-50 (H^+ form) resin. The eluate was concentrated, and boric acid removed by distillation three times with methanol. The crystalline diol (15 mg, 81%), m.p. 87–88.5° (raised by sublimation to m.p. 93.5–94°), was identical to an authentic sample kindly given to us by Dr. E.J. Hedgley[15].

*3,5-Anhydro-1,2-*O*-isopropylidene-α-*D*-xylose (XXI)*

The anhydro-compound was prepared from D-xylose, according to Levene and Raymond's method[12].

Acid hydrolysis. (*a*) The anhydro-compound (4 mg) was hydrolysed with N sulphuric acid (0.1 ml) at 100° and the reaction followed by paper chromatography. After 2 min, xylose was detected in addition to 3,5-anhydroxylose. After 10 min, only xylose was detected. For R_F values, see Table I.

TABLE I

PAPER CHROMATOGRAPHY OF ACID HYDROLYSIS PRODUCTS OF 3,5-ANHYDRO-COMPOUNDS[a]

Sugar	*Colour of spot*	*R_F value*
D-Xylose	Red-brown	0.22
D-Glucose	Brown	0.12
L-Idose	Brown	0.26
3,5-Anhydro-D-xylose	Red-brown	0.52
3,5-Anhydro-D-glucose	Brown	0.40
3,5-Anhydro-L-idose	Brown	0.38

[a]For conditions, see under Chromatographic Methods.

(*b*) The anhydro-compound (0.16 g) was treated with N sulphuric acid (3 ml) at 100° for 2 h. The solution was neutralised with Dowex-2 (CO_3^{2-} form) resin,

filtered, and concentrated to a syrup. The syrup was dissolved in water (3 ml) and sodium borohydride (0.04 g) in water (3 ml) added, and the solution left at room temperature for 6 h. Excess of borohydride was destroyed with acetic acid, sodium ions were removed by passage through a column of Dowex-50 (H^+ form) resin, and the solution was evaporated to dryness. Boric acid was removed as methyl borate by methanol distillation, and the residue acetylated with acetic anhydride (1 ml) and pyridine (2 ml). The product was isolated using chloroform, and recrystallised from ethanol–light petroleum to give xylitol penta-acetate (0.25 g, 73%), m.p. 61–62°, identical with an authentic sample.

Alkaline hydrolysis. The anhydro-compound (0.19 g) was dissolved in N sodium hydroxide (2.3 ml) and heated at 100° for 16 h. The solution was neutralised (N sulphuric acid) and evaporated to dryness. A benzene extract was chromatographed on silica gel. Benzene–ether (9:1) eluted starting material (34 mg, 18%), $[\alpha]_D$ +9.2° (*c* 1.53, chloroform) [lit.[12], $[\alpha]_D$ +11.7° (chloroform)]; it is probable that some was lost owing to the volatility of this compound. Chloroform–ethanol (9:1) eluted 1,2-*O*-isopropylidene-α-D-xylofuranose (83 mg, 40%), which was converted, in 79% yield, into its 3,5-ditoluene-*p*-sulphonate, m.p. 98°, $[\alpha]_D^{22}$ −33.8° (*c* 1.89, chloroform). This is a new crystalline form, whose infrared spectrum was not identical with that of an authentic sample, m.p. 89–90°, $[\alpha]_D$ −36°, kindly given to us by Mr. P.R.H. Speakman, but the mixed m.p. was 98–99°. Karrer and Boettcher[24] give m.p. 91–92°, $[\alpha]_D$ −37.91° for this compound. When the sample of m.p. 89–90° was recrystallised from ethanol using seeds of the higher-melting form, only the latter, m.p. 100°, crystallised; the infrared spectra were identical.

3,5-Anhydro-1,2-O-isopropylidene-α-D-glucofuranose (XVIII)

5,6-Anhydro-1,2-*O*-isopropylidene-β-L-idofuranose (1.45 g) was dissolved in N sodium hydroxide (15 ml) and heated at 100° for 7 min. The solution was cooled, and passed through a column of Dowex-50 (NH_4^+ form) resin, and the eluate and washings were concentrated to a syrup. The residual syrup was extracted several times with hot benzene, and the benzene solution chromatographed on silica gel. Ether eluted first 3,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose (39 mg, 3%), m.p. 101–102°, followed by 3,5-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (0.168 g, 12%), m.p. 68–69° (from ether–light petroleum), $[\alpha]_D^{21}$ +38.4° (*c* 1.66, chloroform). (Found: C, 53.5; H, 7.1. $C_9H_{14}O_5$ calc.: C, 53.5; H, 6.9%). Some rechromatography of mixed fractions was necessary.

Acid hydrolysis. (*a*) The anhydro-compound (2 mg) was heated with 0.1 N sulphuric acid (0.1 ml) at 100°, and the hydrolysis followed by paper chromatography (see Table I). The isopropylidene group was removed within 5 min to give 3,5-anhydroglucose; idose was detectable after 15 min. When N sulphuric acid was used, idose was present after 4 min.

(*b*) The 3,5-anhydride (42 mg) was heated with N sulphuric acid (0.8 ml) at 100° for 14 h. The cooled solution was neutralised with Dowex-2 (CO_3^{2-} form) resin, filtered, and concentrated. Idose was removed by passing the solution through

a column of Dowex-1 (HO^- form) resin, and syrupy 1,6-anhydro-β-L-idopyranose (15 mg) was obtained on evaporation of the eluate. The product was acetylated with acetic anhydride and pyridine, and the acetate isolated using chloroform. The resulting syrup crystallised slowly and was purified by sublimation to give 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-L-idopyranose (23 mg, 39%), m.p. 63°, indistinguishable from an authentic sample, m.p. 63.5–64.5°. This compound exists in two crystalline forms, m.p. 66-67° (D-series)[25] and m.p. 85–86° (L-series)[26], 86–87° (D-series)[27]

Alkaline hydrolysis. 3,5-Anhydro-1,2-*O*-isopropylidene-α-D-glucose (0.14 g) was heated with N sodium hydroxide (1.5 ml) at 100° for 16 h. The cooled solution was passed through a column of Dowex-50 (NH_4^+ form) resin, and the eluate and washings evaporated to dryness. The syrup was dissolved in chloroform–ethanol (9:1) and chromatographed on silica gel. The first fractions were evaporated, and the residue was dissolved in ether and rechromatographed on silica gel, when ether eluted 3,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose, purified by sublimation (7 mg, 5%), m.p. 101°, identical with an authentic sample. Later fractions from the first column were dissolved in ethyl acetate and rechromatographed on silica gel to give 1,2-*O*-isopropylidene-β-L-idose (eluted with ethyl acetate and purified by sublimation, 34 mg, 22%), m.p. 112–114°, identical with an authentic sample.

3,5-Anhydro-1,2-O-isopropylidene-β-L-idofuranose (V)

(*a*) 5,6-Anhydro-1,2-*O*-isopropylidene-α-D-glucose (0.5 g) was heated with N sodium hydroxide (5 ml) at 100° for 3 min. The solution was immediately cooled and passed through a column of Dowex-50 (NH_4^+ form) resin. The eluate and aqueous washings were evaporated to a syrup which was dissolved in chloroform–ethanol (9:1) and chromatographed on silica gel. The first fractions were evaporated, and the residue was dissolved in benzene and rechromatographed on silica gel. Ether eluted first 3,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (89 mg, 18%), m.p. 54° (lit.[7], m.p. 55–56°), followed by a mixture (60 mg) of the 3,6- and 3,5-anhydro-compounds. The syrup was dissolved in benzene and chromatographed on neutral alumina. Elution with ether–ethanol (9:1) gave a pure fraction (8 mg), m.p. 48–49°.

(*b*) Crude 3-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-6-*O*-triphenylmethyl-α-D-glucofuranose (60 g) was heated under reflux in methanol (200 ml) containing sodium methoxide [from sodium (4 g)] for 1 h. Saturated aqueous potassium hydrogen carbonate (10 ml) was added and the solution evaporated. The residue was extracted thrice with chloroform, and the combined extracts were washed with water, dried (sodium sulphate), and evaporated to a syrup. Trituration with chloroform caused crystallisation of 5-deoxy-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-*xylo*-hexofuran-5-enose (24 g), m.p. 82–85°, $[\alpha]_D^{26}$ −14.7° (*c* 1.6, benzene). The infrared spectrum showed a strong band at 1667 cm^{-1} (C = C). Recrystallised from benzene–light petroleum, the product had m.p. 85–92°. For analysis, a sample was dried *in vacuo* at 50° to constant weight;

it then had m.p. 85–115°, and was still homogeneous on t.l.c. (Found: C, 76.2; H, 6.6. $C_{28}H_{28}O_5$ calc.: C, 75.7; H, 6.3%).

Concentration of the chloroform mother-liquors gave a syrup which was dissolved in benzene and chromatographed on neutral silica gel[5]. Benzene–ether (49:1) eluted 3,5-anhydro-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-β-L-idofuranose as a chromatographically homogeneous syrup (4.5 g). Elution with benzene–ether (9:1) yielded further enol ether (1.3 g). The above anhydro-compound (4.5 g) was heated under reflux in ethanol (15 ml), acetic acid (48 ml), and water (12 ml) for 12 min. Triphenylmethanol was filtered off from the cooled solution, and the filtrate evaporated to dryness. The residue was dissolved in benzene and chromatographed on silica gel. Benzene eluted more carbinol, and elution with ether afforded 3,5-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose, further purified by vacuum distillation. Care must be taken to avoid over-heating of the syrup. Yield, 1.04 g (6%), m.p. 49–50°, $[\alpha]_D^{27}$ +53.2° (*c* 1.2, chloroform). (Found: C, 53.3; H, 6.7. $C_9H_{14}O_5$ calc.: C, 53.5; H, 6.9%).

Acid hydrolysis. (*a*) The anhydro-compound (2 mg) was heated with N sulphuric acid (0.1 ml) at 100°, and samples were subjected to paper chromatography (see Table I). Initial hydrolysis gave 3,5-anhydroidose, which was further hydrolysed to glucose, first detectable after 12 min.

(*b*) The anhydro-compound (23 mg) was heated with N sulphuric acid (0.5 ml) for 7 h at 100°. The solution was neutralised with Dowex-2 (CO_3^{2-} form) resin, filtered, and evaporated to a syrup (17 mg). The syrup was dissolved in water (1.0 ml), sodium borohydride (20 mg) added, and the solution kept at 20° for 5 h. Excess of borohydride was destroyed with acetic acid and sodium ions were removed by passage through Dowex-50 (H^+ form) resin. After evaporation of the eluate and washings to dryness, boric acid was removed as methyl borate by distillation with methanol. The resulting syrup was acetylated with acetic anhyride and pyridine overnight, and the product isolated using chloroform. The crude hexa-acetate (32 mg, 62%) crystallised, and was purified by sublimation to give D-glucitol hexa-acetate, m.p. 96–98°, indistinguishable from an authentic sample, m.p. 98°.

Alkaline hydrolysis. (*a*) The anhydro-compound (2 mg) was heated in N sodium hydroxide (0.1 ml) at 100°. Samples were examined by t.l.c., using ether as solvent. After 30 min starting material was still present, together with a compound whose R_F value and colour reaction with the anisaldehyde spray resembled that of 3,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose; compounds of low R_F value, resembling 1,2-*O*-isopropylidene-α-D-glucofuranose, were also detected. After 3 h, no starting material could be detected.

(*b*) The anhydro-compound (0.12 g) was heated under reflux with sodium methoxide [from sodium (0.06 g)] in methanol (1 ml) until t.l.c. showed that no starting material was present. The solution was neutralised with N sulphuric acid and evaporated to dryness, and a benzene extract of the resulting product subjected to chromatography on silica gel. Ether eluted 1,2-*O*-isopropylidene-6-*O*-methyl-

α-D-glucofuranose (63 mg, 45%) which, after recrystallisation from ether–light petroleum had m.p. 69–70.5°, and was indistinguishable from an authentic sample, m.p. 69–70°[28].

Triphenylmethylation of 3,5-anhydro-1,2-O-isopropylidene-β-L-idofuranose and treatment of the product with sodium methoxide

The 3,5-anhydride (0.12 g) was dissolved in pyridine (2 ml), triphenylmethyl chloride (0.2 g) added, and the mixture kept at 37° for 2 days. Methanol (0.1 ml) was added and, after 1 h, the mixture was poured into water. The product was isolated using chloroform, and the final syrup was dissolved in benzene–light petroleum (1:1) and chromatographed on silica gel. After elution of non-carbohydrate triphenylmethyl compounds with benzene–light petroleum (1:1), benzene eluted 3,5-anhydro-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-β-L-idofuranose (VI) (0.2 g, 78%), $[\alpha]_D^{24}$ +31.4° (*c* 0.94, chloroform); it was homogeneous on t.l.c.

The above triphenylmethyl ether (91 mg) was heated in a sealed tube with methanol (0.5 ml), containing sodium methoxide [from sodium (10 mg)], at 65° for 2 h. Examination of the products by t.l.c. [benzene–ether (9:1)] showed the presence only of a compound having the same R_F value as starting material [the enol ether (XIII), which has a lower R_F value, was clearly absent]. The solution was neutralised with N sulphuric acid, filtered, and evaporated to dryness. The product was heated with aqueous acetic acid (80% v/v, 1 ml) at 95° for 10 min, and the cooled solution evaporated to dryness. The product was dissolved in benzene and chromatographed on silica gel. Benzene–ether (9:1) eluted triphenylmethanol (41 mg, 78%), and ether eluted a compound (37 mg) indistinguishable from 3,5-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose on t.l.c. (ether). Part of the product, on distillation, gave the 3,5-anhydride, m.p. 47°, identical with an authentic sample.

ACKNOWLEDGEMENTS

We thank Dr. J. Conn for communicating to us his early observations on this problem, Dr. E.J. Hedgley for a sample of 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose, and the Department of Scientific and Industrial Research for a maintenance grant (to E.M.O.).

SUMMARY

3,5-Anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose and -β-L-idofuranose have been prepared, and their behaviour towards aqueous acid and alkali examined. Dilute sulphuric acid causes removal of the isopropylidene group, followed by specific ring cleavage at C-5, in each case. Under alkaline conditions, the 3,5-anhydro-compounds undergo nucleophilic attack by the oxygen atom on C-6 to give the 5,6-epoxides. This reversible reaction is the first example of an oxide migration involving interconversion of an oxetan and oxiran.

The mechanism of an elimination reaction undergone by certain 5-toluene-*p*-sulphonates of 1,2-*O*-isopropylidene-α-D-glucofuranose is discussed.

REFERENCES

1 S. PEAT, *Advan. Carbohydrate Chem.*, 2 (1946) 37.
2 F.H. NEWTH, *Quart. Rev. (London)*, 13 (1959) 30.
3 J.G. BUCHANAN AND J. CONN, *J. Chem. Soc.*, (1965) 201.
4 J.G. BUCHANAN AND R.M. SAUNDERS, *J. Chem. Soc.*, (1964) 1791.
5 J.G. BUCHANAN AND J.C.P. SCHWARZ, *J. Chem. Soc.*, (1962) 4770.
6 J.G. BUCHANAN, *J. Chem. Soc.*, (1958) 995, 2511.
7 E. SEEBECK, A. MEYER, AND T. REICHSTEIN, *Helv. Chim. Acta*, 27 (1944) 1142.
8 J. CONN, Ph.D. Thesis, University of Newcastle, 1964.
9 A.S. MEYER AND T. REICHSTEIN, *Helv. Chim. Acta*, 29 (1946) 152.
10 J.G. BUCHANAN AND E.M. OAKES, *Tetrahedron Letters*, No. 30 (1964) 2013.
11 H. OHLE AND R. LICHTENSTEIN, *Ber.*, 63 (1930) 2905.
12 P.A. LEVENE AND A.L. RAYMOND, *J. Biol. Chem.*, 102 (1933) 331.
13 R.E. GRAMERA, T.R. INGLE, AND R.L. WHISTLER, *J. Org. Chem.*, 29 (1964) 1083.
14 R.E. GRAMERA, T.R. INGLE, AND R.L. WHISTLER, *J. Org. Chem.*, 29 (1964) 2074.
15 E.J. HEDGLEY, O. MÉRÉSZ, W.G. OVEREND, AND R. RENNIE, *Chem. Ind. (London)*, (1960) 938.
16 M.L. WOLFROM, K. MATSUDA, F. KOMITSKY, JR., AND T.E. WHITELEY, *J. Org. Chem.*, 28 (1963) 3551.
17 R.E. GRAMERA, T.R. INGLE, AND R.L. WHISTLER, *J. Org. Chem.*, 29 (1964) 878.
18 J.P. HORWITZ, J. CHUA, M.A. DA ROOGE, AND M. NOEL, *Tetrahedron Letters*, No. 38 (1964) 2725.
19 E. STAHL AND U. KALTENBACH, *J. Chromatog.*, 5 (1961) 351.
20 M. JACKSON AND L.D. HAYWARD, *J. Chromatog.*, 5 (1961) 166.
21 S.M. PARTRIDGE, *Nature*, 164 (1949) 443.
22 R.E. GRAMERA, R.M. BRUCE, S. HIRASE, AND R.L. WHISTLER, *J. Org. Chem.*, 28 (1963) 1401.
23 L.D. HALL, L. HOUGH, AND R.A. PRITCHARD, *J. Chem. Soc.*, (1961) 1537.
24 P. KARRER AND A. BOETTCHER, *Helv. Chim. Acta*, 36 (1953) 837.
25 E. SORKIN AND T. REICHSTEIN, *Helv. Chim. Acta*, 28 (1945) 1.
26 P.J. STOFFYN AND R.W. JEANLOZ, *J. Biol. Chem.*, 235 (1960) 2507.
27 L.F. WIGGINS, *J. Chem. Soc.*, (1949) 1590.
28 K. FREUDENBERG AND G. HÜLL, *Ber.*, 74 (1941) 237.