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FURTHER OBSERVATIONS ON DERIVATIVES OF 1,6-ANHYDRO-β-D-TALOPYRANOSE; AN EXAMPLE OF ACETAL MIGRATION ACCOMPANYING HYDROLYSIS

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ABSTRACT

2-*O*-Acetyl-1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose and 1,6-anhydro-3,4-*O*-isopropylidene-2-*O*-methylthiomethyl-β-D-galactopyranose were identified as by-products in the methyl sulphoxide–acetic anhydride oxidation of 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose to 1,6-anhydro-3,4-*O*-isopropylidene-β-D-*lyxo*-hexopyranosulose (isolated as the stable 2,2-*gem*-diol derivative). Syntheses of 1,6-anhydro-3,4-*O*-isopropylidene-2-*O*-methyl-β-D-talopyranose and 1,6-anhydro-2-*O*-methyl-β-D-talopyranose from 1,6-anhydro-3,4-*O*-isopropylidene-β-D-talopyranose are described. The former compound exhibited unusual chromatographic behaviour. 1,6-Anhydro-2,3-*O*-isopropylidene-β-D-talopyranose was isolated from an incomplete hydrolysis of 1,6-anhydro-3,4-*O*-isopropylidene-β-D-talopyranose to 1,6-anhydro-β-D-talopyranose, indicating that acetal migration was accompanying hydrolysis. The 2,3-acetal was the major product of reaction of acetone with 1,6-anhydro-β-D-talopyranose in the presence of sulphuric acid.

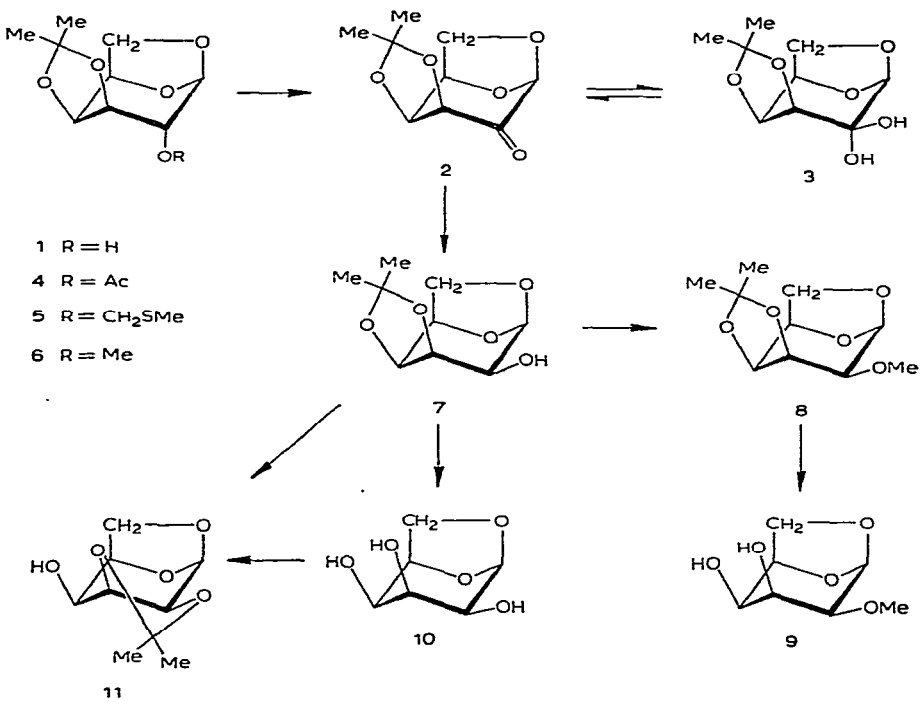
INTRODUCTION

In connection with other work[1], an unambiguous synthesis of 1,6-anhydro-3,4-*O*-isopropylidene-2-*O*-methyl-β-D-talopyranose (**8**) was desirable. An obvious route to the necessary 1,6-anhydro-3,4-*O*-isopropylidene-β-D-talopyranose (**7**) was to invert C-2 of the known[2] 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose (**1**) by an oxidation–reduction sequence[3]. When this work was completed, two other groups[4,5] independently reported this inversion; oxidation of compound **1** with ruthenium tetraoxide or methyl sulphoxide–acetic anhydride gave 1,6-anhydro-3,4-*O*-isopropylidene-β-D-*lyxo*-hexopyranosulose (**2**) which was stereospecifically reduced to compound **7** with sodium borohydride. The results obtained in the present work supplement these observations.

DISCUSSION

Oxidation of compound **1** with methyl sulphoxide–acetic anhydride proceeded smoothly, and the product was isolated from ether, not as the ketone **2**, but as the

gem-diol **3**. The previous workers[4,5] have described only the ketonic form **2**. The *gem*-diol **3** could be converted into the ketone **2** by vacuum sublimation, but, on standing in air, the ketone **2** reverted to the *gem*-diol **3**. This behaviour is in keeping with previous work[6], in which it was suggested that formation of *gem*-diols from pyranosuloses was particularly favourable due to an electron-withdrawing effect from C-1. Reduction of the *gem*-diol **3**, or the crude product isolated from the oxidation by removal of solvents *in vacuo*, with sodium borohydride gave the required *talo*-compound **7**. Two by-products were observed in the oxidation. One was the known[2] 2-*O*-acetyl-1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose (**4**). The second compound was identified as 1,6-anhydro-3,4-*O*-isopropylidene-2-*O*-methylthiomethyl-β-D-galactopyranose (**5**). The n.m.r. spectrum contained a singlet at τ 7.91 (SCH_3), and, on desulphurisation, compound **5** gave a product that was chromatographically indistinguishable from 1,6-anhydro-3,4-*O*-isopropylidene-2-*O*-methyl-β-D-galactopyranose[7] (**6**). Similar thio-ether derivatives have been isolated as by-products in methyl sulphoxide–acetic anhydride oxidations of alkaloids and steroids[8] and, very recently, of carbohydrates[9]. Their mode of formation has been discussed[8].



Methylation of compound **7** with methyl sulphate gave the required methyl ether **8**; the n.m.r. spectrum of ether **8** contained a singlet at τ 6.62 (OCH_3), and the mass spectrum was virtually identical with that of the isomeric *galacto*-compound **6**. Mild hydrolysis with 80% acetic acid removed the acetal group to give 1,6-anhydro-2-*O*-methyl-β-D-talopyranose (**9**). More-vigorous hydrolysis with dilute hydrochloric acid gave a reducing syrup, presumably 2-*O*-methyl-D-talose, since it gave D-*lyxo*-

hexose phenylosazone on treatment with phenylhydrazine–acetic acid. 2-*O*-Methyl sugars are known[10] to give osazones under these conditions.

A curious feature of the methyl ether **8** was its mobility on t.l.c. In one system (alumina–ether), this was barely greater than that of the parent alcohol **7**, and in another (silica gel–ether), it was actually less. The related *galacto*-compounds behaved as expected in these systems, with the methyl ether **6** having approximately twice the mobility of the alcohol **1**. The reason for this anomalous behaviour is not apparent, but it should be noted that the methyl ether **8** also has a relatively high melting point (see Table I for R_F values and melting points).

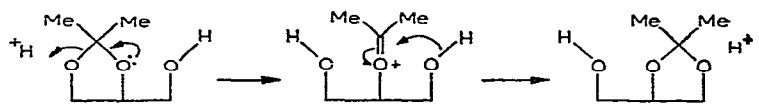
TABLE I

MELTING POINTS AND R_F VALUES FOR SOME DERIVATIVES OF D-GALACTOSE AND D-TALOSE

Compound	*M.p. (degrees)*	R_F[a]	R_F[b]
1,6-Anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose (**1**)	154–156	0.49	0.35
1,6-Anhydro-3,4-*O*-isopropylidene-2-*O*-methyl-β-D-galactopyranose (**6**)	37– 39	0.77	0.87
1,6-Anhydro-3,4-*O*-isopropylidene-β-D-talopyranose (**7**)	120–122	0.57	0.47
1,6-Anhydro-3,4-*O*-isopropylidene-2-*O*-methyl-β-D-talopyranose (**8**)	99–101	0.39	0.62

[a] For silica gel–ether. [b]For alumina–ether.

The use of 80% acetic acid for removing the acetal group from the methyl ether **8** is convenient, since the reagent is without effect on the anhydro structure. In a similar manner, compound **7** was hydrolysed to 1,6-anhydro-β-D-talopyranose (**10**) without any further hydrolysis to D-talose. When the progress of this hydrolysis was followed by t.l.c., the transient appearance of a third compound in addition to **7** and **10** was observed. Its mobility was only slightly less than that of the starting material **7**. It was isolated by preparative t.l.c. and found to be 1,6-anhydro-2,3-*O*-isopropylidene-β-D-talopyranose[4] (**11**), indicating that acetal migration was competing with hydrolysis. Since it is unlikely that acetone would recombine with compound **10** n the aqueous conditions, the reaction is presumably intramolecular:



When the acetal fraction was isolated from an incomplete hydrolysis, the proportion of 2,3-acetal **11** to 3,4-acetal **7** was approximately 3:1 (estimated by g.l.c.). Treatment of 1,6-anhydro-β-D-talopyranose **10** or the 3,4-acetal **7** with acetone containing sulphuric acid gave predominantly the 2,3-acetal **11**, the proportion of

3,4-acetal **7** formed was less than 10%. Evidently the 2,3-acetal **11** is the preferred isomer, possibly because of steric interactions between the C-6 methylene group and the *endo*-methyl group in the 3,4-acetal **7**. A related acetal rearrangement in acidified acetone has been observed recently in the case of 1,2:4,5-di-*O*-isopropylidene-D-psicopyranose, which has a similar arrangement of acetal and hydroxyl groups[9].

It is generally assumed that acetals do not migrate under hydrolysis conditions. Support for this assumption came from experiments with acetals in which hydrolyses were followed spectroscopically when, even in favourable cases, no evidence for migration was obtained[11]. An exception[12] is 2,4-*O*-ethylidene-D-erythrose which rearranges to the 2,3-acetal in dilute sulphuric acid. However, in this case, the acetal rearrangement is accompanied by a cyclisation of the sugar chain to give the favourable[13] bicyclic 2,3-*O*-ethylidene-D-erythrofuranose. The present result appears to be the first example of a simple acetal rearrangement in aqueous solution.

EXPERIMENTAL

General methods. — Unless stated otherwise, R_F values refer to paper chromatography (ascending development) on Whatman No. 1 paper in the system butyl alcohol–water (86:14, v/v). α-Glycols were detected by the periodate–Schiff reagent[14]; reducing sugars were detected with aniline hydrogen phthalate[15]. Silica gel G, Merck, and alumina G, Merck, were used for thin-layer chromatography (t.l.c.); compounds were detected by charring with sulphuric acid. Compounds were converted into their trimethylsilyl derivatives for gas–liquid chromatography on 3% SE-52 silicone rubber gum on 80–100 mesh acid-washed silanised "Celite". N.m.r. spectra were measured for solutions in carbon tetrachloride or deuteriochloroform, with tetramethylsilane as internal standard.

Oxidation of 1,6-anhydro-3,4-O-isopropylidene-β-D-galactopyranose (**1**). — A solution of anhydride **1** (1.0 g) in methyl sulphoxide (10 ml) and acetic anhydride (7 ml) was left for 22 h at room temperature, after which the solvents were removed *in vacuo*. A solution of the residue in ether (10 ml) deposited the *gem*-diol **3** (0.78 g) as needles which, when recrystallised from ether, had m.p. 104–109°; $[\alpha]_D$ −55° (*c* 0.76, water), −87° (*c* 0.64, dichloromethane); ν_{max} 3320, 3480 cm^{-1} (OH) (Found: C, 49.3, H, 6.3. $C_9H_{14}O_6$ calc.: C, 49.5; H, 6.5%). A portion of the hydrate **3** was vacuum-sublimed (100°/0.1 mm) to give the crystalline ketone **2**, m.p. 94–97°, $[\alpha]_D$ −86° (*c* 1.1, dichloromethane) (lit.[4], m.p. 92–93°, $[\alpha]_D$ −89°; lit.[5], m.p. 96–97°, $[\alpha]_D$ −110°), ν_{max} 1755 cm^{-1} (C=O) (Found: C, 54.4; H, 6.2. $C_9H_{12}O_5$ calc.: C, 54.0; H, 6.0%). On standing in the open laboratory overnight, the ketone **2** reverted to the *gem*-diol **3**, m.p. and mixed m.p. 104–109°.

The mother liquors, on standing, gave a small crop of 2-*O*-acetyl-1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose (**4**), m.p. and mixed m.p. 135–136° after recrystallisation from isopropyl ether.

1,6-Anhydro-3,4-O-isopropylidene-2-O-methylthiomethyl-β-D-galactopyranose (**5**). — Chromatography, on silica gel, of the mother liquors from the preceding experiment and elution with benzene–ether (9:1) gave the thio-ether **5** as a colourless oil

(0.12 g), b.p. 120° (bath)/0.2 mm, $[\alpha]_D$ −146° (*c* 1.4, chloroform), n_D 1.4985; τ 4.92 (1-proton singlet, H-1), 5.48 (2-proton singlet, OCH_2S), 7.91 (3-proton singlet, SCH_3) (Found: C, 50.4; H, 6.7; S, 12.2. $C_{11}H_{18}O_5S$ calc.: C, 50.4; H, 6.9; S, 12.2%).

A sample of the thio-ether **5** (65 mg) was desulphurised by being heated under reflux in ethanol (4 ml) containing Raney nickel (0.5 ml) for 70 min. T.l.c. indicated a single product having the same mobility as 1,6-anhydro-3,4-*O*-isopropylidene-2-*O*-methyl-β-D-galactopyranose (**6**).

1,6-Anhydro-3,4-O-isopropylidene-β-D-talopyranose (**7**). — (*a*) *From the* gem-*diol* **3**. Sodium borohydride (200 mg) was added to a solution of the *gem*-diol **3** (200 mg) in ethanol (2 ml) and water (2 ml). After 45 min, most of the ethanol was removed by evaporation, and the aqueous solution was extracted with dichloromethane. The extract was dried and evaporated, and recrystallisation of the residue from isopropyl ether gave the product **7** (164 mg), m.p. 120–122°, $[\alpha]_D$ −122° (*c* 0.7, chloroform) (lit.[4], m.p. 112–113°, $[\alpha]_D$ −112.5°; lit.[5], m.p. 117–118°, $[\alpha]_D$ −115°); τ 4.74 (1-proton doublet, H-1, $J_{1,2}$ ~3 Hz) (Found: C, 53.4; H, 6.9. $C_9H_{14}O_5$ calc.: C, 53.5; H, 7.0%).

(*b*) *From the crude oxidation product.* The crude oxidation product (from **1**, 1.0 g) was dissolved in ethanol (10 ml) and water (10 ml), and treated with sodium borohydride (1.0 g). After 45 min, work-up as in (*a*) gave the product **7** (0.57 g), m.p. 120–122°.

1,6-Anhydro-3,4-O-isopropylidene-2-O-methyl-β-D-talopyranose (**8**). — Methyl sulphate (0.6 ml) was added to acetone (16 ml) containing the acetal **7** (240 mg) and crushed potassium hydroxide (0.7 g). The mixture was stirred under reflux for 3 h. N Sodium hydroxide (16 ml) was added, and heating was continued for a further hour. The acetone was evaporated off, and the aqueous solution was neutralised with solid carbon dioxide before being extracted with dichloromethane. Evaporation of the dried extract and recrystallisation of the residue from light petroleum gave the methyl ether **8** (220 mg), m.p. 99–101°, $[\alpha]_D$ −53° (*c* 0.6, methanol); τ 4.85 (1-proton doublet, H-1, $J_{1,2}$ ~3 Hz) 6.62 (3-proton singlet, OCH_3) (Found: C, 56.0; H, 7.45. $C_{10}H_{16}O_5$ calc.: C, 55.50; H, 7.45%).

1,6-Anhydro-2-O-methyl-β-D-talopyranose (**9**). — A solution of the acetal **8** (100 mg) in 80% acetic acid (2 ml) was kept for 1 h at 90°. Evaporation of solvents left a crystalline residue. Recrystallised from isopropyl ether, the product **9** (57 mg) had m.p. 90–92°, $[\alpha]_D$ −50° (*c* 0.8, methanol), R_F 0.46 (Found: C, 48.1; H, 7.0. $C_7H_{12}O_5$ calc.: C, 47.7; H, 6.9%).

Hydrolysis of 1,6-anhydro-2-O-methyl-β-D-talopyranose (**9**). — The anhydro compound **9** (90 mg) in N sulphuric acid (2 ml) was kept for 4 h at 100°. The solution was passed through Dowex-1 (OAc^-, 5 ml) and evaporated to dryness. The syrupy residue (100 mg), presumably 2-*O*-methyl-D-talose, had $[\alpha]_D$ −4° (*c* 0.9, water), R_F 0.26.

A solution of the syrup (20 mg) in water (0.3 ml) containing phenylhydrazine (0.04 ml) and acetic acid (0.025 ml) was kept for 2 h at 100°. The yellow crystals, which started to form within 1 h, were filtered off, and washed successively with 10%

acetic acid, water, ethanol, and ether to give D-*lyxo*-hexose phenylosazone (6 mg), m.p. and mixed m.p. 180–185°; the infrared spectrum was identical with that of an authentic sample.

1,6-Anhydro-β-D-talopyranose (**10**). — A solution of the acetal **7** (50 mg) in 80% acetic acid (1 ml) was kept for 30 min at 90°. Solvents were evaporated, and the product **10** (29 mg), recrystallised from acetone, had m.p. 202–205°, $[\alpha]_D$ −82° (*c* 0.7, water) (lit.[4], m.p. 185–186°, $[\alpha]_D$ −80°; lit.[5], m.p. 206–208°, $[\alpha]_D$ −80.5°), R_F 0.34 (Found: C, 44.3; H, 6.2. $C_6H_{10}O_5$ calc.: C, 44.4; H, 6.2%).

Reaction of 1,6-anhydro-β-D-talopyranose (**10**) *with acetone containing sulphuric acid.* — The anhydro compound **8** (80 mg) in acetone (8 ml) containing conc. sulphuric acid (0.08 ml) was kept for 30 min at room temperature. After neutralisation (Na_2CO_3), the solution was evaporated to a crystalline residue. A portion was analysed by g.l.c., and the remainder was recrystallised from isopropyl ether to give the 2,3-acetal **11** (62 mg), m.p. 104–107°, $[\alpha]_D$ −35° (*c* 0.7, chloroform) (lit.[4], m.p. 107–108° $[\alpha]_D$ −34°), τ 4.80 (1-proton doublet, H-1, $J_{1,2}$ ~3 Hz) (Found: C, 53.65; H, 7.1. $C_9H_{14}O_5$ calc.: C, 53.4; H, 7.0%).

Reaction of 1,6-anhydro-3,4-O-isopropylidene-β-D-talopyranose (**7**) *with acetone containing sulphuric acid.* — The acetal **7** (100 mg) was treated with acetone (7 ml) containing sulphuric acid (0.07 ml), as described in the previous experiment, to give the 2,3-acetal **11** (60 mg), m.p. 104–107°.

Partial hydrolysis of acetal 7. — A solution of the acetal **7** (100 mg) was kept in 80% acetic acid (2 ml) for 5 min at 90°. After removal of solvents, the residue was partitioned between dichloromethane and water. Evaporation of the dried dichloromethane extract gave a crystalline residue (57 mg); t.l.c. (silica gel–ether) indicated the two acetals **7**, R_F 0.53, and **11**, R_F 0.46. A portion of the residue was analysed by g.l.c., and a pure sample of the 2,3-acetal **11** (6 mg), m.p. and mixed m.p. 104–107°, was obtained by preparative t.l.c. (silica gel–ether), and recrystallisation from light petroleum.

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