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SOME ASPECTS OF THE ISOPROPYLIDENATION OF D-GLUCITOL UNDER NEUTRAL CONDITIONS*

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ABSTRACT

Isopropylidenation of D-glucitol (**1**) under neutral conditions, by treatment with 2,2-dimethoxypropane in 1,2-dimethoxyethane, has been studied. An improved procedure for the isolation of 1,2:5,6-di-*O*-isopropylidene-D-glucitol, the main equilibrium product, by direct crystallisation or *via* the 3,4-dibenzoate is described. Some aspects of the reaction are discussed and compared with results obtained previously from the isopropylidenation of **1** in the presence of zinc chloride.

INTRODUCTION

The acid-catalysed isopropylidenation of D-glucitol (**1**) has been severally investigated[1-4]. A comprehensive study of the acetalation using acetone–zinc chloride has been described[5] in which the reaction was monitored by g.l.c. This study revealed that at least twelve products were formed instead of the six reported[2] earlier. It was concluded that the initial stage of the reaction was under kinetic control, when terminal acetals preponderated. In the thermodynamically controlled equilibrium, reached after five days, the 1,2:3,4:5,6-triacetal **2** and the 2,3:5,6-diacetal **3** were present in almost equal proportions. The acetalation of HO-3,4 was a sterically hindered process, and the 3,4-acetal, once formed, was not prone to migration. A new triacetal was isolated which was assigned the 1,2:3,5:4,6 structure **4** on the basis of mass-spectrometric and ^{13}C-n.m.r. data. A more recent[6] report on the assignment of ring size to isopropylidene acetals by ^{13}C-n.m.r. spectroscopy favoured the alternative 1,3:2,4:5,6 structure **5**. The signals for the acetal carbons fitted each structure, whereas the methyl group signals were consistent with structure **5**. Furthermore, **5** contains the more favourable "O-inside" arrangement of fused dioxane rings, whereas the diaxial interaction of C-2 and the axial methyl of the 3,5-*O*-isopropylidene group in **4** would cause skewing of the dioxane ring, with consequent effect on the ^{13}C-n.m.r. spectrum.

The acetalation of D-mannitol under neutral conditions, by treatment with 2,2-dimethoxypropane in 1,2-dimethoxyethane, has been described[7] and some mechanistic

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*Acetalation Studies, Part IV. For Part III, see ref. 8.

aspects of the reaction were discussed. The terminal 1,2:5,6-diacetal was shown to be the major equilibrium product, which did not undergo further substitution. In continuation[8] of these studies, the reaction of **1** under similar conditions has been investigated.

RESULTS AND DISCUSSION

When anhydrous D-glucitol (**1**) was treated with a boiling mixture of 2,2-dimethoxypropane and 1,2-dimethoxyethane, as described[7] for D-mannitol, a clear solution was obtained within 60 h. T.l.c. revealed at least six products. G.l.c. confirmed this result and showed that the products corresponded to the 1,2:3,4:5,6-triacetal **2** (9%), compound **5** (3.3%), the 2,3:5,6-diacetal **3** (18%), the 1,2:5,6-diacetal **6** (41%), 3,4:5,6-di-*O*-isopropylidene-D-glucitol (**9**, trace), and 1,2:4,6-di-*O*-isopropylidene-D-glucitol (**10**, 6%). No monoacetals could be detected and the remainder of the peaks were unidentified. In some mixtures, small amounts (2–4%) of unreacted **1** were detectable.

Crystallisation and recrystallisation of the concentrated reaction mixture gave 27–30.5% of **6** characterised as the 3,4-diacetate **8**. Treatment of the concentrated mother liquors with pyridine–toluene-*p*-sulphonyl chloride gave 16.5% of the 1,4-ditosylate **11** of the diacetal **3**; **11** has been isolated[4] after treatment of **1** with acetone–zinc chloride.

The yield of **6** could be increased to 38% by using chromatography on silica gel. Compound **6** was not isolated directly by this procedure, but was obtained in admixture with **3** from which it was separated by recrystallisation from cyclohexane. Tosylation of the material in the mother liquors, which contained some **6**, gave 11.5% of **11**. The other products from the chromatography were the triacetals **2** and **5**, which were not separated. The diacetal **6** was isolated[1] directly, but in low yield, after treatment of **1** with acetone–zinc chloride. An improved procedure[9] involving formation of the 3,4-dibenzoate **7**, with subsequent debenzoylation, gave 16.8% of **6**. Benzoylation of the crude product mixture, obtained from **1** as described above, gave 40.5% of **7**, and subsequent debenzoylation afforded **6** in 37% overall yield from **1**.

When D-mannitol was treated[7] under conditions similar to those described here and the methanol formed during the reaction was removed by allowing the reflux condensate to percolate through activated molecular sieve, transacetalation was severely inhibited. After 11 days, 66% of D-mannitol remained. When **1** was treated similarly, homogeneity was obtained after 5 days. G.l.c. revealed the formation of **2** (3%), **3** (17%), **5** (0.8%), **6** (51.5%), **9** (1%), and **10** (5%). Crystallisation gave 39.5% of **6**. This procedure, taking into consideration the scale and duration of the reaction, is the best method for the direct synthesis of the 1,2:5,6-diacetal **6**.

The presence of water would be expected to inhibit the acetal-exchange reaction. It has been suggested[10] that the diol and ketone are the reactants under conditions of acid catalysis, with the acetal acting as a desiccant. However, a study of the alkylidenation of nucleosides suggested[11] that the acetal is the effective reagent and not a dehydration agent.

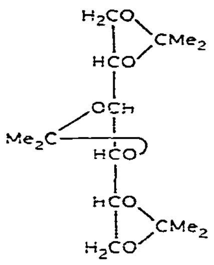
When the acetal-exchange reaction was performed on D-glucitol (**1**) hydrate, the reaction mixture tended to coagulate after ~15 min, and complete dissolution occurred after 15–20 h. G.l.c. then revealed **2** (5.6%), **3** (15.7%), **5** (2.6%), **6** (42%), and **10** (6%). Thus, the effect of a small amount of water of crystallisation is not marked, since the nature and relative proportions of the products were similar to those obtained using anhydrous **1**. However, when 1 equiv. of water was added, the reaction was completely inhibited and no products were formed during 7 days. The result suggested that, with **1**-hydrate, the reagent acted as a dehydrating agent with a slow, gradual removal of water as products were formed, which were then solubilised.

After treatment of 1,2-*O*-isopropylidene-D-glucitol (**12**) with boiling 2,2-dimethoxypropane in 1,2-dimethoxyethane for 72 h, g.l.c. revealed 63.5% of the triacetal **2**, ~1% of the triacetal **5**, and the diacetals **3** (3%) and **6** (12%); the 1,2:3,4-diacetal **13** and the 1,2:4,6-diacetal **10** were not detected. It is probable that **13** was formed, but was immediately converted into **2**. This could account for the relatively high yield of **2**, which is unlikely to have been formed exclusively *via* the diacetal **6**, since treatment of **6** in a similar manner yielded (g.l.c.) only 29.75% of **2**; 70% of **6** remained. The corresponding 3,4-acetal **14** gave **2** almost exclusively; t.l.c. and g.l.c. revealed <0.2% of **9** and **13**.

Attempts were made to prepare the 5,6-acetal **15** by the method of Bonner *et al.*[3]. The syrupy product was difficult to purify and decomposed, even on storage *in vacuo*. Treatment of this material with boiling 2,2-dimethoxypropane in 1,2-dimethoxyethane for 65 h gave 65% of a syrupy, approximately equimolar mixture of the diacetals **3** and **6**, in addition to the triacetal **2** (20%). The remainder of the product was not identified. This result may be unreliable in view of the instability[3] of **15**.

The results of acetalation under neutral conditions differ from those[1–4] for the acid-catalysed isopropylidenation of **1**. They are closest to those[5] for zinc chloride catalysis after a reaction time of 4 h, when the combined yield of the diacetals **3** and **6** in the ratio 31:76 was 57%; *cf.* 59% and a ratio of 18:41 for the reaction under neutral conditions. The higher proportion of **3** formed under acidic conditions is accounted for, in part, by the migration of the 1,2-*O*-isopropylidene group in **6** to the 2,3-position. This is a thermodynamically favoured process, as the *trans*-substituted dioxolane involving two secondary hydroxyl groups is more stable than that involving a terminal position[13]. Under conditions of acid catalysis, the terminal hydroxyl groups of the hexitol react first[3,5], so that relatively high proportions of the monoacetals **12** and **15** are present at an early stage in the reaction. Further substitution then takes place at the remaining terminal groups to give **6**, and to a limited extent at the 2,3-position of **15** to give **3**.

A similar sequence of events appears to take place under neutral conditions, with a higher proportion of **12** being produced. It is unlikely that significant migration of the 1,2-acetal in **6** occurs, since treatment of **6** under the same conditions[7] failed



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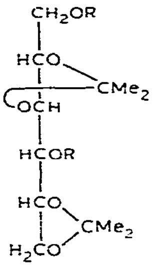

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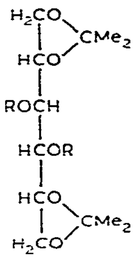
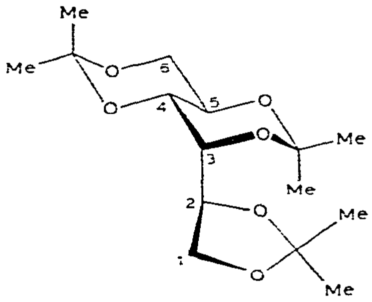
11 R = Ts



6 R = H

7 R = Bz

8 R = Ac



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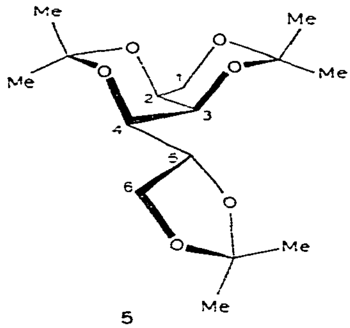

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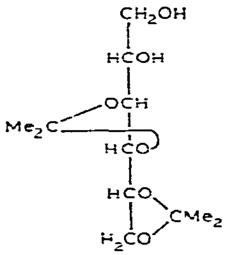

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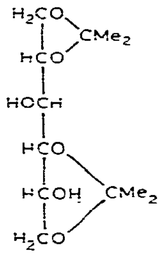

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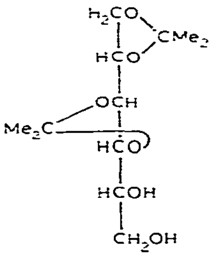

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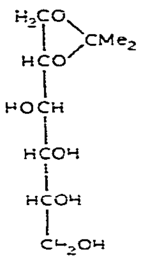

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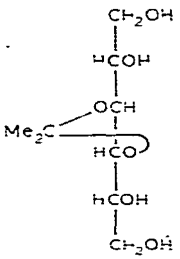

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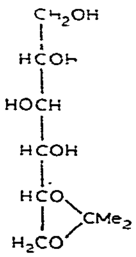

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to yield any diacetal **3**, but gave only 30% of the triacetal **2**. The amount of **2** formed was significantly higher than that of the corresponding D-mannitol triacetal derivative under similar conditions. This may be due to the fact[14] that D-glucitol (**1**) has a bent chain conformation in the crystal form, whereas D-mannitol has a planar zigzag conformation leading to greater accessibility of the 3,4- diol group by the proposed[7] reagent complex. The small amount (3%) of the diacetal **3** that was produced from the reaction of **12** with the reagent was unexpected, and implied limited migration of the 1,2-acetal group during the reaction, prior to attachment of the second ring. No acetal migration between D-mannitol derivatives occurred[7] under similar conditions.

The presence of the triacetal **5** and diacetal **10** in the crude reaction product from **1** showed that the acetal exchange is not restricted to vicinal diol systems, but can lead to six-membered ring products, albeit in low yield. The absence of **10** in the product from **12** indicates that formation of the terminal dioxane ring occurs at an early stage in the reaction. The high conversion of **14** into the triacetal **2** was not unexpected.

EXPERIMENTAL

Optical rotations were determined in chloroform unless otherwise stated. Kieselgel 60 (Merck) was used for column chromatography, and silica gel (Merck, DC Fertig-platten) for t.l.c., using 1,2-dimethoxyethane–cyclohexane (3:2) and detection with 0.1M $KMnO_4$–M sulphuric acid (1:1) at 110°. G.l.c. was conducted with a Hewlett-Packard 5830 A gas chromatograph, using a capillary column (31 m) of Carbowax 20M, a temperature programme from 160 to 200° at 1 °/min, and nitrogen at 10 p.s.i. as the carrier gas. Where necessary, samples were treated with pyridine–acetic anhydride prior to analysis. Compounds were identified by peak matching with authentic samples.

Reactions of 2,2-dimethoxypropane in 1,2-dimethoxyethane. — (*a*) *With anhydrous* D-*glucitol* (**1**). Anhydrous **1** (10 g) was stirred vigorously with 1,2-dimethoxyethane (60 mL), 2,2-dimethoxypropane (40 mL) was added, and the mixture was heated under reflux with continuous stirring until a clear solution was obtained 56–65 h). The cooled solution was concentrated *in vacuo* and the partially crystalline product was extracted with boiling dibutyl ether (31 mL). The residue (0.2–0.4 g) had m.p. 106–108°, and treatment with acetic anhydride–pyridine gave the hexaacetate[12] of **1**.

From the above extract, **6** deposited as fine needles (3.9–4.4 g, 27–30.5%), m.p. 93–95°, $[\alpha]_D^{20}$ +0.1° (*c* 12, pyridine); lit.[1] m.p. 95–95.5°, $[\alpha]_D$ −0.25°. Treatment of the product with acetic anhydride–pyridine gave the 3,4-diacetate **8**, m.p. 63–66° (from ethanol–water), $[\alpha]_D^{21}$ +25° (*c* 1); lit.[1] m.p. 64–65°, $[\alpha]_D$ +26°.

The remaining extract was concentrated *in vacuo* and a solution of the syrupy residue in dry pyridine (50 mL) at 0° was treated with toluene-*p*-sulphonyl chloride (17.2 g) overnight at room temperature. The mixture was cooled to 5° and treated with water (5 mL); after 2 h at room temperature, it was processed in the usual manner. Treatment of the product with methanol (30 mL) afforded 2,3:5,6-di-*O*-isopropylidene-1,4-di-*O*-toluene-*p*-sulphonyl-D-glucitol (**11**; 5.17 g, 16.5%), m.p. 135–137°, $[\alpha]_D^{22}$ +7° (*c* 2); lit.[9] m.p. 136–138°, $[\alpha]_D$ +6.8°.

In another experiment, the crude product obtained by treating **1** (5 g) with 2,2-dimethoxypropane, as described above, was eluted from Kieselgel 60 (120 g) with ethyl acetate–cyclohexane (1:1, 10-mL fractions), to give a mixture (0.91 g, 11%; fractions 5–16) of triacetals **2** and **5**, and a mixture (3.72 g, 51.6%; fractions 18–31) of diacetals **3**, **6**, and **9**. Further elution gave an unidentified oil. The combined fractions 18–31 were concentrated *in vacuo* and the residue was recrystallised from cyclohexane, to give **6** (2.73 g, 38%), m.p. 94–95°, $[\alpha]_D^{22}$ +0.2° (*c* 9.5, pyridine).

The mother liquor was concentrated, and the residue was treated with pyridine–toluene-*p*-sulphonyl chloride, as described above, to yield **11** (1.89 g, 11.5%), m.p. 135–137°, $[\alpha]_D^{21}$ +6° (*c* 2.8).

In another experiment, the crude product obtained by treating **1** (10 g) with 2,2-dimethoxypropane, as described above, was extracted overnight at room temperature with pentane (50 mL). The pentane was then decanted and the residue was washed with more pentane (50 mL). The combined extracts were concentrated *in vacuo*, to give a colorless syrup (4.02 g) that contained (t.l.c.) at least six components. To a solution of the crystalline residue (remaining after the pentane extraction) in pyridine (55 mL) was added benzoyl chloride (12 mL) dropwise while the temperature of the mixture was maintained below 5°. The mixture was kept overnight at room temperature and then cooled to 5°, ice–water (8 mL) was added slowly, and the mixture was poured into ice–water. The usual work-up gave a syrupy product which, when treated with methanol at −5°, afforded the 3,4-dibenzoate **7** (10.46 g, 40.5%), m.p. 134–136°, $[\alpha]_D^{21}$ +54° (*c* 2.5); lit.[1] m.p. 134–135°, $[\alpha]_D^{20}$ +53.7°.

A suspension of **7** (10 g) in dry methanol (120 mL) was stirred with methanolic 2M sodium methoxide (1.5 mL) at room temperature for 28 h, and then neutralised with methanol-washed, Dowex-50 (H^+) resin. The solids were collected, and washed with methanol, and the combined filtrate and washings were concentrated. The residue was recrystallised from dibutyl ether, to give **6** (5.33 g, 95.6%), m.p. 93–95°.

(*b*) *With* D-*glucitol* (**1**) *hydrate*. A suspension of **1**-hydrate (10 g) in 1,2-dimethoxyethane (60 mL) and 2,2-dimethoxypropane (40 mL) was stirred vigorously and heated under reflux. After 15 min, the mixture coagulated into small lumps that gradually dissolved during 15–20 h. The diacetal **6** (3.67 g, 28%), m.p. 94–95°, was obtained from the reaction mixture by the work-up procedure described in (*a*).

(*c*) *With* D-*glucitol* (**1**) *in the presence of molecular sieve*. A mixture of **1** (10 g), 1,2-dimethoxyethane, and 2,2-dimethoxypropane was heated as in (*a*), except that the reflux condensate was percolated through molecular sieve type 4A (30 g) contained in a Soxhlet extractor. After 5 days, the mixture was homogeneous. The work-up procedure described in (*a*) then yielded **6** (5.68 g, 39.5%), m.p. 92–94°.

(*d*) *With 1,2:5,6-di-*O*-isopropylidene-*D*-glucitol* (**6**). A mixture of **6** (4 g), 1,2-dimethoxyethane (25 mL), and 2,2-dimethoxypropane (15 mL) was stirred and boiled under reflux for 65 h, and then concentrated *in vacuo*. The crude, crystalline product was treated with water (100 mL) at 65°, and the mixture was stored overnight at 0°. Recrystallisation of the product from aqueous acetone gave 1,2:3,4:5,6-tri-*O*-isopropylidene-D-glucitol (**2**; 1.05 g, 23%), m.p. 43–45°, $[\alpha]_D^{20}$ +15° (*c* 4, methanol); lit.[2] m.p. 46°, $[\alpha]_D$ +13.8°.

The aqueous filtrate was concentrated *in vacuo* and the residue was recrystallised from dibutyl ether, to give **6** (2.25 g, 56%), m.p. 93–95°.

(*e*) *With 1,2-*O*-isopropylidene-D-glucitol* (**12**). Compound **12**[1] (1 g) was treated as in (*d*). The crude product was recrystallised from aqueous acetone, to give **2** (0.76 g, 56%), m.p. 44–46°, $[\alpha]_D^{22}$ +14.5° (*c* 2, methanol). Treatment of the aqueous filtrate as in (*d*) yielded **6** (70 mg, 6%), m.p. 92–95°.

(*f*) *With 3,4-*O*-isopropylidene-D-glucitol* (**14**). Compound **14**[2] (1.5 g) was treated as in (*d*). The product was recrystallised from aqueous acetone, to give **2** (1.65 g, 81%), m.p. 43–45°, $[\alpha]_D^{21}$ +14° +14° (*c* 5, methanol).

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