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Note

Some new aspects of the synthesis and isolation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol*

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1,2:5,6-Di-*O*-isopropylidene-D-mannitol (**1**) is the most important source of D-glyceraldehyde derivatives which are used[1–3] widely in synthesis. The formation of **1** from D-mannitol (**2**) has been studied severally[4–15]. All of the syntheses require the separation of **1** from the accompanying 1,2:3,4:5,6-triacetal **3** by crystallisation. Recent studies[14–16] of the acetonation of **2** have shown that complex mixtures of products are formed under most of the reaction conditions.

An unusual synthesis of **1**, conducted in pyridine solution, resulted during studies of the development of alternative catalysts for the acetalation of acid-sensitive substrates. An effective, alternative procedure for the isolation and purification of **1** was also developed and applied to some known alternative syntheses of **1**. The results of these studies are described below.

A solution of D-mannitol (**2**) in pyridine containing a catalytic amount of *p*-toluenesulfonic acid was treated at reflux temperature with 2,2-dimethoxypropane for 3.5–4 h. T.l.c. then demonstrated the absence of **2** and the presence of **1** and **3** as the main components. Treatment of the neutralised mixture with acetic anhydride–pyridine and then with ice–water precipitated only the pure crystalline 3,4-diacetate (**4**) of **1**. The yield of **4** (51–54%), although modest, represents an approximate average for many of the various acetonation reactions of **2**.

The material in the aqueous phase was deacetylated and column chromatography then gave **3** (18%), **1** (9%), and syrupy mixtures of other acetals which were not investigated further. Deacetylation of the diacetate **4** in methanolic potassium cyanide[17] yielded pure **1** in almost quantitative yield (96–98%). No reaction occurred when **2** in pyridine was treated with 2,2-dimethoxypropane in the absence of *p*-toluenesulfonic acid.

The catalytic effect of *p*-toluenesulfonic acid in pyridine solution has been employed[18] for the esterification of phenols and alcohols in the presence of dicyclohexylcarbodi-imide. In the absence of the catalyst, the yields were poor due to the formation of *N*-acylurea. The relative acidities of several organic acids have been compared[19,20] in

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pyridine and water. Most aromatic acids and aliphatic monocarboxylic acids maintained the same relative relationship, and most short-chain dicarboxylic acids became stronger in pyridine[19]. Non-carboxylic acids and non-phenolic organic acids showed a relative increase in acidity in pyridine compared to carboxylic acids[20]. Crystalline pyridinium *p*-toluenesulfonate is a y acidic salt which can catalyse some[21–23] acetalation reactions, but has found [24,25] application in carbohydrate chemistry.

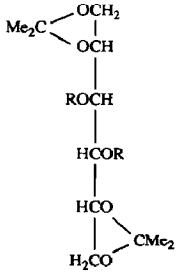
The forgoing mild acetalation system is currently being applied to other carbohydrate molecules.

The high purity of **1** and **4** suggested that the above procedures could be useful for the processing of other preparations of **1**, despite the additional steps. Thus, the product obtained by the treatment of **2** with acetone and anhydrous zinc chloride, a method originally described by Baer[4,6] and later improved[7,14], gave, after acetylation, 65–68% of pure **4** (*cf.* 75% of **1** estimated[14] by g.l.c).

Treatment of **2** with 2,2-dimethoxypropane in 1,2-dimethoxyethane containing a trace of tin(II) chloride[10] and acetylation of the crude product yielded 62–65% of pure **4** (*cf.* 65–68% obtained[10] by a combination of crystallisation and chromatography).

Treatment of **2** with 2-methoxypropene in *N*,*N*-dimethylformamide that contained a catalytic amount of *p*-toluenesulfonic acid has been claimed[12] to yield 92% of **1**. More recent[15] investigations have disputed this claim. Detailed analysis[15] of the mixture of products suggested that only 36% of **1** was present, together with the 1,2:4,6- (**5**) and the 1,2:3,6-diacetal (**6**), which were isolated by column chromatography and characterised spectroscopically.

Acetylation of the crude material obtained by the above procedure[12] furnished 41% of **4**, which supported the results of the later[15] study.



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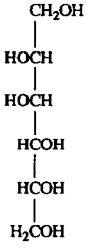
4 R = Ac



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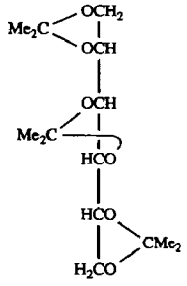

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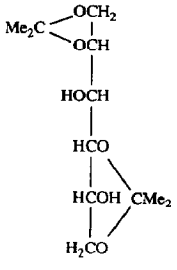

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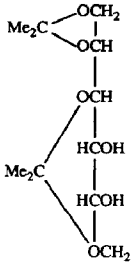

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Treatment[3] of **2** in methyl sulfoxide with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid was reported to provide 62% of **1**. Acetylation of the material obtained in this manner gave 59% of **4**. A disadvantage of the procedure is the need to remove the methyl sulfoxide prior to acetylation, because of its oxdising properties[26] in admixture with acetic anhydride. When the methyl sulfoxide was replaced by *N*,*N*-dimethylformamide and the crude product mixture was acetylated, 69–72% of **4** was obtained which was deacetylated[17] to give **1** (67–71% from **2**).

The above modified conditions now provide a practicable and acceptable alternative route to **1**.

EXPERIMENTAL

Optical rotations were determined on solutions in dichloromethane at 20° with a Perkin–Elmer Model 241 polarimeter. T.l.c. was performed on Kieselgel 60 (Merck) with 1,2-dimethoxyethane–cyclohexane (3:2) and detection by charring with 0.1M $K_2Cr_2O_7$ in M sulfuric acid. Column chromatography was performed on Silica Gel 60 (Merck). ^{1}H-N.m.r. spectra were recorded with a Varian EM 2940 (90 MHz) spectrometer on solutions in $CDCl_3$ (internal Me_4Si) and were used routinely to identify products.

Acetonation of D-*mannitol* (**2**). — *(a) With 2,2-dimethoxypropane in pyridine in the presence of* p-*toluenesulfonic acid.* — A stirred suspension of **2** (18.2 g) in pyridine (80 mL) containing *p*-toluenesulfonic acid (400 mg) was treated with 2,2-dimethoxypropane (40 mL). The mixture was heated under reflux for 3.5–4 h, cooled, treated with sodium acetate (1 g), concentrated *in vacuo* to approximately half volume, cooled (−5°), and treated with acetic anhydride (50 mL) and pyridine (70 mL). The mixture was set aside at room temperature for 48 h, and then poured into ice–water (1 L). The crystalline material was collected, washed with ice–water, and dried *in vacuo* (P_4O_{10}) to give 3,4-di-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol (**4**; 17.65–18.7 g, 51–54%), m.p. 121–123°, $[\alpha]_D$ +27° (*c* 3.6); lit.[11] m.p. 121–122°, $[\alpha]_D$ +26°. ^{1}H-N.m.r. data: δ 5.3 (d, 2 H, *J* 6 Hz, H-3,4), 4.1–3.7 (m, 6 H, H-1a,1b,2,5,6a,6b), 2.05 (s, 6 H, 2 Ac), 1.38 and 1.32 (2 s, each 3 H, CMe_2).

The combined filtrate and washings were concentrated *in vacuo* and a solution of the resulting syrup in dichloromethane (200 mL) was washed successively with 2M hydrochloric acid (100 mL), saturated aqueous sodium hydrogen carbonate (50 mL), and water (100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. A solution of the residue in methanol (100 mL) was treated with triethylamine (1 mL), stored at room temperature for 24 h, then concentrated *in vacuo*. Column chromatography (ethyl acetate–carbon tetrachloride, 1:1) of the residue gave 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol (**3**; 5.43 g, 18%), m.p. 67–69°, $[\alpha]_D$ +14° (*c* 2); lit.[17] m.p. 70–71°, $[\alpha]_D$ +13.8° (chloroform). Further elution (ethyl acetate–carbon tetrachloride, 3:1) yielded syrupy material (3.72 g) which crystallised on storage and gave 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**1**; 2.36 g, 9%), m.p. 117–119° (from isopropyl ether); lit.[7] m.p. 121–122°.

A suspension of **4** (10 g) in methanol (100 mL) containing potassium cyanide (600 mg) was stirred at room temperature for 18–24 h, then filtered through a layer (3 ×

3.5 cm) of Silica Gel 60. The inorganic material was washed with methanol (2 × 30 mL), and the filtrate and washings were combined and concentrated *in vacuo* to give **1** (7.27–7.42 g, 96–98%), m.p. 120–121°.

(b) With acetone in the presence of zinc chloride[14]. The crude product obtained by treatment of **2** (9.1 g) with acetone in the presence of anhydrous zinc chloride was acetylated and processed as in (*a*) to give **4** (11.2–11.75 g, 65–68%), m.p. 119–122°, $[\alpha]_D$ +26° (*c* 4.3).

(c) With 2,2-dimethoxypropane–tin(II) chloride[10]. Treatment of **2** (9.1 g) with 2,2-dimethoxypropane–tin(II) chloride, followed by acetylation and processing of the crude product as in (*a*), gave **4** (10.7–11.25 g, 62–65%), m.p. 120–122°, $[\alpha]_D$ +26° (*c* 2.4).

(d) With 2-methoxypropene in N,N-*dimethylformamide in the presence of* p-*toluenesulfonic acid*[12]. Compound **2** (9.1 g) was treated in the manner described, and the product was acetylated and processed as in (*a*) to give **4** (7.1 g, 41%), m.p. 119–121°, $[\alpha]_D$ +25° (*c* 4).

(e) With 2,2-dimethoxypropane in methyl sulfoxide in the presence of p-*toluenesulfonic acid.*[13]. Treatment of **2** (9.1 g), followed by acetylation and processing as in (*a*), gave **4** (10.29, 59%), m.p. 119–121°, $[\alpha]_D$ +26° (*c* 3.6).

(f) With 2,2-dimethoxypropane in N,N-*dimethylformamide in the presence of p-toluenesulfonic acid.* A suspension of **2** (27.3 g) in *N,N*-dimethylformamide (50 mL) containing *p*-toluenesulfonic acid monohydrate (100 mg) was stirred with 2,2-dimethoxypropane (42 mL) at room temperature for 16 h. The clear solution was treated with sodium acetate (1 g), and concentrated *in vacuo* at 25° to remove excess of volatile reagent and by-products. The residual solution was cooled (−5°), and treated with acetic anhydride (50 mL) and pyridine (80 mL) at room temperature for 36 h. The mixture was poured into ice–water (1400 mL), and the crystalline material was collected, washed with ice–water, and dried *in vacuo* (P_4O_{10}) to give **4** (35.8–37.4 g, 64–72%), m.p. 120–122°, $[\alpha]_D$ +26° (*c* 1.9).

Treatment of **4** (36 g) in methanol (250 mL) with potassium cyanide (1.2 g), as described in (*a*), gave **1** (26.17–26.72 g, 96–98%), m.p. 119–121°.

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