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CYCLIC ACETALS OF KETOSES

PART III*. RE-INVESTIGATION OF THE SYNTHESIS OF THE ISOMERIC DI-*O*-ISOPROPYLIDENE-β-D-FRUCTOPYRANOSES

ROBERT F. BRADY, JR.
Institute for Materials Research, National Bureau of Standards, Washington, D. C. 20234 (U. S. A.)

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ABSTRACT

Condensation of D-fructose with acetone in the presence of sulfuric acid gave first 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose. This compound isomerizes, at a rate dependent on the concentration of the acid, to 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose. Careful selection of reaction conditions permits the synthesis of either isomer in satisfactory yield. In acetone containing 5% of sulfuric acid, either compound is converted into an equilibrium mixture (3:47) of 1,2:4,5- and 2,3:4,5-diacetal within 5 min at room temperature, but, when anhydrous zinc chloride is used as the catalyst, the 1,2:4,5-diacetal does not rearrange to the 2,3:4,5-diacetal.

INTRODUCTION

Two crystalline diisopropylidene acetals have been isolated from the condensation of D-fructose with acetone, namely, 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose ("α-diacetone-D-fructose") (**3**) and 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose ("β-diacetone-D-fructose") (**5**). E. Fischer[3] synthesized **3** in 1895 by action of acetone containing 0.2% of hydrochloric acid on D-fructose; in only one of these preparations did he isolate a small amount of **5**, and, on repetition of the experiment, he could isolate none of **5**. When Irvine and Garrett[4] studied the reaction, they concluded that **5** could only be produced in small quantities under these conditions. Ohle and Koller[5] and Bell[6] reported a series of experiments in which low concentrations ($\leq$0.5%) of sulfuric acid catalyst led to the formation of **3**. Slightly higher concentrations of catalyst and short reaction times (3–24 h) favored an increase in the proportion of **5**, and led to the isolation of mixtures of diacetals **3** and **5**. However, at high concentrations of acid ($\geq$4%), compound **5** was found to be the preponderant product. The use of zinc chloride as the catalyst was reported[7] to favor the formation of **3**.

Large amounts of **3** were required as the starting material for a synthetic program leading to crystalline derivatives of rare sugars. For example, compound **3** can be oxidized to 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyran-

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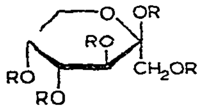
*For previous papers in this series, see Refs. 1 and 2.

ose (7) with methyl sulfoxide–acetic anhydride[8,9] or ruthenium tetraoxide[9,10]; compound 7 may then serve as a precursor to amino, branched-chain, deoxy, and other rare sugars[11]. However, it was found that acetal 3, either synthesized by the foregoing procedures or purchased from commercial sources, is often contaminated with 5. Moreover, the yields given in the literature for synthetic 3 are variable, ranging from 50% (Ref. 3) to 66% (Ref. 6). Consequently, it was desired to devise a method that would give, in high yield, 3 free from traces of 5.



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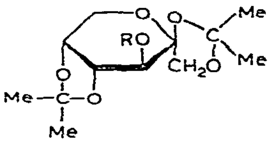
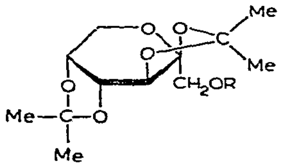
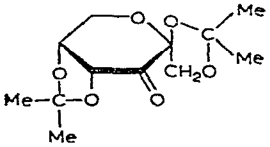
2 R = SiMe$_3$



3 R = H
4 R = SiMe$_3$



5 R = H
6 R = SiMe$_3$



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RESULTS AND DISCUSSION

It has now been found that, when a suspension of crystalline D-fructose (1) in acetone containing sulfuric acid as catalyst is stirred, and the reaction is monitored by g.l.c. analysis of neutralized, per(trimethylsilyl)ated aliquots of the mixture, withdrawn after various time-intervals, the diacetal observed first is compound 3. At low concentrations of catalyst ($\leq$0.5%), this compound slowly isomerizes to 5; but, if the reaction is arrested before attainment of equilibrium between 3 and 5, at the point at which the concentration of 3 is maximal, compound 3 may be isolated in satisfactory yield. At high concentrations of sulfuric acid catalyst ($\geq$5%), 3 is formed first, but does not preponderate; instead, it isomerizes rapidly to 5. The concentration of 5 is maximal at equilibrium, and 5 is isolable in satisfactory yield if the mixture of reactants is allowed to reach equilibrium. Intermediate concentrations of catalyst, or premature processing of the reaction mixture, lead to mixtures of diacetals 3 and 5. Ohle and Koller[5] and Bell[6] performed experiments under these conditions and isolated mixtures of diacetals. All preparations of either diacetal are contaminated by the isomeric diacetal, and it is difficult to obtain either isomer in pure form.

Apparently, 3 is the product of the kinetically controlled condensation of D-fructose with acetone; it is observed first, presumably as a consequence of the higher reactivity of the primary hydroxyl group on C-1. Diacetal 5 greatly preponderates at equilibrium; thus, it is thermodynamically more stable than 3.

In acetone containing 5% of sulfuric acid, the rearrangement of 3 to 5 has been found to be quite rapid at room temperature; within 5 min, each pure isomer is converted into an equilibrium mixture consisting of 94% of **5** and 6% of **3**.

G.l.c. examination of the per(trimethylsilyl) derivatives of the products of the reaction of D-fructose (**1**, 50 parts, wt.) with acetone (1000 parts, vol.), catalyzed by concentrated sulfuric acid (3 parts, vol.), indicated that the yield of diacetals was maximal (61%) as soon as the sugar had completely dissolved (3 h). Analysis by g.l.c. of the per(trimethylsilyl)ated crude mixture of diacetals showed that it consisted of ~88% of **3** and ~12% of **5**. Storage of the mixture of reactants for 2 h or longer at −10° did not improve the yield, contrary to a statement in an earlier report[12].

Increase of the concentration of sulfuric acid to 5 parts (vol.) caused the sugar to dissolve within 1.5 h. Five compounds were observed in the reaction mixture; after trimethylsilylation, two were identified as 1,2:4,5-di-*O*-isopropylidene-3-*O*-(trimethylsilyl)-β-D-fructopyranose (**4**) and 2,3:4,5-di-*O*-isopropylidene-1-*O*-(trimethylsilyl)-β-D-fructopyranose (**6**) and three are thus far unidentified, but have retention times suggesting that they are monoacetals or their anhydrides. No peak for trimethylsilyl tetra-*O*-(trimethylsilyl)-β-D-fructopyranoside (**2**) was observed, showing that all of compound **1** was consumed. The yield of crude diacetals (81%, composed of ~89% of **3** and ~11% of **5**) was maximal after 1.5 h of reaction. G.l.c. studies showed that, if the reaction mixture was kept at room temperature for extended periods of time, the concentration of **3** slowly diminished while that of **5** slowly increased; after 96 h, the diacetals were present in approximately equal proportions, and, after 168 h, 94% of the mixture of products was **5**. The yield of crude diacetals was not improved by addition of anhydrous copper(II) sulfate (1 part, wt.) or of anhydrous sodium sulfate (0.4 part, wt.) to the mixture of reactants.

When the concentration of sulfuric acid was increased to 25 parts (vol.), the sugar dissolved within 20 min. Diacetal **3** was observed first, and was the main product after 20 min. However, after 90 min, g.l.c. analysis showed that ~90% of the diacetals in the reaction mixture was **5**. Processing of the reaction mixture after 90 min gave a 79% yield of mixed diacetals, shown by g.l.c. analysis of their trimethylsilyl ethers to be 92% of **5** and 8% of **3**.

At a concentration of 50 parts (vol.) of sulfuric acid, the sugar dissolved within 8 min; diacetal **3** was again observed first, but never preponderated, and it was rapidly isomerized to **5**. After 90 min, the reaction had attained equilibrium, and the proportion of **5** was maximal. Processing afforded an 81% yield of mixed diacetals, shown by g.l.c. analysis of their trimethylsilyl ethers to consist of 94% of **5** and 6% of **3**.

When a suspension of crystalline D-fructose (**1**) (1 part, wt.) in a solution of anhydrous zinc chloride (2 parts, wt.) in absolute acetone (10 parts, vol.) was stirred, the sugar dissolved within 1.5 h. G.l.c. of the per(trimethylsilyl)ated reaction mixture then revealed the presence of 14 compounds*; three were identified as **2**, **4**, and **6**, but

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*A g.l.c. study of a solution of zinc chloride in acetone did not reveal formation of any products of acetone self-condensation during 24 h. Thus, the fourteen compounds detected when D-fructose is present must be derivatives of the sugar.

eleven are thus far unidentified. Thus, the reaction catalyzed by zinc chloride produces compounds that are not detectable in the reactions catalyzed by concentrated sulfuric acid. Compound **3** was the preponderant product and its yield was maximal after 4 h. G.l.c. studies showed that, even after 168 h, **3** was still the preponderant product, confirming the report of H. O. L. Fischer and Taube[7]. Although use of this catalyst precludes the presence of a large proportion of **5**, the total yield of crude diacetals is lower (59%, of which 86% is **3** and 14% is **5**), and processing[13] is more difficult than for the reaction catalyzed by sulfuric acid.

Purification of the crude diacetals by recrystallization could not be achieved with high recoveries. When impure **3** was recrystallized from boiling hexane (15 ml/g), an 82% recovery was realized, but, by g.l.c. of the trimethylsilyl ethers, this recrystallized material was shown still to contain ~5% of **5**. When crude **3** was recrystallized from boiling ether (5 ml/g) by the addition of pentane (5 ml/g), 54% of compound **3** was recovered, and this was shown by g.l.c. of its 3-(trimethylsilyl) ether (**4**) to be free from **5**. Likewise, **3** free from **5** was obtained (49% recovery) when impure **3** was recrystallized from a boiling mixture of absolute ethanol (2 ml/g) and water (2 ml/g) by cooling, adding water (6 ml/g), and long standing at −10°.

In contrast, **5** free from **3** was obtained from crude **5** by recrystallization from ether–pentane (53% recovery); the recovery of still-impure material from (*a*) hexane was 71%, and (*b*) ethanol–water was 35%.

EXPERIMENTAL

General methods. — G.l.c. was performed on a Varian Aerograph Model 2100-20 gas chromatograph, by use of glass columns (5 ft × 2 mm i.d.) of 3% SE-30 on VarAport 30 (100–200 mesh) kept at 170°. The flow rate of the nitrogen carrier-gas was 25 ml/min, and hydrogen-flame detectors were used. Aliquots (1 ml) of the reaction mixture were shaken with finely powdered, anhydrous sodium carbonate (100 mg). Tri-Sil 'Z' [*N*-(trimethylsilyl)imidazole in pyridine, Pierce Chemical Company, Rockford, Illinois, U. S. A.] was then used for preparing the trimethylsilyl derivatives. Retention times and response ratios were determined with authentic samples of compounds **4** and **6**. Optical rotations were determined, for solutions in 1-dm cells, with a Perkin–Elmer Model 141 automatic polarimeter. I.r. spectra were recorded with a Perkin–Elmer Model 257 grating i.r. spectrophotometer. (The i.r. spectra of compounds **3** and **5** have been published[14].) Melting points were determined in a silicone oil-bath and are uncorrected. Solutions were evaporated below 40° under diminished pressure.

*Preparation of 1,2:4,5-*di-*O-isopropylidene-β-*D*-fructopyranose* (**3**). — *A. Catalysis by sulfuric acid.* A suspension of dry, finely powdered D-fructose (**1**; 36.0 g, 200 mmoles) in acetone (700 ml, reagent grade) and conc. sulfuric acid (3.5 ml) in a 1-liter, round-bottomed flask was stirred magnetically at room temperature, with the exclusion of moisture, until the sugar had dissolved (1.5 h). G.l.c. analysis of the neutralized, per(trimethylsilyl)ated mixture showed 5 peaks, with retention times of 75, 87, 100, 114, and 132 sec. Immediately, an ice-cold solution of 11.0 g (1.1 equiv.) of sodium hydroxide in 100 ml of water was gradually added, with stirring. The solution was freed of acetone by evaporation under diminished pressure, and the resulting aqueous suspension was extracted with three 100-ml portions of dichloromethane. The extracts were combined, washed with two 50-ml portions of water, dried (anhydrous sodium sulfate), and evaporated to a crystalline solid, wt. 40.1 g (77%), m.p. 104–109°, $[\alpha]_D^{25}$ $-125.3°$ (*c* 1.1, acetone); after trimethylsilylation, g.l.c. analysis of the mixture revealed that it consisted of 88% of **4** and 12% of **6**. Recrystallization, by dissolving in boiling ether (5 ml/g), cooling, and adding pentane (5 ml/g), gave 22.4 g (43%) of compound **3** as long needles, m.p. 119°, $[\alpha]_D^{25}$ $-154.8°$ (*c* 1.0, acetone), $-145.0°$ (*c* 1.4, chloroform); lit.[5] m.p. 118–119°, $[\alpha]_D^{23}$ $-154°$ (acetone); lit.[15] m.p. 118–119°, $[\alpha]_D^{20}$ $-146.6°$ (chloroform). The i.r. spectrum matched the published spectrum[14]; g.l.c. analysis of the trimethylsilyl ether **4** showed only one peak, having a retention time of 100 sec.

B. Catalysis by anhydrous zinc chloride. The method of H. O. L. Fischer and Taube[7] was modified. Anhydrous zinc chloride (70.0 g, 514 mmoles) and 350 ml of dry acetone were stirred magnetically at room temperature for 1.5 h without external warming. The suspension was then filtered (fluted paper) into a 1-liter, round-bottomed flask containing anhydrous, finely-powdered D-fructose (36.0 g, 200 mmoles, **1**). The suspension was stirred magnetically at room temperature, with the exclusion of moisture, until the sugar had dissolved (3 h). G.l.c. analysis of the neutralized. per(trimethylsilyl)ated mixture showed 14 peaks with retention times of 76, 86, 100, 114, 128, 145, 156, 165, 179, 204, 228, 268, 308, and 350 sec. The solution was kept for 1 h at room temperature, an ice-cold solution of potassium carbonate (78.0 g, 565 mmoles) in water (100 ml) was added gradually, with stirring, and the product was isolated exactly as described[13]. The crude product was a crystalline solid, wt. 30.7 g (59%), that, by g.l.c. of its trimethylsilyl ethers, contained 14% of **5**; recrystallization as described in *A* gave 16.3 g (31%) of compound **3** as long needles, m.p. 119°, $[\alpha]_D^{22}$ $-154.3°$ (*c* 1.1, acetone). The i.r. spectrum agreed with the published spectrum[14]; g.l.c. analysis of the trimethylsilyl ether **4** showed only one peak, having a retention time of 100 sec.

*Preparation of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose* (**5**). — Dry, finely powdered D-fructose (**1**, 36.0 g, 200 mmoles) was added to a cooled solution of conc. sulfuric acid (35.0 ml) in acetone (700 ml, reagent grade) in a 2-liter Erlenmeyer flask, and the suspension was stirred magnetically at room temperature, with exclusion of water, until all of the sugar had dissolved (8 min). The solution was kept at room temperature for an additional 82 min, and then cooled in ice. An ice-cold solution of sodium hydroxide (110 g, 1.1 equiv.) in water (500 ml) was gradually added, with stirring, and the product was isolated exactly as for **3** (method *A*); the crude product was a crystalline solid, wt. 41.6 g (80%), m.p. 89–92°, $[\alpha]_D^{25}$ $-38.7°$ (*c* 0.9, acetone); after trimethylsilylation, g.l.c. analysis of the mixture revealed that it consisted of 94% of **6** and 6% of **4**. Recrystallization as for **3** gave 22.1 g (42%) of compound **5** as rosettes of needles, m.p. 97°, $[\alpha]_D^{25}$ $-38.1°$ (*c* 1.7, acetone), $-24.7°$ (*c* 1.1, chloroform), $-33.6°$ (c 1.1, water); lit.[6] m.p. 97°, $[\alpha]_D^{16}$ $-33.1°$ (c 7.0, water); lit.[7]: $[\alpha]_D$ $-33.8°$ (acetone). The i.r. spectrum agreed with the published spectrum[14]; g.l.c. analysis of the trimethylsilyl ether **6** showed only one peak, having a retention time of 114 sec.

Equilibration of **3** *or* **5**. — Conc. sulfuric acid (5.00 ml) was diluted to 100.00 ml with acetone. Separate solutions of diacetal **3** and diacetal **5** (500 mg per 10.00 ml) in this acidic acetone were made in volumetric flasks, and the isomerization of each was monitored by g.l.c. analysis of neutralized, per(trimethylsilyl)ated aliquots of the mixture. After equilibrium had been reached, the observed optical rotation of each solution (1-dm tube) was $-2.295°$, corresponding to an equilibrium composition of 94% of **5** and 6% of **3**. These proportions were also established from results obtained by g.l.c.

*Trimethylsilyl tetra-*O*-(trimethylsilyl)-β-*D*-fructopyranoside* (**2**). — A suspension of D-fructose (D-levulose "Special"; Pfanstiehl Chemical Co., Waukegan, Illinois, U. S. A.) (10 mg) in 1 ml of Tri-Sil 'Z' was heated at 60° until the sugar had dissolved (5 min). The solution was cooled and injected directly into the chromatograph; only one peak, having a retention time of 268 sec, was observed.

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