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1,2-Isopropylidene-D-glucitol, 1,2:5,6-Diisopropylidene-D-glucitol and a New Synthesis of D,L-Glyceraldehyde Dimer[1,2]

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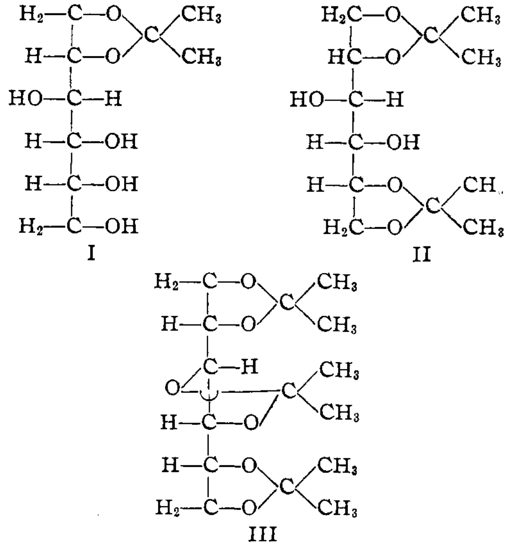
The only hexitols whose acetonation has been extensively studied are mannitol and galactitol (dulcitol). A tri-, two mono- and two diisopropylidenemannitols are known, while two diisopropylidenegalactitols have been characterized. A triisopropylidenesorbitol has also been described.[3]

Hann and Hudson[4] have developed principles for predicting what course the substitution of methylene and benzylidene groups takes in the hexitols. Unfortunately a sufficient number of derivatives are not known to allow similar generalizations to be evolved for the analogous isopropylidene compounds. If such information could be secured it would be extremely useful since the ease with which the isopropylidene group can be removed by acid hydrolysis, coupled with the protection to oxidation or substitution it affords to the acetalated hydroxyl groups, makes it a valuable blocking agent. For example, it is utilized in the laboratory syntheses of active glyceraldehyde and glycerides[5] from the mannitols and in the commercial production of ascorbic acid from sorbose.

In the course of this investigation a mono- (I) and a diisopropylidenesorbitol (II) were isolated along with the previously reported triisopropylidenesorbitol (III). Evidence was also secured that other isopropylidene derivatives are present in the sirupy residues from the crystallization of I and II, but these compounds have thus far resisted isolation. Under the conditions here employed only a portion of the sorbitol underwent acetonation. Increasing the reaction time, however, merely increased the amount of the uncrystallizable sirups and decreased the quantities of I and II that could be obtained. Owing to the difficulty of crystallizing the unreacted sorbitol, yields are reported on the basis of the total quantity of sorbitol originally used rather than on the sorbitol actually reacted and are therefore understandably low.



Structure

An acetone analysis showed the presence of one isopropylidene group in I. The compound consumed three moles of periodate reagent. This information definitely limits the position of the single isopropylidene group to the 1,2 or 5,6 positions as all other possible structures call for the consumption of less of the glycol-splitting reagent. Oxidation of I with lead tetraacetate led to the isolation of L-glyceraldehyde. This could only arise from carbons 1,2 and 3 of the original D-glucitol, thus indicating that these were the carbons protected from oxidation by the isopropylidene group. The structure of I is then definitely established as 1,2-isopropylidene-D-glucitol.

Two isopropylidene groups were found on analysis of II. The two free hydroxyl groups are vicinal, as the compound consumed one mole of periodate, but cannot be at either end position of the sorbitol molecule, since formaldehyde was not one of the cleavage products. These facts eliminate all possible structures for II except that of 1,2:5,6-diisopropylidene-D-glucitol. Corroborating evidence for this structure was obtained by the successful conversion of II, on oxidation with lead tetraacetate, to D,L-glyceraldehyde.

Although the structure of III is usually accepted as that of 1,2:3,4:5,6-triisopropylidene-D-glucitol, the positions of the isopropylidene groups cannot be taken entirely for granted as compounds are known in which a condensing acetone molecule forms a six membered ring (*e. g.*, 1,2:4,6-diisopropylidene-L-sorbose). Thus it is possible for the isopropylidene groups to assume "interlocking" positions. The conversion of II to III accomplished here is still not final proof of the structure of III, since, under the experimental conditions employed, it would have been possible

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[2] In accordance with current usage in carbohydrate nomenclature, the reduction product of D-glucose is referred to as D-glucitol in the formal naming of derivatives where it is necessary to number the carbon atoms of the chain. Where no confusion could arise the common name *sorbitol* is used.

[3] Up-to-date tables of hexitol derivatives together with references are to be found in Lohmar and Goepp, *Adv. Carbohydrate Chem.*, **IV**, 211 (1949).

[4] Hann and Hudson, THIS JOURNAL, **66**, 1909 (1944).

[5] Fischer and Baer, *Chem. Rev.*, **29**, 287 (1941).

for the isopropylidene groups to migrate. Nevertheless it offers good substantiating evidence for the structure as shown.

Experimental

1,2-Diisopropylidene-D-glucitol (I).—To 180 g. of a 25% solution of zinc chloride sticks in dried acetone 100 g. of sorbitol[6] was added. The suspension was shaken mechanically and at the end of about two and one-half hours (depending on the room temperature) the sorbitol had completely gone into solution. One hundred eighty grams of 50% potassium carbonate solution was added and the shaking resumed for fifteen minutes. To insure complete neutralization of all acid, 25 ml. of 60% potassium hydroxide solution was added followed by fifteen additional minutes of shaking. The resulting slurry of zinc carbonate and other inorganic materials was removed by filtration under suction and washed with 150 ml. of acetone. The solvent was removed from the combined filtrates *in vacuo* and the resulting sirup dried on a steam-bath at water pump pressure. The sirup was then taken up in 400 ml. of boiling acetone by swirling until only a small opaque mass remained undissolved. This consisted of a portion of the unreacted sorbitol together with quantities of inorganic substances. The acetone extract was cooled at −5° for two days whereupon crude I was deposited. The supernatant liquid contained in addition to the bulk of the unreacted sorbitol both II and III which can be isolated, but these were more conveniently prepared as described later. On recrystallizing the crude I from absolute ethanol, about 5 g. of the compound of m. p. 155–160° was obtained; yield, 4.1%. On repeated recrystallization the m. p. rose to 167.5–168°; $[\alpha]^{25}\text{D}$ −10.8° (*c*, 5 in pyridine). The compound is moderately soluble in ethanol (from which, when pure, it crystallizes in rectangular blades), water, acetone and pyridine and insoluble in petroleum ether.

Anal.[7] Calcd. for $C_9H_{18}O_6$ (222.2): C, 48.64; H, 8.16; $(CH_3)_2CO$, 26.1. Found: C, 48.91; H, 8.03; $(CH_3)_2CO$, 25.4.

1,2-Isopropylidene-3,4,5,6-tetraacetyl-D-glucitol.—To 4 ml. of acetic anhydride and 30 ml. of dried pyridine was added 1 g. of I and the reaction was allowed to progress at room temperature for three days. The product was then concentrated over a steam-bath *in vacuo*. The resulting sirup was taken up with hot ethanol and on cooling the crude product of m. p. 85–90° crystallized spontaneously in virtually quantitative yield. On repeated recrystallization from ethanol irregular flat plates were obtained, m. p. 93–94°; $[\alpha]^{25}\text{D}$ 25.2° (*c*, 5 in chloroform).

Anal. Calcd. for $C_{17}H_{26}O_{10}$ (390.4): C, 52.30; H, 6.70; $(CH_3)_2CO$, 14.9; sapn. eq., 97.6. Found: C, 52.36; H, 6.68; $(CH_3)_2CO$, 15.0; sapn. eq., 95.2.

1,2-Isopropylidene-3,4,5,6-tetrabenzoyl-D-glucitol.—A solution of 1 g. I in 30 ml. of dried pyridine was cooled in an ice-bath and 4 ml. of benzoyl chloride was added. The reaction mixture was allowed to stand at room temperature five days and then the bulk of the solvent was removed over a steam-bath *in vacuo*. The residue was taken up in 10 ml. of chloroform and washed with cold, dilute sulfuric acid followed by sodium bicarbonate solution, then dried over sodium sulfate. After removal of the chloroform *in vacuo*, the residual sirup was taken up in 10 ml. of ethanol and treated with norite. On cooling to −5° and seeding, 2.15 g. of the crude product of m. p. 70–80° was obtained, corresponding to a yield of 74%. The original seeds required five weeks at −5° to form. On repeated slow crystallizations from ethanol rosettes of hexagonal prisms were obtained; m. p. 98°; $[\alpha]^{25}\text{D}$ 26.0° (*c*, 5 in chloroform).

Anal. Calcd. for $C_{37}H_{34}O_{10}$ (638.7): C, 69.57; H, 5.37; $(CH_3)_2CO$, 9.10; sap. eq., 160. Found: C, 69.51; H, 5.29; $(CH_3)_2CO$, 9.06; sap. eq., 159.

Periodate Oxidation of I.—The ease of acid hydrolysis of the isopropylidene groups necessitated the use of buffered periodate. The oxidizing reagent was 0.1 *M* and was prepared immediately before use from periodic acid and sodium bicarbonate. A 33% excess was used. The results obtained, as shown in Fig. 1, indicate the consumption of three moles of periodate.

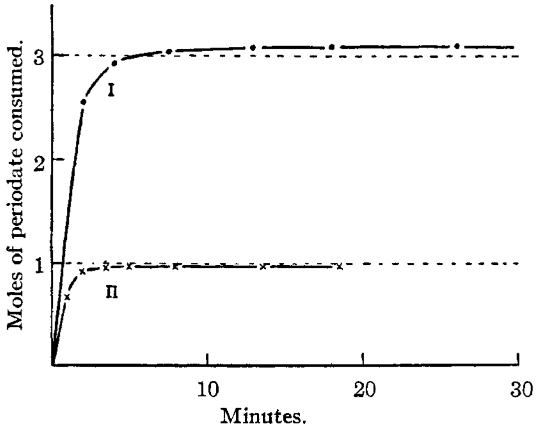

Fig. 1.—Periodate oxidation of 1,2-isopropylidene-D-glucitol (I) and 1,2:5,6-diisopropylidene-D-glucitol (II).

Oxidation of I with Lead Tetraacetate and Identification of the L-Glyceraldehyde Produced.—Following the method of Baer and Fischer,[8] 4 g. of I and 24 g. of lead tetraacetate reacted in 200 ml. of dried benzene. Owing to the difficulty of working up the small amounts of materials here used, only about 100 mg. of glyceraldehyde was obtained. Its rotation, $[\alpha]^{25}\text{D}$, −9.2° (*c*, 2.5 in water after 1 day), falls within the accepted range.[9] The 2,4-dinitrophenylhydrazone was prepared and its m. p., 147°, agreed with the reported value for L-glyceraldehyde 2,4-dinitrophenylhydrazone.[9] On cocrystallization with an equal weight of the 2,4-dinitrophenylhydrazone of D-glyceraldehyde the m. p. was elevated to 167° which agrees with the figure reported[10] for the racemic 2,4-dinitrophenylhydrazone. These data indicate an L-configuration for the glyceraldehyde obtained on oxidation of I.

Enzymatic Confirmation of the Configuration of the Glyceraldehyde Obtained from I.—Hexokinase activity was measured by the procedure of Colowick and Kalckar[11] using 0.01 *M* glucose and 0.006 *M* adenosine triphosphate as substrates and a stable, dialyzed, lyophilyzed extract of beef brain as the source of the enzyme.[12] The addition of L-glyceraldehyde to this enzyme preparation inhibits the hexokinase activity while addition of D-glyceraldehyde shows no effect. The glyceraldehyde obtained from I was found to be as inhibitory to hexokinase as an authentic sample of L-glyceraldehyde.[9] These results are shown in Table I.

1,2,:5,6-Diisopropylidene-D-glucitol (II).—The same reaction mixture employed in the preparation of I was allowed to react for four hours and was then worked up into a dry sirup in the same manner. This was then re-

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[6] Passed through a 100 mesh screen and dried two days at 65° *in vacuo*; m. p. 97°.

[7] Carbon and hydrogen analyses by the Clark Microanalytical Laboratory, Urbana, Illinois. Acetone analyses were performed by a modification of Messner's method after hydrolysis of the samples with dioxane-hydrochloric acid in the apparatus of Lester and Greenberg, *J. Biol. Chem.*, **154**, 177 (1944).

[8] Baer and Fischer, *J. Biol. Chem.*, **128**, 163 (1939).

[9] Baer and Fischer, THIS JOURNAL, **61**, 761 (1939), report that L-glyceraldehyde exhibits a mutarotation from −14° to an equilibrium value of −7.8°.

[10] Neuberg, *Biochem. Z.*, **255**, 11 (1932).

[11] Colowick and Kalckar, *J. Biol. Chem.*, **148**, 117 (1943).

[12] Wiebelhaus and Lardy, *Arch. Biochem.*, **21**, 321 (1949).

TABLE I

ENZYMATIC DETERMINATION OF CONFIGURATION OF GLYCERALDEHYDE

Inhibitor		% Inhibition of hexokinase
$1.6 \times 10^{-4}M$	L-glyceraldehyde from L-mannitol	40
$4.1 \times 10^{-4}M$	L-glyceraldehyde from L-mannitol	>95
$1.6 \times 10^{-4}M$	L-glyceraldehyde from I	43
$4.1 \times 10^{-4}M$	L-glyceraldehyde from I	81
$4 \times 10^{-2}M$	D-glyceraldehyde from D-mannitol	<16

fluxed (*ca.* 90°) with 500 ml. of dry Skellysolve C for three hours with occasional swirling. The resulting solution was decanted from the residue (which contained mostly unreacted sorbitol together with inorganic material and small amounts of I) and allowed to cool to room temperature. A sirup settled out which showed, on analysis, an acetone content close to that expected for a diisopropylidenesorbitol. However, its low periodate consumption indicated the absence of free vicinal hydroxyl groups. All attempts to crystallize such a compound from the sirup failed. The solvent was decanted from this sirup, cooled to −5° and seeded with II. The original seed crystals were obtained by allowing the reaction product to stand at −5° for two months. After two days about 30 g. of oily crystals had deposited. The solvent was decanted and discarded. Crude II was obtained from the residue by dissolving it in 10 volumes of dibutyl ether and cooling the solution to −5° overnight. The dibutyl ether mother liquors, on removal of the solvent *in vacuo*, yielded another uncrystallizable sirup whose chemical properties (*i. e.*, acetone content, periodate consumption) resembled those of the sirup which settled from the original extraction at room temperature. The impure II was recrystallized from 20 volumes of Skellysolve C. About 11 g. of product (m. p. 93°) was obtained: yield 7.7%. By repeated recrystallization from Skellysolve C long hexagonal prisms of m. p. 95–95.5°, $[\alpha]^{25}_{\text{D}}$ −0.25 (*c*, 10 in pyridine), were obtained. The compound is very soluble in water, ethanol and pyridine and moderately so in dibutyl ether and Skellysolve C.

Anal. Calcd. for $C_{12}H_{22}O_6$ (262.3): C, 54.96; H, 8.46; $(CH_3)_2CO$, 44.3. Found: C, 54.95; H, 8.45; $(CH_3)_2CO$, 44.2.

1,2:5,6-Diisopropylidene-3,4-dibenzoyl-D-glucitol.—A solution of 1 g. II in 20 ml. of dried pyridine was cooled in an ice-bath and 1.1 ml. of benzoyl chloride added. Twenty-four hours later the excess solvent was distilled off on a steam-bath *in vacuo*. After the addition of 20 ml. of sodium bicarbonate solution to the residue the crude product was crystallized in virtually quantitative yield by scratching with a glass rod. It was dissolved in hot ethanol, treated with norite and recrystallized. The product was obtained as very regular hexagonal plates of m. p. 134–135°, $[\alpha]^{25}_{\text{D}}$ 53.7° (*c*, 10 in chloroform).

Anal. Calcd. for $C_{26}H_{30}O_8$ (470.5): C, 66.37; H, 6.43; $(CH_3)_2CO$, 24.75; sap. eq., 235. Found: C, 66.51; H, 6.33; $(CH_3)_2CO$, 24.80; sap. eq., 235.

1,2:5,6-Diisopropylidene-3,4-diacetyl-D-glucitol was prepared exactly as the corresponding I derivative. From the original reaction mixture seed crystals were obtained only on allowing it to stand ten days at −5°. When recrystallized from ethanol rectangular blades were deposited, m. p. 64–65°, $[\alpha]^{25}_{\text{D}}$ 26.1° (*c*, 10 in chloroform).

Anal. Calcd. for $C_{16}H_{26}O_8$ (346.4): C, 55.49; H, 7.57; $(CH_3)_2CO$, 33.6; sap. eq., 173. Found: C, 55.48; H, 7.49; $(CH_3)_2CO$, 32.9; sap. eq., 172.

Oxidation of II with Periodate.—The same procedure that was employed in the periodate oxidation of I was followed. The results are shown in Fig. 1. The reaction mixture was tested for formaldehyde by distillation with a stream of carbon dioxide into a solution of dimedon reagent; no precipitate formed, indicating the absence of formaldehyde.

Oxidation of II with Lead Tetraacetate and Isolation of DL-Glyceraldehyde Dimer.—The Baer and Fischer oxidation and hydrolysis procedure[8] was carried out on a 15.6 g. quantity of II. The product was obtained in the form of a thick sirup which crystallized slowly over a period of about a month on the addition of a small amount of ethanol. The yield of 6.0 g. of crystalline D,L-glyceraldehyde dimer of m. p. 142–145° represented 56% of the theoretical.

1,2:3,4:5,6-Triisopropylidene-D-glucitol (III).—To 250 ml. of acetone, 20 g. of sorbitol and 2 ml. of sulfuric acid were added. The sorbitol went into solution quickly and the mixture was allowed to stand overnight. The acid was then neutralized with 7 ml. of concd. ammonium hydroxide, 50 g. of potassium carbonate was added and after thirty minutes of shaking the suspension was filtered. The residue was washed with an additional 50 ml. of acetone and the combined filtrates concentrated *in vacuo* to 50 ml. This was then added with vigorous stirring to 1 l. of a mixture of ice and water. The product was recrystallized from a mixture of 1 part acetone and 2 parts water made slightly ammoniacal to retard hydrolysis. The yield was 15 g. or 53%; m. p. 48°. The procedure is more convenient than the older ones in which anhydrous hydrogen chloride is used as a catalyst. The recorded physical constants of the compound are: m. p.[13] 46–47° and[14] $[\alpha]_{\text{D}}$ 14.2°.

Anal. Calcd. for $C_{15}H_{26}O_6$ (302.4): $(CH_3)_2CO$, 57.6. Found: $(CH_3)_2CO$, 57.2.

Conversion of II to III.—To 25 ml. of acetone, 2 g. of II and 0.2 ml. of sulfuric acid were added. After four hours at room temperature the acid was neutralized with 0.7 ml. of concd. ammonium hydroxide followed by 5 g. of potassium carbonate. The suspension was filtered and the solvent removed from the filtrate *in vacuo*. The resulting sirup was taken up in ethanol–water and by seeding and scratching 1.5 g. of III was obtained. The product melted at 45–46° and did not depress the m. p. of the compound produced directly from sorbitol by the above method. It also exhibited the same rotation as the above prepared compound, $[\alpha]^{25}_{\text{D}}$ 14.3° (*c*, 10 in ethanol).

Summary

1. The zinc chloride catalyzed condensation of acetone with sorbitol has been studied. Two new acetonated sorbitols have been isolated and characterized as 1,2-isopropylidene-D-glucitol and 1,2:5,6-diisopropylidene-D-glucitol. Their acetyl and benzoyl derivatives were also prepared.

2. A new procedure for the production of D,L-glyceraldehyde dimer has been described which gives promise to becoming a useful laboratory preparation.

3. The 1,2:3,4:5,6-structure previously suggested for triisopropylidene-D-glucitol has been substantiated by the synthesis of this compound from a partially acetonated sorbitol of proved structure.

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[13] Asahina and Shinoda, *Chem. Abs.*, **24**, 1704 (1930).

[14] Strain, THIS JOURNAL, **56**, 1756 (1934).