lead to inactivation of the enzyme, French and co-workers[17] found measurable quantities of amylopentaose. It is possible that some enzyme molecules became inactivated sufficiently so that, because of their changed physical state, they were unable to form a complex with the entire substrate molecule.

French and co-workers explain the single chain hydrolysis theory by assuming that intermediate products of hydrolysis do not diffuse from the locality of their production with sufficient rapidity to escape further attack by the enzyme, whereas we have been led to speculate that complex formation between the enzyme and substrate involves a considerably longer portion of the substrate chain than the two terminal glucose units, possibly the entire length of some linear amylose molecules, and that virtually complete hydrolysis ensues at the instant of dissociation of the complex.

Argo, Illinois Received December 4, 1950

[17] D. French, D. W. Knapp and J. H. Pazur, This Journal, **72**, 1866 (1950).

[Contribution from the Northern Regional Research Laboratory[1]]

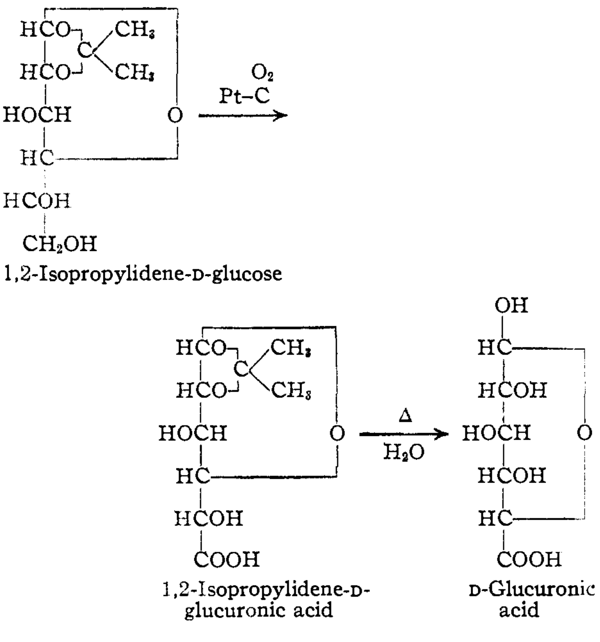
A Practical Synthesis of D-Glucuronic Acid through the Catalytic Oxidation of 1,2-Isopropylidene-D-glucose[2]

By C. L. Mehltretter, B. H. Alexander, R. L. Mellies and C. E. Rist

A practical synthesis of D-glucuronic acid has been developed in which 1,2-isopropylidene-D-glucose is catalytically oxidized to 1,2-isopropylidene-D-glucuronic acid in a yield of 50–60% of theory using platinum–carbon catalyst and air. By simple hydrolysis 1,2-isopropylidene-D-glucuronic acid is nearly quantitatively converted to D-glucuronic acid. A key step in the synthesis is the separation of 1,2-isopropylidene-D-glucuronic acid from contaminating by-products in the oxidation mixture as the insoluble calcium salt. The barium and sodium salts of 1,2-isopropylidene-D-glucuronic acid also have been prepared. To facilitate this synthesis an improved procedure has been devised for the preparation of 1,2-isopropylidene-D-glucose in aqueous solution in 93% yield. A small quantity of by-product isolated was shown to be isopropylidene-bis-(diisopropylidene-D-glucose). Its structure, however, has not yet been completely established.

The oxidation of carbohydrate substances to sugar acids with oxygen in the presence of noble metal catalysts has been shown to be preferential for aldehyde and primary alcohol groups. Busch[3] quantitatively converted D-glucose to D-gluconic acid with air in the presence of palladium–calcium sulfate catalyst. With the more active platinum-activated carbon catalyst Heyns[4] was able to oxidize L-sorbose to 2-keto-L-gulonic acid under neutral or slightly alkaline conditions. Similarly Trenner[5] converted 2,3-isopropylidene-L-sorbose in aqueous solution to 2,3-isopropylidene-2,5-anhydro-L-gulosaccharic acid. More recently[6] D-glucose has been catalytically oxidized to D-glucosaccharic acid in 54% yield by use of platinized–activated carbon and air, a result contradictory to the findings of Heyns and Heinemann.[7]

This procedure has now been successfully used as the basis of a synthesis of D-glucuronic acid from 1,2-isopropylidene-D-glucose in an over-all yield of at least 43%. Optimum conditions have been found for the catalytic oxidation of 1,2-isopropylidene-D-glucose to 1,2-isopropylidene-D-glucuronic acid. The latter substance was best isolated as the calcium salt from which a mixture of D-glucuronic acid and D-glucuronolactone was obtained in 85% yield by acid hydrolysis. The barium and sodium salts of 1,2-isopropylidene-D-glucuronic acid have also been prepared. The sequence of reactions may be illustrated as



1,2-Isopropylidene-D-glucose

1,2-Isopropylidene-D-glucuronic acid

D-Glucuronic acid

The results of several experiments are given in Table I to show the effect of temperature, air velocity and rate of stirring on the reaction time and on the yield of 1,2-isopropylidene-D-glucuronic acid.

The temperature of the reaction appeared to be optimum at about 50°. Lowering the temperature to 28° decreased the rate of oxidation below the limit of practicability. On the other hand, a temperature of 100°, although it hastened the reaction, caused enough decomposition to reduce

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[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

[2] This paper was presented before the Division of Sugar Chemistry and Technology at the 118th Meeting of the American Chemical Society, Chicago, Illinois, September 3-8, 1950.

[3] M. Busch, German Patent 702,729 (1941).

[4] K. Heyns, *Ann.*, **558**, 177 (1947); O. Dalmer and K. Heyns, U. S. Patent 2,190,377 (1940).

[5] N. R. Trenner, U. S. Patent 2,428,438 (1947).

[6] C. L. Mehltretter, C. E. Rist and B. H. Alexander, U. S. Patent 2,472,168 (1949).

[7] K. Heyns and R. Heinemann, *Ann.*, **558**, 187 (1947).

TABLE I

EFFECT OF TEMPERATURE, AIR VELOCITY AND RATE OF STIRRING ON THE REACTION TIME AND ON THE YIELD OF 1,2-ISOPROPYLIDENE-D-GLUCURONIC ACID

In all of these experiments 13.2 g. (0.06 mole) of 1,2-isopropylidene-D-glucose and 5.0 g. (0.06 mole) of sodium bicarbonate were dissolved in 600 ml. of water and oxidation carried out in a creased flask using air and 7.0 g. of platinum (13%)-activated carbon catalyst.

T, °C.	Air flow, liters/hr.	Stirring, r.p.m.	Reaction time, hr.	Yield, %
50	112	3500	4.5	57
50	30	3500	10.5	57
50	112	1000	22.5	57
28	112	3500	32.5	..[a]
100	112	3500	2.75	46

[a] Reaction incomplete.

the yield of 1,2-isopropylidene-D-glucuronic acid appreciably.

A maximum rate of stirring is desirable in such a heterogeneous reaction mixture. It was limited, however, by the foaming produced.

Although the optimum rate of aeration was not determined, an air velocity of more than 30 liters per hour was required for a rapid oxidation under the conditions used. No doubt more efficient systems of aeration and agitation could be utilized in large-scale operations.

To facilitate this synthesis it was desirable to develop a more efficient method for preparing 1,2-isopropylidene-D-glucose. Numerous satisfactory procedures are available for the acetonation of D-glucose to 1,2;5,6-diisopropylidene-D-glucose,[8] and several investigators have preferentially hydrolyzed this compound to 1,2-isopropylidene-D-glucose in yields up to 89% of theory.[8a,9] However, using these methods in succession for the preparation of 1,2-isopropylidene-D-glucose has obvious disadvantages. It requires the isolation of the diisopropylidene-D-glucose by solvent extraction and fails to utilize the monoisopropylidene derivative formed in appreciable quantity during the acetonation step.

Improvements in operation and in yield of 1,2-isopropylidene-D-glucose were effected by combining these procedures.

D-Glucose was acetonated by a modification of Bell's[8] method and after removal of unreacted D-glucose, sulfuric acid catalyst, acetone and acetone polymers, there remained a mixture containing approximately 11 g. of 1,2;5,6-diisopropylidene-D-glucose and 4 g. of 1,2-isopropylidene-D-glucose per 100 ml. Extraction of a portion of this mixture with benzene showed diisopropylidene-D-glucose to be present in a yield of 69.5%. The aqueous layer, by analysis, contained 1,2-isopropylidene-D-glucose in 28% yield.

Acid hydrolysis studies on an artificial mixture of the isopropylidene derivatives of D-glucose revealed conditions whereby 99% of the 1,2;5,6-diisopropylidene-D-glucose was converted to 1,2-isopropylidene-D-glucose. Less than 5% of the latter substance was hydrolyzed to D-glucose (Table II).

TABLE II

ACID HYDROLYSIS OF A MIXTURE OF 1,2;5,6-DIISOPROPYLIDENE-D-GLUCOSE AND 1,2-ISOPROPYLIDENE-D-GLUCOSE[a]

			% hydrolysis of	
pH	T, °C.	Hours	1,2;5,6-diisopropylidene-D-glucose	1,2-isopropylidene-D-glucose
2.0	30	5	96	3
2.0	40	4	99	4
3.7	75	4	99	5
6.0	100	5	95	4

[a] 11.00 g. of 1,2;5,6-diisopropylidene-D-glucose and 4.40 g. of 1,2-isopropylidene-D-glucose in 100 ml. of hydrochloric acid solution.

The conditions for optimum hydrolysis, namely, *p*H2 at 40° for four hours, were applied to the aqueous mixture from the acetonation and 1,2-isopropylidene-D-glucose was produced in solution in 93% yield. The pure crystalline product was isolated in 55% yield by concentrating the hydrolyzate *in vacuo* to a small volume. That remaining in the mother liquor could readily be isolated in less pure form by further evaporation to near dryness.

A small quantity of insoluble material which separated from the hydrolyzate of the mixture obtained from the acetonation was shown to be isopropylidene *bis*-(diisopropylidene-D-glucose). Its structure has not yet been established.

Experimental

Preparation of Catalyst.—The platinum–activated carbon catalyst was prepared by a modification of the procedure described by Trenner.[5] Darco G-60 brand of activated carbon was digested overnight with 1:1 hydrochloric acid, filtered and washed free of acid with water. After drying for several hours at 100°, 87 g. of the purified carbon was added to a solution of 35 g. of chloroplatinic acid ($H_2PtCl_6 \cdot 6H_2O$) in 600 ml. of water in a 1,500-ml. beaker. The mixture was stirred mechanically and neutralized by the careful addition of sodium bicarbonate. It was then heated to 80° in a water-bath with the gradual addition of 55 ml. of 38% formaldehyde over a 45-minute period. Sodium bicarbonate was added in portions simultaneously to neutralize the formic acid formed and to maintain a slightly alkaline mixture. After all of the formaldehyde had been introduced, the mixture was held at 80° for two hours with constant stirring. It was then cooled to room temperature, filtered and washed successively with hot solutions of potassium chloride of decreasing concentrations and finally with hot water. The washings with hot water were continued until the catalyst was free of chloride ions. The air-dried product contained 13% platinum by weight.

Oxidation of 1,2-Isopropylidene-D-glucose to 1,2-Isopropylidene-D-glucuronic Acid (a).—Sixty-six grams (0.3 mole) of 1,2-isopropylidene-D-glucose was dissolved in 900 ml. of water in a 3-liter, 3-neck, creased, round-bottom flask[10] and 6.3 g. (0.075 mole) of sodium bicarbonate added. After solution, 6.8 g. of platinum (13%)-Darco G-60 catalyst was introduced and the mixture vigorously stirred at about 3,000 r.p.m. Compressed air which had been cleaned by passage through concentrated sulfuric acid was forced into the reaction mixture through an inlet tube at the rate of 112 liters per hour. The reaction temperature was maintained at 50° by means of a water-bath. After 1.25 hours the *p*H of the solution dropped to 7.5. Three more

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[8] (a) E. Fischer and C. Rund, *Ber.*, **49**, 88 (1916); (b) K. Freudenberg and K. Smeykal, *ibid.*, **59**, 100 (1926); (c) H. O. L. Fischer and C. Taube, *ibid.*, **60**, 485 (1927); (d) D. J. Bell, *J. Chem. Soc.*, 1874 (1935); (e) H. Van Grunenberg, C. Bredt and W. Freudenberg, THIS JOURNAL, **60**, 1507 (1938); (f) O. T. Schmidt and A. Simon, *J. prakt. Chem.*, **152**, 190 (1939).

[9] (a) J. C. Irvine and J. Macdonald, *J. Chem. Soc.*, 1701 (1915); (b) K. Freudenberg, W. Dürr and H. von Hochstetter, *Ber.*, **61**, 1735 (1928); (c) H. W. Coles, L. D. Goodhue and R. M. Hixon, THIS JOURNAL, **51**, 523 (1929); (d) A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29**, 139 (1946).

[10] Purchased from Scientific Glass Apparatus Company, Bloomfield, N. J. The effective volume was approximately 2500 ml.

portions of 6.3 g. of sodium bicarbonate were added over a period of seven hours. After 11.5 hours the reaction mixture had a *p*H of 7. The reaction was stopped and the light brown solution filtered from catalyst and the latter washed with hot dilute sodium chloride solution. The combined filtrate and washings were concentrated *in vacuo* to about 200 ml. and cooled to 15°. Concentrated hydrochloric acid was added slowly with stirring to obtain *p*H 2. The cold solution was extracted with ten 200-ml. portions of ethyl acetate and the combined extracts dried over anhydrous sodium sulfate. After filtration, the ethyl acetate solution was concentrated *in vacuo* at low temperature to a nearly white crystalline residue. The product, 1,2-isopropylidene-D-glucuronic acid, melted at 140–143°; (lit.[11] m.p. 146–147°; $[\alpha]^{20}\mathrm{D}$ −9.2° (water)). The yield was 37.5 g. (53.5%). Recrystallization from ethyl acetate gave a melting point of 145–146°; $[\alpha]^{25}\mathrm{D}$ −7.4° (*c*, 2.34; water (after ten minutes)). The material gave a positive naphthoresorcinol test for glucuronic acid.

Anal. Calcd. for $C_9H_{14}O_7$: C, 46.2; H, 6.0; neut. equiv., 234. Found: C, 46.0; H, 6.0; neut. equiv., 236.

(b).—In an analogous experiment in which 60 g. (0.27 mole) of 1,2-isopropylidene-D-glucose was oxidized, the oxidation mixture containing sodium 1,2-isopropylidene-D-glucuronate was concentrated *in vacuo* to about 175 ml. The mixture was heated to 70° and the oxalic acid present was precipitated as calcium oxalate by the addition of 2 g. of calcium chloride. After filtration the solution was treated with 13 g. of calcium chloride in concentrated water solution. Calcium 1,2-isopropylidene-D-glucuronate crystallized almost immediately. The mixture was cooled to 15–20° for one-half hour and filtered. The product was triturated with 50% ethanol, filtered and air-dried. It weighed 41.8 g. and gave a positive naphthoresorcinol test for D-glucuronic acid.

A sample was dried at 110° (2 mm.) for two hours and lost 14.8% water.

Anal. Calcd. for $Ca(C_9H_{13}O_7)_2$: Ca, 7.9. Found: Ca, 7.7.

The yield of anhydrous calcium 1,2-isopropylidene-D-glucuronate was 35.6 g. (51.6%).

Preparation of Salts of 1,2-Isopropylidene-D-glucuronic Acid (a) Calcium 1,2-Isopropylidene-D-glucuronate.—Five grams of 1,2-isopropylidene-D-glucuronic acid was dissolved in 20 ml. of water and 0.8 g. of calcium hydroxide in water suspension was added in small portions with vigorous stirring. Calcium 1,2-isopropylidene-D-glucuronate crystallized and was removed by filtration. After having been washed with ice water, the slightly yellow product was air-dried and weighed 4.0 g. For analysis the salt was recrystallized from water and air-dried; $[\alpha]^{25}\mathrm{D}$ −1.54° (*c*, 1.97; water).

Anal. Calcd. for $Ca(C_9H_{13}O_7)_2 \cdot 5.5H_2O$: Ca, 6.6; H_2O, 16.4. Found: Ca, 6.7; H_2O, 16.7.

The hydrate was converted to the anhydrous form by drying *in vacuo* over phosphorus pentoxide for two hours at 110°.

Anal. Calcd. for $Ca(C_9H_{13}O_7)_2$: C, 42.7; H, 5.2. Found: C, 42.8; H, 5.0.

(b) **Barium 1,2-Isopropylidene-D-glucuronate.**—Six grams of 1,2-isopropylidene-D-glucuronic acid was dissolved in 25 ml. of water and a hot aqueous solution containing 4 g. of barium hydroxide octahydrate gradually added with stirring. The barium 1,2-isopropylidene-D-glucuronate that precipitated was slightly yellow. The mixture was cooled and then acidified with acetic acid to remove the color, and to neutralize any excess barium hydroxide present. After the barium salt was filtered and washed with 50% ethanol, it was air-dried and weighed 5.7 g. It was quite insoluble in hot water.

The substance was dried *in vacuo* over phosphorus pentoxide at 110° for one hour and lost 3.0% water. The theoretical amount of water for a monohydrate is 2.9%.

Anal. Calcd. for $Ba(C_9H_{13}O_7)_2$: Ba, 22.8. Found: Ba, 22.7.

(c) **Sodium 1,2-Isopropylidene-D-glucuronate.**—To a hot solution of 1.01 g. of sodium oxalate in 50 ml. of water was added in portions with vigorous stirring 4.54 g. of hydrated calcium 1,2-isopropylidene-D-glucuronate. The mixture was cooled after 20 minutes and filtered from precipitated calcium oxalate. The clear filtrate was concentrated *in vacuo* nearly to dryness and the white residue triturated with absolute ethanol. The alcohol-insoluble sodium 1,2-isopropylidene-D-glucuronate was removed by filtration and washed with absolute ethanol. After air-drying, it weighed 3.46 g.; $[\alpha]^{25}\mathrm{D}$ −2.58° (*c*, 10.74; water). The product was dried *in vacuo* over phosphorus pentoxide at 110° for one hour.

Anal. Calcd. for $NaC_9H_{13}O_7$: C, 42.2; H, 5.1; Na, 9.0. Found: C, 42.1; H, 5.1; Na, 8.8.

Conversion of Calcium 1,2-Isopropylidene-D-glucuronate to D-Glucuronic Acid.—To a solution of 10.1 g. of oxalic acid dihydrate (theoretical amount) in 275 ml. of water at 90–100° was gradually added with stirring 48.6 g. of hydrated calcium 1,2-isopropylidene-D-glucuronate. Heating and stirring of the mixture which contained liberated 1,2-isopropylidene-D-glucuronic acid was continued for 1.75 hours with the addition of decolorizing carbon during the last half hour. Water was added at intervals to replace that lost by evaporation. The filtered mixture contained 29.0 g. of D-glucuronic acid (theory, 29.7 g.). The solution was concentrated *in vacuo* to a sirup which crystallized on seeding. The mass was triturated with 95% ethanol and filtered. The white crystalline product obtained was dried at 50° and weighed 21.3 g. It melted at 150–151° (dec.) and mutarotated in water; $[\alpha]^{25}\mathrm{D}$ +28° was the value obtained after two hours (lit.[12] for D-glucuronic acid, m.p. 165°; $[\alpha]^{25}\mathrm{D}$ +36° after three hours). Titration of a solution of the product in ice-water with 0.1 *N* sodium hydroxide solution showed it to be composed of 60% D-glucuronic acid and 40% lactone. It gave the characteristic naphthoresorcinol test for D-glucuronic acid and assayed 100% as D-glucuronic acid by reducing value (Munson–Walker method).

A second crop of product weighing 3.8 g., m.p. 152–154° (dec.), was obtained from the mother liquor upon concentration. The total recovery was 25.1 g. (84.5%).

Conversion of D-Glucuronic Acid–Glucuronolactone Mixture to D-Glucuronolactone.—Four hundred and forty-six grams of a crystalline mixture of D-glucuronic acid and D-glucuronolactone was dissolved in 350 ml. of water by warming. The solution was concentrated on the steam-bath until crystallization began, and then quickly cooled to room temperature with stirring. After two hours the crystalline product was isolated by filtration, washed with cold ethanol and air-dried. A yield of 253 g. of D-glucuronolactone was obtained; m.p. 174–175°; $[\alpha]^{25}\mathrm{D}$ +19.8° (*c*, 5.19; water); (lit.[13] m.p. 176–178°; $[\alpha]^{20}\mathrm{D}$ 20° (water)). The amount of free D-glucuronic acid present was found to be 0.2% by titration of an ice-cold aqueous solution of the product with standard alkali. The filtrate and wash liquors were combined and more lactone was recovered by a repetition of the above procedure.

Preparation of 1,2-Isopropylidene-D-glucose

Acetonation of D-Glucose.—To a stirred suspension of 250 g. of anhydrous D-glucose in 5 liters of technical grade acetone cooled to 15° was added 200 ml. of concentrated sulfuric acid over a 10-minute period. In this way the temperature of the reaction was kept below 25°. The mixture was stirred for three hours at 20–25° and the unreacted D-glucose (23.8 g.) was recovered by filtration and washed with acetone. With stirring and outside cooling to keep the temperature of the mixture below 40°, the combined filtrate and washings were gradually made slightly alkaline with 580 ml. of 50% sodium hydroxide solution. The precipitated sodium sulfate was allowed to settle overnight, and the clear supernatant liquor was siphoned off. The residual slurry was then filtered and the sodium sulfate washed with acetone. The combined filtrates and washings amounted to 6,140 ml. Only 1,2;5,6-diisopropylidene-D-glucose, 1,2-isopropylidene-D-glucose, D-glucose and acetone condensation products were assumed to be present in this solution.

One-half of the acetonation solution (3.070 ml.) was concentrated *in vacuo* to remove practically all of the acetone. One liter of water was then added to the residual mixture and the distillation continued at 60–70° to remove traces of acetone and acetone polymers. The final solution was diluted with water to 2 liters to dissolve the 1,2;5,6-diisopropylidene-D-glucose. The aqueous solution was extracted

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[11] L. Zervas and P. Sessler, *Ber.*, **66**, 1326 (1933).

[12] W. F. Goebel and F. H. Babers, *J. Biol. Chem.*, **100**, 573 (1933).

[13] M. Stacey, *J. Chem. Soc.*, 1529 (1939).

with seven 300-ml. portions of benzene to remove the 1,2;5,6-diisopropylidene-D-glucose. The combined benzene extracts were dried over anhydrous sodium sulfate and evaporated on a steam-bath to a nearly white residue. After drying at 75° to constant weight, the residue weighed 110.5 g.; m.p. 104–106°; $[\alpha]^{25}\text{D}$ −16° in water; (lit.[8a] m.p. 110–111°; $[\alpha]^{20}\text{D}$ −18.5° in water). The yield of 1,2;5,6-diisopropylidene-D-glucose was 69.5%, based on the D-glucose that was acetonated.

Analysis for 1,2-Isopropylidene-D-glucose.—The water layer containing 1,2-isopropylidene-D-glucose and D-glucose was concentrated *in vacuo* to a small volume and diluted with water to 300 ml. Ten milliliters of this solution was evaporated to dryness on the steam-bath and heated at 100° for one hour. The white mixture weighed 1.40 g. After subtraction of the amount of D-glucose present, the residue contained 1.29 g. of 1,2-isopropylidene-D-glucose; $[\alpha]^{25}\text{D}$ −12.4° in water (corrected for D-glucose present); (lit.[8a] $[\alpha]^{19}\text{D}$ −11.8° in water; our value $[\alpha]^{25}\text{D}$ −12.2°). This calculation shows a yield of 28.8% based on the D-glucose that was acetonated.

The quantity of 1,2-isopropylidene-D-glucose formed was also determined indirectly. Ten milliliters of the water solution was hydrolyzed at 100°, *p*H 1 (with hydrochloric acid) for three hours to convert all of the 1,2-isopropylidene-D-glucose to D-glucose. A control experiment with D-glucose alone showed no appreciable change in reducing value under these conditions. The amount of 1,2-isopropylidene-D-glucose present was estimated from the difference in the D-glucose content of the solution before and after hydrolysis. The D-glucose content before hydrolysis was 1.12 g. per 100 ml. of solution and after hydrolysis 11.04 g. per 100 ml. The difference, 9.92 g., calculated as 1,2-isopropylidene-D-glucose, is 12.20 g. per 100 ml. or a 27.3% yield, based on the D-glucose acetonated. The average yield from the two analyses is 28%.

Acid Hydrolysis of a Mixture of 1,2;5,6-Diisopropylidene-D-glucose and 1,2-Isopropylidene-D-glucose.—Hydrolysis experiments were performed on mixtures of 11.00 g. of 1,2;5,6-diisopropylidene-D-glucose and 4.40 g. of 1,2-isopropylidene-D-glucose in water adjusted to the desired *p*H with hydrochloric acid and diluted to 100 ml. When temperatures of hydrolysis of 75 and 100° were used, the 250-ml. reaction flasks were fitted with 10-inch air condensers to allow the acetone liberated to escape with no appreciable loss of water. All of the mixtures were mechanically stirred. The hydrolyses below 100° were carried out in electrically heated water-baths maintained to within ±1° of the desired temperature. A steam-bath was used for the 100° hydrolysis.

At the end of each hour a portion of the reaction mixture was removed and its D-glucose content determined by the Munson–Walker method with permanganate titration of the reduced copper. The angular rotation of the solution was measured at the same time and was corrected for the D-glucose present. The reaction was terminated when the corrected angular rotation reached the range −1.5 to −1.7°. This occurred usually between the third and fifth hour under the conditions studied. From the specific rotation of 1,2;5,6-diisopropylidene-D-glucose (−18.5°) and 1,2-isopropylidene-D-glucose (−11.8°) the angular rotation of the mixture before hydrolysis was calculated as −2.6° and after complete hydrolysis to 1,2-isopropylidene-D-glucose, as −1.6°.

At the end of the reaction, 10 ml. of the solution was extracted three times with 20-ml. portions of benzene. The benzene extracts were combined and evaporated to dryness in a small tared dish. From the weight of the 1,2;5,6-diisopropylidene-D-glucose residue the percentage of hydrolysis of this substance in the mixture was calculated. The percentage of hydrolysis of the 1,2-isopropylidene-D-glucose was estimated from the amount of D-glucose formed. The results of the hydrolysis experiments are shown in Table II. It is seen that various combinations of acidity, temperature and time may be used for efficient conversion of 1,2;5,6-diisopropylidene-D-glucose to 1,2-isopropylidene-D-glucose with a minimum of hydrolysis of the latter substance to D-glucose.

Acid Hydrolysis of the Aqueous Mixture from the Acetonation of D-Glucose.—The second half (3,070 ml.) of the acetonation solution was concentrated *in vacuo*, 1,600 ml. of water was added and the mixture distilled at 60–70° under reduced pressure as was done previously to remove acetone and acetone condensation products. The final alkaline aqueous mixture (1,020 ml.) was adjusted to *p*H 2 with concentrated hydrochloric acid and hydrolyzed at 40° for four hours with constant stirring. The hydrolyzate was neutralized to *p*H 8 with sodium hydroxide and filtered from 1.7 g. (m.p. 116–117°) of insoluble material. The filtrate was concentrated *in vacuo* to remove the acetone liberated by hydrolysis and then diluted to 1,800 ml. with water. It contained 9.4 g. of D-glucose by the Munson–Walker method. A 10-ml. sample was extracted with three 20-ml. portions of benzene. The combined benzene extracts were evaporated to a crystalline residue of 0.0134 g. of 1,2;5,6-diisopropylidene-D-glucose. From these values, it was calculated that only 2–3 g. of the diisopropylidene derivative was not hydrolyzed (98% conversion) and that a yield of 1,2-isopropylidene-D-glucose of 93% in aqueous solution was obtained. The hydrolysate was concentrated *in vacuo* to incipient crystallization of 1,2-isopropylidene-D-glucose. The product was removed by filtration and washed with cold ethanol. After air-drying it weighed 50.8 g.; m.p. 161°; $[\alpha]^{25}\text{D}$ −12.2° (*c*, 8.3; water); (lit.[8a] m.p. 161–162.5°; $[\alpha]^{19}\text{D}$ −11.8° (water)). Concentration of the mother liquor gave a second crop of 21.0 g.; m.p. 161°; $[\alpha]^{25}\text{D}$ −12.2° (*c*, 8.1; water). The total yield of pure 1,2-isopropylidene-D-glucose isolated was 55%. Evaporation of the final mother liquor to near dryness gave 52 g. of crude product melting at 148–152°. Since it was difficult to purify this material by recrystallization from ethyl acetate or ethanol–water mixtures it was preferred to add the final mother liquor to the hydrolysate of a succeeding run for isolation of the residual 1,2-isopropylidene-D-glucose.

Isopropylidene Bis-(diisopropylidene-D-glucose).—The insoluble by-product (m.p. 116–117°) removed from the hydrolysate of the mixture obtained from the acetonation was recrystallized from 50% ethanol to a constant melting point of 120–121°; $[\alpha]^{25}\text{D}$ +52.8° (*c*, 1.00; acetone).

Anal. Calcd. for $C_{27}H_{44}O_{12}$: C, 57.8; H, 7.9; mol. wt., 561. Found: C, 57.9; H, 7.8; mol. wt. (modified Signer method in acetone against 1,2;5,6-diisopropylidene-D-glucose), 552.

One gram of isopropylidene bis-(diisopropylidene-D-glucose) was suspended in 100 ml. of *N* hydrochloric acid and hydrolyzed at 90° for two hours. The acetone liberated was passed into a cold dilute acetic acid solution of *p*-nitrophenylhydrazine where it formed a precipitate of acetone *p*-nitrophenylhydrazone (0.15 g.); m.p. 148° (lit.[14] m.p. 148–148.5°). The melting point of a mixture of this substance with an authentic sample of acetone *p*-nitrophenylhydrazone (m.p. 148°) was not depressed.

The acid hydrolysate contained 0.62 g. of D-glucose (97% of theoretical for complete hydrolysis). It was neutralized with dilute sodium hydroxide solution and concentrated *in vacuo* to about 40 ml. A solution of 5 g. of phenylhydrazine in 10 ml. of glacial acetic acid was added and the mixture heated at 100° for three hours. D-Glucosazone crystallized from the cooled mixture and, after recrystallization from dilute ethanol, melted at 200°. The melting point of a mixture of the product with an authentic specimen of D-glucosazone[15] (m.p. 204°) was 200°.

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[14] E. Bamberger and H. Sternitski, *Ber.*, **26**, 1306 (1893).

[15] E. Fischer, *ibid.*, **41**, 73 (1908).