alcohol, and then adding a small quantity of sodium hydroxide solution. On shaking in the cold, the solid soon dissolves. It separates again on diluting the solution with water or on neutralizing with glacial acetic acid. A similar solubility of phthaloylnaphthalene was noted first by one of us[4] and later by Rieche.[5] A theoretical interpretation of the phenomenon will be presented in a later paper.

## Summary

A product previously obtained by the oxidation of 1,8-phthaloyl-2-naphthol has been reëxamined and the structure originally assigned has been confirmed. Since it is difficult to account for the formation of this oxidation product on the basis of the structure indicated for the starting material, a new and reliable synthesis was developed. This synthesis establishes the correctness of the formula, and, at the same time, affords a general method of obtaining derivatives of an interesting type of aromatic hydrocarbon for which we have suggested the name "pleiadene."

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RECEIVED MARCH 10, 1933
PUBLISHED JULY 6, 1933

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

# Studies in the Ketone Sugar Series. III. Open-Chain Derivatives of Fructose and Turanose*

BY EUGENE PACSU AND FRANK V. RICH

In Part I[1] of this series it has been shown that on direct acetylation of turanose by acetic anhydride in the presence of zinc chloride at room temperature, three octaacetates are obtained. One of these behaves in many respects differently from the other two and also from the fourth octaacetate obtained from the stable bromoacetylturanose. A colorless acetone solution of this isomer, described in Part I as "the third octaacetate," becomes yellow on the addition of a few drops of dilute sodium hydroxide solution. After neutralization with dilute sulfuric acid, the color disappears and the solution will reduce potassium permanganate solution. None of the other known octaacetates shows such behavior when submitted to the same test. Furthermore, this same octaacetylturanose can be recovered unchanged after treatment with hydrogen bromide dissolved in glacial acetic acid. This observation led to the assumption that the octaacetate contains no active acetoxyl group and that it is a derivative of the open-chain fructose with a free ketone group. It was found that this compound could be prepared from β-heptaacetylturanose by acetylating with acetic anhydride and zinc chloride. In Part II[2] it has been shown that the β-heptaacetate very probably contains an "ortho-ester" structure. Since

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* The conclusions referring to the fructose derivatives have already been reported [Pacsu and Rich, THIS JOURNAL, **54**, 1697 (1932)].

(1) Pacsu, THIS JOURNAL, **54**, 3649 (1932).

(2) Pacsu, *ibid.*, **55**, 2451 (1933).

the mechanism of the acetylation with acetic anhydride and zinc chloride is unknown, it is impossible to advance a theory which would explain the tautomeric change that must take place when the starting material is an orthoacetic acid derivative.

In order to prove the hypothesis that the "third octaacetylturanose" is a derivative of the open-chain fructose, an attempt was made to combine the free ketone group of the molecule with hydroxylamine in alcoholic solution. Although there was a definite change in the rotation of the reaction mixture from 7.22 to 6.45°, it was not possible to isolate any condensation product.

If this octaacetate contains a free ketone group, on reduction a secondary carbinol group should be formed. Reduction was effected by the use of hydrogen in the presence of a platinum catalyst. After twenty-seven hours the substance lost its ability to reduce Fehling's solution. On working up the reaction mixture, a sirup was obtained, which contained two epimeric alcohols, since the carbonyl group had been made asymmetric by the reduction. After acetylation of the sirup, there was obtained a mixture of nonaacetyl-5-glucosidosorbitol and nonaacetyl-5-glucosidomannitol. It was possible to separate these two compounds by fractional crystallizations. To establish its structure, the nonaacetylglucosidosorbitol was converted into hexaacetylsorbitol by hydrolysis and re-acetylation.

From the above results it is obvious that the third octaacetylturanose must contain a free ketone group and should be named octaacetyl-*keto*-turanose. This is the first case in which the formation of a straight chain derivative by the direct acetylation of a sugar, has been observed.

Hudson and Brauns[3] have prepared a positively rotating pentaacetylfructose by the acetylation of the crystalline tetraacetate in the presence of zinc chloride. Since this compound is different from the $\beta$-pentaacetate obtained from the same tetraacetate by using sulfuric acid with acetic anhydride for the acetylation, it was assigned the $\alpha$-configuration. On the assumption that the two known chloroacetylfructoses constitute an $\alpha,\beta$-pair, Hudson[4] calculated the rotation of the $\alpha$-pentaacetate. Since his result did not agree with the observed rotation, he concluded that the pentaacetate probably is not the true $\alpha$-form.

In their paper, Hudson and Brauns state that this compound does not react with hydrogen bromide dissolved in glacial acetic acid. In view of this fact, it appeared probable that it differs structurally from the $\beta$-compound and that it might be a derivative of the open-chain fructose, containing a free ketone group. Experiments confirm this.

By the same method as that used on octaacetyl-*keto*-turanose, the fructose pentaacetate was reduced in six hours to a product which would not reduce Fehling's solution. After acetylation of the free hydroxyl group

(3) Hudson and Brauns, THIS JOURNAL, **37**, 2736 (1915).

(4) Hudson, *ibid.*, **46**, 477 (1924).

formed by the reduction of the ketone, it was possible to isolate the two well-known compounds, hexaacetyl-*d*-sorbitol and hexaacetyl-*d*-mannitol. Authentic samples of each of these substances, prepared by the acetylation of *d*-sorbitol and *d*-mannitol, were identical in melting points and rotations with the respective acetates obtained from the reduction. This experiment indicates that this fructose pentaacetate must possess a free ketone group, in contrast to the β-pentaacetate, which, under similar conditions, could not be reduced. Therefore, the pentaacetate containing the free ketone group should be named pentaacetyl-*keto*-fructose.

It is noteworthy that both octaacetyl-*keto*-turanose and pentaacetyl-*keto*-fructose were obtained by the zinc chloride method of acetylation from β-heptaacetylturanose and β-tetraacetylfructose, respectively, although heptaacetylturanose seems to possess an ortho-ester structure, while a normal ring structure is assumed for tetraacetylfructose.

"α-Chlorotetraacetylfructose" prepared from the β-tetraacetate of this sugar by the action of phosphorus pentachloride, is described by Brauns[5] as a very stable derivative in which the chlorine atom is so firmly bound that the compound fails to give a test for halogen with alcoholic silver nitrate. It has been found that an acetic anhydride solution of this chloro compound will not react with silver acetate in the cold. On refluxing, a silver mirror is deposited on the wall of the flask but no silver chloride is formed. This behavior is in strong contrast to that of the very unstable β-chlorotetraacetylfructose, which, in the cold, reacts with silver acetate to give an almost quantitative yield of the β-pentaacetate. Although these two compounds have been assumed to constitute an α,β-pair, it does not seem probable that a stereochemical difference would account for such a profound dissimilarity in behavior.

On investigation of this problem it was found that a colorless acetone solution of the stable chloro compound becomes yellow on the addition of dilute alkali. The color disappears after neutralization with sulfuric acid and then the solution will reduce potassium permanganate solution. This indicates that the compound possesses a structure similar to that of pentaacetyl-*keto*-fructose, and, therefore, the chlorine cannot be attached to the second carbon. Since the halogen behaves like a stable primary chlorine atom, it seems probable that it is bound to one of the terminal carbon atoms. According to Brauns, the de-acetylated compound, containing chlorine, forms an osazone which melts at 173°, and so the chlorine atom must be attached to the sixth carbon and not to the first.

To prove that a free ketone group is present in the "α-chlorotetraacetylfructose," an attempt was made to reduce it by the method used on octaacetyl-*keto*-turanose. After twenty hours the solution would not reduce

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[5] Brauns, THIS JOURNAL, **42**, 1846 (1920). This compound was originally named, by Brauns, β-chlorotetraacetylfructose. Subsequently it was designated as α-chlorotetraacetylfructose at the suggestion of Hudson [*ibid.*, **46**, 477 (1924)].

Fehling's solution. A sirup was obtained which should be a mixture of 1,3,4,5-tetraacetyl-6-chloro-sorbitol and 1,3,4,5-tetraacetyl-6-chloro-mannitol. Hydrolysis with alkali in the cold showed that four acetyls and one chlorine could be removed from the molecule. After acetylation of the sirup, hydrolysis indicated the presence of five acetyls and one chlorine atom. Using the same method of analysis on the original chloroacetylfructose, the four acetyls and only about 30% of the chlorine were removed. Brauns stated that "the quantitative estimation of acetyl showed that only very small amounts of chlorine are split off by alkali at 0°." This difference in ease of removal of the chlorine before and after reduction indicates that the formation of a 2,6 oxygen ring by the elimination of hydrogen chloride is preferred to the formation of a 1,6 or 3,6 ring. The formation of a ring is proved by the fact that on re-acetylation of the hydrolyzed sirup, a product is obtained which contains only four acetyl groups. This is a mixture very probably consisting of the acetylated polygalitol (2,6-anhydro-mannitol) prepared by Sato,[6] and the corresponding 2,6-anhydro-sorbitol derivative. It has not been possible to separate these two substances.

Experimental evidence, therefore, indicates that "$\alpha$-chlorotetraacetylfructose" contains a free ketone group and a primary chlorine atom and should be named 6-chlorotetraacetyl-*keto*-fructose.

Since it has been shown that the two pentaacetates and the two chloroacetates of fructose do not represent real $\alpha,\beta$-stereoisomeric pairs, calculations made on the basis that these substances constitute such pairs are invalid. Austin[7] has used the rotations of the pentaacetates to calculate the value of the end asymmetric carbon atom in the acetylated ketone sugars. He found that the value for $A_{\mathrm{AC}}$ is much greater for the derivatives of fructose than for the corresponding derivatives of the aldoses and stated that, "the reason for these differences between the corresponding coefficients of fructose and the aldoses is not definitely known." It is now apparent that such a calculation is not permissible since the two fructose pentaacetates are structural isomers and not $\alpha,\beta$-stereoisomers.

## Experimental Part

**Reduction of Octaacetyl-*keto*-turanose (the "Third Octaacetate").**—*Five grams of* octaacetyl-*keto*-turanose, prepared according to directions in Part I of this series, was dissolved in 150 cc. of absolute alcohol and 0.1 g. of platinum catalyst[8] was added to the solution. The mixture was shaken with hydrogen at four atmospheres absolute pressure until, after twenty-seven hours, a sample of the solution would not reduce Fehling's solution. After filtering off the catalyst, the alcohol was removed by distillation under reduced pressure. A solution of the residue in 20 cc. of acetic anhydride containing 0.5

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[6] Shinoda, S. Sato and D. Sato, *Ber.*, **65**, 1219 (1932).

[7] Austin, THIS JOURNAL, **54**, 1925 (1932).

[8] Adams, Voorhees and Shriner, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1928, Vol. VIII, p. 92.

g. of fused zinc chloride was heated on the steam-bath for an hour and then poured into ice water. A sirup separated, which soon turned into a solid mass and was filtered off. The filtrate was neutralized with solid sodium bicarbonate and extracted with chloroform. This extract, combined with a chloroform solution of the solid that first separated, was washed with water, dried with calcium chloride and evaporated under reduced pressure to a sirup, which was then dissolved in 95% alcohol. On cooling the solution, 4.3 g. of crystalline material was obtained. By repeated fractional crystallizations from 95% alcohol, this solid was separated into two compounds, which were unchanged in melting points and specific rotations by further recrystallizations. The nonaacetyl-5-glucosidosorbitol melted at 116.5° and showed $[\alpha]^{20}_{\mathrm{D}}$ 70.9°, $[\alpha]^{20}_{\mathrm{C}}$ 56.2°, $[\alpha]^{20}_{\mathrm{HgI}}$ 83.4° (0.2114 g. substance, 25 cc. chloroform solution, 2-dm. tube; rotations 1.20, 0.95 and 1.41° to the right, respectively). The acetyl content was found to be 53.5%, which agrees with the calculated value of 53.6% for $C_{12}H_{15}O_{11}(CH_3CO)_9$. The nonaacetyl-5-glucosidomannitol melted at 142° and showed $[\alpha]^{20}_{\mathrm{D}}$ 89.3°, $[\alpha]^{20}_{\mathrm{C}}$ 70.6°, $[\alpha]^{20}_{\mathrm{HgI}}$ 105.0° (0.2072 g. substance, 25 cc. chloroform solution, 2-dm. tube; rotations 1.48, 1.17 and 1.74° to the right, respectively). The acetyl content was 52.8% in comparison with 53.6% for $C_{12}H_{15}O_{11}(CH_3CO)_9$.

**Preparation of Hexaacetyl-*d*-sorbitol from Nonaacetyl-5-glucosido-*d*-sorbitol.**—Three grams of nonaacetylglucosidosorbitol in methyl alcohol was de-acetylated according to the method of Zemplén and Pacsu.[9] To remove the glucosido group, the product was dissolved in 50 cc. of 5% sulfuric acid and heated on the steam-bath for four hours. Ability to reduce Fehling's solution was developed during that period. The acid was neutralized with solid calcium carbonate and yeast was added to ferment the glucose. The mixture was kept at about 40° until, after twenty hours, the solution would no longer reduce Fehling's solution. After filtering off the solid material, the filtrate was evaporated to a sirup. The residue was extracted with 20 cc. of hot alcohol, filtered, and the alcohol removed under reduced pressure. The sirup thus obtained was mixed with 20 cc. of acetic anhydride containing 2 g. of anhydrous sodium acetate, and heated on the steam-bath for an hour. On pouring into ice water, a small amount of solid material separated. The water was neutralized with solid sodium bicarbonate and extracted with chloroform. The chloroform solution was dried with calcium chloride and evaporated to a sirup. Pure hexaacetyl-*d*-sorbitol crystallized from an alcoholic solution of the sirup. This substance melted at 98° and showed $[\alpha]^{20}_{\mathrm{D}}$ 10.0°, $[\alpha]^{20}_{\mathrm{C}}$ 7.7°, $[\alpha]^{20}_{\mathrm{HgI}}$ 11.6° (0.2198 g. substance, 10 cc. chloroform solution, 2-dm. tube; rotations 0.44 0.34, 0.51°, to the right, respectively). These values agree with those of hexaacetylsorbitol obtained by the acetylation of *d*-sorbitol.

**Preparation of Tetraacetylfructose.**—By modification of the method of Hudson and Brauns, a better yield of tetraacetylfructose was obtained. Sixty-six grams of finely powdered and sieved fructose was added to a solution of 6 g. of anhydrous zinc chloride in 340 cc. of acetic anhydride, cooled by an ice and salt mixture. During sixteen hours of stirring at 0°, the fructose gradually disappeared and small needles crystallized from the solution. Then the mixture was stirred at −15° for one hour and filtered with suction. The crystals were not washed but were transferred to a desiccator and dried under 1 mm. pressure over sodium hydroxide until, after one or two days, the smell of acetic anhydride disappeared. Forty-seven grams of dry material was obtained. On neutralizing the mother liquor with solid sodium bicarbonate, a half solid, sticky mass separated. Its chloroform solution was washed three times with water, dried with calcium chloride, and concentrated under reduced pressure to a thin sirup. This was dissolved in ether, poured into a crystallizing dish, and allowed to stand in a desiccator. Thirteen grams of the tetraacetate crystallized. This was combined with the first crop, dissolved in chloroform, filtered and evaporated under reduced pressure to a thin sirup.

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(9) Zemplén and Pacsu, *Ber.*, **62**, 1613 (1929).

This substance was dissolved in ether and the solution was placed in the ice box. Pure tetraacetylfructose crystallized; yield, 57 g. or 45%. The rotation of the tetraacetate in pyridine was found to be $[\alpha]^{20}_{D}$ −101.6°. This value changed in eighteen hours to $[\alpha]^{20}_{D}$ −100.5°. After several days the rotation became constant at $[\alpha]^{20}_{D}$ −99.9° (1.2467 g. substance, 25 cc. pyridine solution, 2-dm. tube; rotations, 10.13, 10.02 and 9.96° to the left, respectively). For measuring the rotation in benzene, a solution was prepared by heating. The solution was cooled rapidly and a reading was taken before the substance crystallized. The specific rotation was $[\alpha]^{20}_{D}$ −97.2° (1.5596 g. substance, 25 cc. benzene solution, 2-dm. tube; rotation, 12.13° to the left). A water solution exhibited no mutarotation and gave a specific rotation $[\alpha]^{20}_{D}$ −74.4° (0.2137 g. substance, 25 cc. water solution, 2-dm. tube; rotation, 1.27° to the left).

**Reduction of Pentaacetyl-*keto*-fructose.**—The "α-pentaacetylfructose" of Hudson and Brauns showed $[\alpha]^{20}_{D}$ 34.96°, $[\alpha]^{20}_{C}$ 25.7°, $[\alpha]^{20}_{HgI}$ 42.3° (0.2187 g. substance, 25 cc. chloroform solution, 2-dm. tube; rotations, 0.61, 0.45, 0.74° to the right, respectively). Five grams of the compound was dissolved in 150 cc. of ethyl alcohol and 0.1 g. of platinum catalyst was added to the solution. The method of reduction was the same as that used on octaacetyl-*keto*-turanose. After six hours the reduction was complete since the solution would no longer reduce Fehling's solution. A sirup was obtained which was found to have an acetyl content of 53.5%. The calculated value for a mixture of pentaacetylsorbitol and pentaacetylmannitol is 54.8%. After acetylation of the sirup, there was obtained 4.5 g. of crystalline material, which, by repeated fractional crystallizations from alcohol, was separated into hexaacetyl-*d*-sorbitol and hexaacetyl-*d*-mannitol. The hexaacetylsorbitol melted at 99° and showed $[\alpha]^{20}_{D}$ 9.9°, $[\alpha]^{20}_{C}$ 7.9°, $[\alpha]^{20}_{Hg}$ 11.9° (0.2516 g. substance, 25 cc. chloroform solution, 2-dm. tube; rotations, 0.20, 0.16, 0.24° to the right, respectively). Bertrand[10] states that for a 5% chloroform solution the rotation is $[\alpha]^{20}_{D}$ 9.33°. The melting point according to Tutin[11] is 99°. Hexaacetylsorbitol, prepared by the acetylation of *d*-sorbitol, was found to melt at 99° and to have $[\alpha]^{20}_{D}$ 10.0°, $[\alpha]^{20}_{C}$ 7.8°, $[\alpha]^{20}_{HgI}$ 12.2° (0.2250 g. substance, 25 cc. chloroform solution, 2-dm. tube; rotations, 0.18, 0.14, 0.22° to the right, respectively). Hexaacetylmannitol, obtained from the reduction of the fructose pentaacetate, melted at 122° and showed $[\alpha]^{20}_{D}$ 24.4°, $[\alpha]^{20}_{C}$ 19.1°, $[\alpha]^{20}_{HgI}$ 29.1° (0.2362 g. substance, 25 cc. chloroform solution, 2-dm. tube; rotations, 0.46, 0.36, 0.55° to the right, respectively). The rotations of a benzene solution were measured, giving the values, $[\alpha]^{20}_{D}$ 17.8°, $[\alpha]^{20}_{HgI}$ 21.2° (0.2178 g. substance, 25 cc. benzene solution, 2-dm. tube; rotations, 0.31 and 0.37° to the right, respectively). Patterson and Todd[12] record a melting point of 126° and the rotations, $[\alpha]^{22}_{5790}$ 18.22°, and $[\alpha]^{22}_{5461}$ 20.55° in benzene. Hexaacetylmannitol, prepared by the acetylation of *d*-mannitol, was found to melt at 122° and to have $[\alpha]^{20}_{D}$ 25.0°, $[\alpha]^{20}_{C}$ 20.0°, $[\alpha]^{20}_{HgI}$ 29.6° (0.2496 g. substance, 25 cc. chloroform solution, 2-dm. tube; rotations, 0.50, 0.40, 0.59° to the right, respectively). The acetyl contents of hexaacetylsorbitol and hexaacetylmannitol were found to be 59.9 and 59.7%, respectively, which agree with the theoretical value of 59.4 for $C_6H_8O_6(CH_3CO)_6$.

**Attempted Reduction of β-Pentaacetylfructose.**—A 1.6854-g. sample of β-pentaacetylfructose, prepared according to the method of Hudson and Brauns, was dissolved in 100 cc. of alcohol and 0.1 g. of platinum catalyst was added to the solution. During thirty-two hours of shaking with hydrogen at four atmospheres absolute pressure, the rotation of the solution in a 2-dm. tube changed from $\alpha_D$ −3.69 to $\alpha_D$ −3.14°. By evaporating the solvent under reduced pressure, 0.9 g. of crystalline β-pentaacetylfructose was recovered.

**Reaction of β-Chlorotetraacetylfructose with Silver Acetate.**—A solution of 12 g.

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(10) Bertrand, *Ann. chim.*, [8] **3**, 243 (1904).

(11) Tutin, *Biochem. J.*, **19**, 416 (1925).

(12) Patterson and Todd, *J. Chem. Soc.*, 2876 (1929).

of β-chloroacetylfructose in 60 cc. of acetic anhydride was shaken with 8.5 g. of silver acetate. The mixture was heated on the water-bath for fifteen minutes. After filtration with charcoal, the acetic anhydride solution was worked up in the usual way; yield 10 g. of crystalline β-pentaacetate, m. p. 108°, $[\alpha]_D^{20}$ $-119.8°$ in chloroform solution. These values agree with those reported by Hudson and Brauns for β-pentaacetylfructose.

**Hydrolysis of 6-Chlorotetraacetyl-*keto*-fructose ("α-Chloroacetylfructose").**—A sample of 6-chloroacetylfructose, which was prepared from the tetraacetate by the method of Brauns, was dissolved in 10 cc. of acetone. The solution was cooled to 0°, 75 cc. of 0.1 *N* alkali was added, drop by drop, and the solution was kept at low temperature for three hours. By this method, 0.2520 g. of the chloroacetate was found to use 30.4 cc. of decinormal alkali in comparison with 34.4 cc. required by theory to remove four acetyl groups and one chlorine atom. A halogen determination on the titrated solution showed that only 3.8% Cl had been removed from the compound although it contains 9.7% Cl.

**Reduction of 6-Chlorotetraacetyl-*keto*-fructose.**—Four grams of 6-chlorotetraacetylfructose was dissolved in 100 cc. of alcohol and 0.2 g. of platinum catalyst was added. After shaking with hydrogen at four atmospheres absolute pressure for twenty-four hours, the solution would not reduce Fehling's solution. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to a sirup. On the hydrolysis of 0.2503 g. of the sirup by the method employed with 6-chlorotetraacetyl-*keto*-fructose, 32.8 cc. of decinormal alkali was used, whereas 33.9 cc. is required by theory for the removal of four acetyl groups and the chlorine atom. A halogen determination on the titrated solution indicated that 10.7% Cl had been removed from the original sample by the alkali. A mixture of 6-chlorotetraacetylsorbitol and 6-chlorotetraacetylmannitol contains 9.7% Cl. The product of the reduction was acetylated with zinc chloride and acetic anhydride, to give a sirup, 0.2219 g. of which used 32.4 cc. of 0.1 *N* sodium hydroxide solution for hydrolysis at 0°. To remove five acetyl groups and one chlorine atom, 32.4 cc. of decinormal alkali is required by theory for $C_6H_8O_5Cl(CH_3CO)_5$. The chlorine content was found to agree with the calculated value. One gram of this sirup was hydrolyzed by dilute sodium hydroxide solution at 0° and then re-acetylated by the zinc chloride method. A 0.2370-g. sample of the sirup thus obtained required 28.0 cc. of 0.1 *N* sodium hydroxide solution for the removal of the acetyl groups whereas the value calculated for a mixture of anhydro-tetraacetylsorbitol and anhydro-tetraacetylmannitol is 28.5 cc. A mixture of hexaacetylsorbitol and hexaacetylmannitol would require 32.8 cc. of decinormal alkali.

## Summary

1. The "third turanose octaacetate" has been shown to be a derivative of the open-chain fructose since, on reduction and subsequent acetylation, crystalline nonaacetyl-5-glucosido-*d*-mannitol and nonaacetyl-5-glucosido-*d*-sorbitol are obtained.

2. An improved method for the preparation of normal tetraacetylfructose has been described.

3. "α-Pentaacetylfructose" and "α-chlorotetraacetylfructose" have been shown to be derivatives of the open-chain fructose and, therefore, calculations based on the assumption that the two pentaacetates and the two chloroacetates of fructose constitute α,β-stereoisomeric pairs, are invalid.

PRINCETON, NEW JERSEY

RECEIVED MARCH 15, 1933
PUBLISHED JULY 6, 1933