[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Keto-Fructose Pentaacetate

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This Laboratory has reported[1] the synthesis of a number of crystalline open chain aldose acetates by the hydrolysis of acetylated thioacetals with mercuric chloride under controlled conditions. The method employed was a modification of the one first used by Levene and Meyer[2] in obtaining corresponding methylated compounds. A thioacetal of fructose has hitherto not been available but we wish now to report the synthesis of the crystalline ethylthioacetal of this sugar. The crystalline pentaacetate of this thioacetal was very readily hydrolyzed by mercuric chloride and produced as the open chain keto-fructose pentaacetate the previously known "α"-fructose pentaacetate obtained nearly twenty years ago by Hudson and Brauns[3] by the acetylation of β-fructose tetraacetate with zinc chloride and acetic anhydride. β-Fructose tetraacetate undoubtedly has a ring structure, which then must open on further acetylation in the presence of zinc chloride. We have shown, however, that the β ring pentaacetate is also formed in this reaction, a point which Hudson and Brauns suspected but did not prove. Increasing the concentration of the tetraacetate favors the formation of the ring pentaacetate, which (or the true α form) should be the normal product of the reaction.

The assignment of an open chain structure to the second or "α" pentaacetate of fructose is a confirmation of the brilliant work of Pacsu and Rich.[4] These workers were able to reduce catalytically this substance to a sirupy mixture of partially acetylated epimeric alcohols and identified these after further acetylation.

Keto-fructose pentaacetate shows a remarkable lack of carbonyl reactivity when contrasted with the highly reactive open chain aldose acetates. This is perhaps to be expected on the basis of the well-known lesser reactivity of ketones as compared with aldehydes. No reaction product could be obtained with hydroxylamine or semicarbazide and no mutarotation was observed in methanol.

Fructose ethylthioacetal pentaacetate was obtained in this work by reaction of the second ("α") pentaacetate of fructose with dry ethyl mercaptan in the presence of zinc chloride and a reaction-insoluble dehydrating agent. Removal of the acetate groups in this compound produced the fructose ethylthioacetal in crystalline condition. This thioacetal is very sensitive to acidity. For example, it loses ethyl mercaptan when dried over an acid dehydrating agent. Re-acetylation of the thioacetal regenerated the same pentaacetate.

When the same thioacetal formation conditions were applied to the aldehydo pentaacetates of glucose and galactose the ethylthioacetal pentaacetates of these sugars were readily formed. β-Fructose pentaacetate underwent reaction under these conditions with replacement of the glycosidic acetate and the smooth formation of crystalline β-thioethyl fructoside tetraacetate. Removal of the acetate groups from the latter compound produced the β-thioethyl fructoside in crystalline condition and with the remarkably high levorotation of $[\alpha]_D$ −233° in methanol. The above results show that this thioacetal formation reaction can of itself be used as a proof of open chain structure in an acetate when a product containing two ethylmercapto groups is obtained without loss of acetyl groups. A similar method has been used by Brigl and Schinle[5] to prove the open-chain structure of a new crystalline pentabenzoate of fructose by reaction of this substance to form a thioacetal with ethyl mercaptan in chloroform solution containing hydrogen chloride. These conditions are too vigorous for the apparently more sensitive acetates and a repetition of their procedure with the "α"-fructose pentaacetate produced considerable decomposition and yielded a dark colored sirup that could not be brought to crystallization.

It thus appears that the ring structure of fructose opens with surprising ease and probably this will be found to be characteristic of the ketoses in general. It is also very probable that those

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(1) M. L. Wolfrom, THIS JOURNAL, **51**, 2188 (1929); **52**, 2464 (1930); M. L. Wolfrom and Mildred R. Newlin, *ibid.*, **52**, 3619 (1930); **53**, 4379 (1931); M. L. Wolfrom and J. A. Orsino, *ibid.*, **56**, 985 (1934).

(2) P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **69**, 175 (1926).

(3) C. S. Hudson and D. H. Brauns, THIS JOURNAL, **37**, 2736 (1915).

(4) E. Pacsu and F. V. Rich, THIS JOURNAL, **54**, 1697 (1932); **55**, 3018 (1933).

(5) P. Brigl and R. Schinle, *Ber.*, **66**, 325 (1933).

ketoses which do not show mutarotation may have open chain structures.

Experimental

Preparation of β-Fructose Pentaacetate by the Acetylation of β-Fructose Tetraacetate with Zinc Chloride.—In the preparation of keto-fructose pentaacetate according to the method of Hudson and Brauns,[3] the first crop of crystals was generally nearly pure "α" form and the second crop was a mixture with another substance of considerably lower rotatory power, as the above authors noted. After these crops had been removed, the mother liquors from about 80 g. of the β-tetraacetate were combined and concentrated to a thick sirup containing crystals. These were removed by the addition of alcohol followed by filtration and were recrystallized from a small amount of absolute alcohol by the addition of ether. Three grams of the characteristic crystals of β-fructose pentaacetate was obtained, m. p. 108° (unchanged on admixture with known β-fructose pentaacetate of m. p. 108°).

In one experiment in which the amount of acetic anhydride used was greatly decreased, the β-form was the only substance that could be crystallized. Five grams of β-fructose tetraacetate and 1 g. of freshly fused zinc chloride were dissolved at room temperature in 20 cc. of acetic anhydride and allowed to stand for twenty-four hours. Considerable darkening developed in the solution. On working up the product according to the procedure of Hudson and Brauns, 0.5 g. of crystals was obtained, m. p. 105°. On recrystallization from ether the melting point was 107–108° (mixed m. p. unchanged) and the rotation in chloroform solution was $[\alpha]^{25}_{D}$ −120°. The constants given for this compound by Hudson and Brauns are m. p. 108–109° and $[\alpha]_D$ −121° ($CHCl_3$).

***d*-Fructose Ethylthioacetal Pentaacetate.**—Eight grams of freshly fused zinc chloride was dissolved in 60 cc. of ethyl mercaptan, previously dried over soluble anhydrite.[6] This solution was cooled in an ice and salt bath and 15 g. of anhydrous sodium sulfate and 20 g. of the "α"-fructose pentaacetate added with shaking. The tube was then sealed and kept in the freezing mixture for three to four hours. At the end of this time the tube was opened and the contents poured into about 150 cc. of a saturated sodium bicarbonate solution. The precipitate formed was filtered and transferred to a beaker for extraction with warm chloroform. The filtrate was also extracted with chloroform and the combined extracts dried and concentrated to a sirup with a stream of air. A small amount of petroleum ether was then added, removed by evaporation with stirring, and the process repeated. After all the chloroform had been removed in this manner a solid mass of crystals was obtained. The substance was recrystallized from ether by the addition of petroleum ether; yield 10.9 g., m. p. 76–78°. After further recrystallization from absolute alcohol, the pure substance melted at 83° and showed a rotation in chloroform of $[\alpha]^{27}_{D}$ +20.0° (*c*, 3.7).[7] The substance crystallized in rectangular plates and showed no reduction toward Fehling solution. It was very soluble in ether, acetone and chloroform and was soluble in hot water, alcohol and hot petroleum ether.

Anal. Calcd. for $(C_2H_5S)_2C_6H_7O_5(OCCH_3)_5$: S, 12.92; acetyl, 10.1 cc. 0.1 *N* NaOH per 100 mg. Found: S, 12.88; acetyl, 10.0 cc.

***d*-Fructose Ethylthioacetal.**—Twelve grams of fructose ethylthioacetal pentaacetate was dissolved in 100 cc. of absolute methanol, cooled in a freezing mixture of ice and salt and a fairly rapid stream of dry ammonia gas passed into the solution for about forty-five minutes. The solution was kept overnight in the ice box and then concentrated to a sirup under reduced pressure at room temperature. The sirup was taken up in methanol and on concentrating this solution to a small volume and adding twice the volume of ether the substance was obtained in crystalline form, filtered and washed with ether; yield, 5.4 g.; m. p. 55–60°. After repeated recrystallizations performed by dissolving in a small amount of methanol and adding twice the volume of ether, the substance melted at 65–67° and the rotation in methanol solution was $[\alpha]^{24}_{D}$ +35.8° (*c*, 4.0).

Fructose ethylthioacetal is soluble in water, alcohol, acetone and warm ether and is practically insoluble in petroleum ether. It is very sensitive to acidity and decomposes when kept in a desiccator over an acid drying agent. For analysis the substance was dried under reduced pressure in an Abderhalden drier at the temperature of boiling chloroform and over a basic absorbent.

Anal. Calcd. for $C_6H_{12}O_5(SC_2H_5)_2$: C, 41.92; H, 7.75; S, 22.40. Found: C, 42.04; H, 8.04; S, 22.24 (Carius).

Re-acetylation of this substance produced the thioacetal acetate previously described. Fructose ethylthioacetal (0.5 g.) was dissolved in 4 cc. of pyridine and 8 cc. of acetic anhydride added with cooling. The solution was kept overnight at room temperature, poured into water and the crystals so obtained recrystallized twice from ether by the addition of petroleum ether; yield, 0.4 g.; m. p. 83° (mixed m. p. unchanged); $[\alpha]^{28}_{D}$ +20.9° (*c*, 3.9, $CHCl_3$).

Preparation of Keto-Fructose Pentaacetate from its Acetylated Thioacetal.—Fructose ethylthioacetal pentaacetate (2.5 g.) was dissolved in 9 cc. of acetone and 5 g. of finely ground cadmium carbonate added. A solution of 5 g. of mercuric chloride in 7 cc. of acetone was then slowly added to the mixture with vigorous mechanical stirring. The reaction was allowed to run at room temperature for fifty minutes with occasional additions of fresh cadmium carbonate and acetone when the mixture became very thick due to the separation of the Et-S-Hg-Cl compound. At the end of this period the mixture was heated at 40° for ten minutes, filtered, the residue washed with acetone and the filtrate concentrated to dryness under reduced pressure in the presence of cadmium carbonate. The residue was extracted with chloroform and the extract concentrated under reduced pressure to a thin sirup. This was dissolved in a small amount of ethyl alcohol, filtered and allowed to crystallize; yield, 0.6 g., m. p. 66°. On recrystallization from alcohol containing a small amount of chloroform the substance melted at 69–70° (mixed m. p. unchanged); $[\alpha]^{31}_{D}$ +35.1° (*c*, 2.8, $CHCl_3$); Hudson and Brauns[3] give the melting point of 70° and $[\alpha]_D$ +35° ($CHCl_3$) for the substance they termed α-fruc-

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[6] W. A. Hammond and J. R. Withrow, *Ind. Eng. Chem.*, **25**, 1112 (1933).

[7] *c* = g. of subs. per 100 cc. of soln.

tose pentaacetate. Therefore the fructose pentaacetate obtained by removing the ethylmercapto groups from fructose ethylthioacetal pentaacetate is identical with the "α"-fructose pentaacetate of Hudson and Brauns.

The substance is not comparable in carbonyl reactivity to the aldehydo-sugar pentaacetates. It showed no mutarotation in methanol. The initial (five minutes) rotation in this solvent was $[\alpha]^{28}_{\mathrm{D}}$ +30° (*c*, 4.5) and this value was unchanged over a period of ninety-six hours, numerous intermediate readings being taken. It showed no tendency to form condensation products with hydroxylamine, semicarbazide or thiosemicarbazide. It did appear to react with phenylhydrazine and substituted phenylhydrazines but as the reaction products were sirups which decomposed readily they were not amenable to thorough investigation.

Preparation of the Ethylthioacetal Pentaacetates of Glucose and Galactose from their Aldehydo Pentaacetates.—Five grams of aldehydo-glucose pentaacetate was treated with ethyl mercaptan and zinc chloride as described under the preparation of fructose ethylthioacetal pentaacetate. The chloroform extract was concentrated under reduced pressure to a sirup and this was crystallized from methanol by the addition of water. After several recrystallizations effected in the same manner, 3.6 g. of product was obtained; m. p. 46–48°; $[\alpha]^{25}_{\mathrm{D}}$ +10.9° (*c*, 3.9, $CHCl_3$). The constants recorded by Wolfrom[1] for this substance are: m. p. 45–47° and $[\alpha]_{\mathrm{D}}$ +11° ($CHCl_3$).

Five grams of aldehydo-galactose pentaacetate ethyl hemi-acetal was treated with ethyl mercaptan and zinc chloride and the product isolated and purified as described above for the aldehydo-glucose pentaacetate; yield, 4.2 g.; m. p. 78–79° (mixed m. p. unchanged); $[\alpha]^{23}_{\mathrm{D}}$ +9.9° (*c*, 4.0, $CHCl_3$). The constants recorded by Wolfrom[1] for this substance are: m. p. 77–78° and $[\alpha]_{\mathrm{D}}$ +9.8° ($CHCl_3$).

β-Ethyl Thiofructoside Tetraacetate.—β-Fructose pentaacetate[8] (31.5 g.) was treated with ethyl mercaptan and zinc chloride as described under the preparation of fructose ethylthioacetal pentaacetate. The chloroform extract was concentrated under reduced pressure to a sirup and this was crystallized from absolute ethyl alcohol; yield, 13.5 g.; m. p. 92–94°. The material was purified in the same manner and the pure substance melted at 96–98° and showed a rotation of $[\alpha]^{22}_{\mathrm{D}}$ −151.9° (*c*, 3.7, $CHCl_3$).

The substance was soluble in acetone, chloroform and hot ethanol and was very slightly soluble in petroleum ether. It showed no reduction toward Fehling solution.

Anal. Calcd. for $(C_2H_5S)C_6H_7O_5(OCCH_3)_4$: S, 8.17; acetyl, 10.19 cc. 0.1 *N* NaOH per 100 mg. Found: S, 8.24; acetyl, 10.06 cc.

β-Ethyl Thiofructoside.—β-Ethyl thiofructoside tetraacetate (5 g.) was de-acetylated with a methanol solution of dry ammonia as described under the preparation of fructose ethylthioacetal pentaacetate. On removal of the methanol and ammonia the substance readily crystallized. After recrystallization from a small amount of absolute ethanol, 2.3 g. of material melting at 140° was obtained. Further recrystallization did not change the melting point and the rotation of the pure substance in methanol solution was $[\alpha]^{26}_{\mathrm{D}}$ −232.9° (*c*, 3.6) without mutarotation.

β-Ethyl thiofructoside crystallizes in large plates and reduces Fehling's solution only after hydrolysis. The latter fact, together with the analytical data, indicates that the compound is a thiofructoside. The substance is soluble in water, hot alcohol and hot acetone and is practically insoluble in chloroform and petroleum ether.

Anal. Calcd. for $C_6H_{11}O_5(SC_2H_5)$: S, 14.30; C, 42.82; H, 7.19. Found: S, 14.12; C, 42.56; H, 7.36.

Summary

1. Fructose ethylthioacetal, β-ethyl thiofructoside and their acetates have been synthesized in pure crystalline condition.

2. Removal of the ethylmercapto groups from fructose ethylthioacetal pentaacetate under controlled conditions produces the "α"-fructose pentaacetate of Hudson and Brauns.

3. A method has been presented for proving the cyclic or non-cyclic nature of a completely acetylated sugar by reaction with ethyl mercaptan under controlled conditions.

4. The work of Pacsu and Rich showing that "α" fructose pentaacetate has an open chain or keto structure, has thus been confirmed by two independent methods.

5. Further acetylation of β-fructose tetraacetate with zinc chloride produces both the β- and keto forms of fructose pentaacetate.

COLUMBUS, OHIO RECEIVED AUGUST 7, 1933

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[8] C. S. Hudson and D. H. Brauns, THIS JOURNAL, **37**, 1283 (1915).