[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

Studies in the Ketone Sugar Series. IV. Preparation of New Methyl- and Ethylfructoside Acetates

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Several years ago Schlubach and Schröter[1] described a new tetraacetyl methylfructoside <2,6>, to which they assigned the α-configuration. In the preparation of this compound from β-acetochlorofructose, the authors employed pyridine and silver nitrate in methyl alcohol solution, since Brauns[2] had previously failed to obtain any definite product from the same starting material by using silver carbonate and methyl alcohol. In contrast to the observation[3] that β-acetochloroglucose in methyl alcohol solution isomerizes to α-acetochloroglucose during the slow process of glycoside formation, giving therefore a mixture of α- and β-methylglucoside, Schlubach and Schröter assumed that their procedure with consequent instantaneous reaction gave only the α-fructoside. In view of the fact that the latter compound, isolated from the sirupy reaction product, amounted to only 16% of the theoretical yield, the uniformity of the reaction seemed doubtful. Indeed, investigations in this Laboratory indicate that the replacement of the chlorine atom in β-acetochlorofructose by a methoxyl group is not the simple exchange reaction which usually occurs in comparable cases in the aldose series. The sirupy reaction product obtained by repeating Brauns' experiment was found to consist of about 2% of β-tetraacetylfructose, 34% of Schlubach's tetraacetylmethylfructoside and 64% of a new tetraacetyl-β-methylfructoside <2,6> possessing "orthoester" structure. When Schlubach's procedure was followed, the percentage of the same products was 2, 18 and 80, respectively, indicating that as far as the yield of Schlubach's fructoside is concerned, the use of silver nitrate and pyridine is less satisfactory than that of silver carbonate.

The new methylfructoside tetraacetate possesses all the characteristic properties of glycosides with orthoester structure.[4] Thus, on treatment with cold or hot alkali, only three of the four acetyl groups can be removed with formation of β-methylfructoside (3)-monoacetate with orthoester structure. Furthermore, the methoxyl group is easily removed by acid hydrolysis. Even in neutral aqueous alcoholic solution the loss of the methoxyl group occurs within a comparatively short time, and pure β-fructose tetraacetate <2,6> can be isolated from the solution. The same change takes place very rapidly on heating the orthoester with distilled water. This behavior provides a very convenient means of isolating Schlubach's compound. The original sirup is heated with water until a clear solution results, which, on cooling, deposits the brilliant, diamond-shaped crystals of Schlubach's fructoside, while the mother liquor contains a large amount of pure β-tetraacetylfructose <2,6> arising through hydrolysis of the unstable orthoester.

Starting from β-acetochlorofructose, and using absolute ethyl alcohol and silver oxide, a new crystalline ethylfructoside tetraacetate <2,6> with m. p. 103–104°, and $[\alpha]^{20}D$ 51.6° in chloroform, was obtained in about 7% yield. This reaction produced again a large quantity (90%) of a sirup, which was found to be a new β-ethylfructoside tetraacetate <2,6> with orthoester structure.

The easy formation of these orthoesters from β-acetochlorofructose is noteworthy in many respects. First, it shows that a normal acetohalogenose may give rise to "abnormal" products, the orthoesters, in such quantity that the reaction yielding the latter substances appears to be the normal one. Second, it indicates that for the formation of orthoesters no congestion of hydroxyl groups on one side of the six-atom ring is necessary, and, therefore, the reaction is not restricted to sugars of the type of β-mannose, -rhamnose and -lyxose.[5] Third, it suggests that the use of pyridine or quinoline instead of silver carbonate or oxide is not essential for orthoester formation.[6] In fact, the former reagents are less satisfactory, since their customary removal with excess of mineral acid may result in a considerable, if not complete, loss of the orthoesters, by the exceed-

(1) Schlubach and Schröter, *Ber.*, **61**, 1216 (1928).
(2) Brauns, THIS JOURNAL, **42**, 1849 (1920).
(3) Schlubach, Stadler and Wolf, *Ber.*, **61**, 287 (1928).
(4) (a) Freudenberg, *Naturwiss.*, **18**, 393 (1930); (b) Freudenberg and Scholz, *Ber.*, **63**, 1969 (1930); (c) Bott, Haworth and Hirst, *J. Chem. Soc.*, 1395 (1930); (d) Haworth, Hirst and Samuels, *ibid.*, 2861 (1931).
(5) Haworth, "Rapports sur les Hydrates de Carbone," Dixième Conférence de l'Union Internationale de Chimie, Liége, 1930.
(6) Bott, Haworth and Hirst, *J. Chem. Soc.*, 1399 (1930).

ingly rapid hydrolysis of these substances in acid medium. Finally, it is to be pointed out that the assignment of the α-configuration by Schlubach to his crystalline product was made in the belief that β-acetochlorofructose gave rise exclusively to α-methylfructoside tetraacetate, just as α-acetohalogenoses, in similar exchange reactions, usually yield only the β-methylglycosides through Walden inversion. In view of the above results it appears desirable to prove the α-configuration of Schlubach's fructoside as well as that of the new crystalline ethylfructoside tetraacetate by some independent method.

It is interesting to note that all the known glycosides with orthoester structure have been obtained from normal acetohalogenoses except those of maltose[7] and turanose,[8] which were prepared from acetohalogenoses, themselves possessing orthoester structure.

Experimental Part

Preparation of β-Acetochlorofructose <2,6>.—This substance was prepared by the method of Brauns[9] with the exception that the chloroform solution was evaporated under diminished pressure instead of passing a current of air over its surface in an open dish. By this slight modification contamination of the water-sensitive product with condensed moisture of the air formed by the rapid evaporation of the solvent can be avoided. The absolute ether solution of the sirupy residue at 0° deposited large crystals of the chloro compound, which could be kept for weeks without decomposition. Melting point and specific rotation agreed with those recorded by Brauns. In absolute pyridine solution, the substance showed $[\alpha]^{20}D$ −150.4° (1.1284 g. in 25 cc. of pyridine solution rotated 13.58° to the left in a 2-dm. tube), and this value remained constant for two days. This is very striking, since acetohalogenoses as a rule exhibit a strong and rapid change of rotation in this solvent.

Reaction of β-Chloroacetylfructose <2,6> with Methyl Alcohol.—(1) The laborious method of Schlubach and Schröter[1] was simplified and the following procedure was adopted. To the clear solution of 17 g. (0.1 mole) of silver nitrate in 150 cc. of absolute methyl alcohol containing 8.2 g. (1/9.6 mole) of absolute pyridine there was added 36.7 g. (0.1 mole) of β-chloroacetylfructose dissolved in 250 cc. absolute ether. A mixture of silver chloride and pyridine nitrate precipitated immediately and was removed by filtration. Then the filtrate was concentrated *in vacuo* to a thick mass which was extracted with benzene. In order to remove the slight amount of β-tetraacetylfructose formed in the reaction, the benzene solution was shaken out about twelve times, with 30 cc. of water, until the last water extract did not reduce Fehling's solution. From the chloroform extractions of the united water layers 0.7 g. of pure β-tetraacetylfructose <2,6> was isolated. The benzene solution was dried with calcium chloride and evaporated under reduced pressure to a colorless, thick sirup, which showed no action toward Fehling's solution. It consisted of a mixture of Schlubach's fructoside and the new isomeride possessing orthoester structure. (2) A mixture of 50 g. of commercial silver carbonate or oxide and 38 g. of β-chloroacetylfructose in 150 cc. of absolute methyl alcohol was shaken at room temperature for two hours, then at the boiling point of the alcohol for fifteen minutes. After filtration, the solution was concentrated *in vacuo* to a thick sirup which was taken up in benzene, the solution filtered through activated carbon, and treated as before with water, to eliminate β-tetraacetylfructose (0.8 g.). The sirup obtained by concentration *in vacuo* of the dried benzene solution was devoid of action toward Fehling's solution.

Isolation and Properties of β-Methylfructoside Tetraacetate <2,6> with Orthoester Structure.—A complete separation of the new orthoester from the accompanying fructoside of Schlubach could not be accomplished, because the solubilities of the isomers do not differ sufficiently in the various solvents. The best result was attained by seeding the absolute ether solution of the above purified sirup with Schlubach's fructoside, and keeping it at 0° for several days, then at −5° for one week. During this time most of Schlubach's fructoside crystallized from the solution and was removed by filtration. From the filtrate, on concentration *in vacuo*, a colorless, glassy mass was obtained, which consisted of the new orthoester. It showed $[\alpha]^{20}D$ −13.6° in chloroform solution (0.7068 g. of substance, 25 cc. of solution, 2-dm. tube; rotation 0.77° to the left). The product was very soluble in most organic solvents except petroleum ether, and it did not reduce Fehling's solution. In an acetyl estimation the quantity of acetic acid obtained corresponded to the quantity calculated by assuming the hydrolysis of only three of the four acetyl groups; 0.5560 g. of the substance required 47.3 cc. of decinormal alkali, while the values calculated for the hydrolysis of three and four acetyl groups are 46.05 cc. and 61.4 cc., respectively. However, when the substance had previously been treated with dilute acid, all the four acetyl groups could be removed; 0.5365 g. of the substance was dissolved in a mixture of 10 cc. acetone and 10 cc. of distilled water, and 10 cc. of decinormal hydrochloric acid was added to the solution. After standing half an hour at room temperature, the acid solution was neutralized, after which it required 58.0 cc. of decinormal alkali, while the values calculated for the hydrolysis of three and four acetyls are 44.4 cc. and 59.2 cc., respectively.

Preparation of (3)-Monoacetyl-β-methylfructoside <2,6> with Orthoester Structure.—On deacetylation of the above tetraacetate by the method of Zemplén and the author,[10] a water soluble, non-reducing, colorless sirup was obtained, which consisted of (3)-mono-acetyl-β-methylfructoside <2,6> with orthoester structure. At low temperature it gradually changed into a crystalline mass, which could not be purified by recrystallization. It was readily soluble in water and in most organic solvents except petroleum ether, and showed $[\alpha]^{20}D$ −12.4° in water solu-

(7) Freudenberg, v. Hochstetter and Engels, *Ber.*, **58**, 666 (1925); Freudenberg and Scholz, *ibid.*, **63**, 1969 (1930).

(8) Pacsu, THIS JOURNAL, **55**, 2451 (1933).

(9) Brauns, *ibid.*, **42**, 1846 (1920).

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

tion (0.3317 g. of substance, 25 cc. of solution, 2-dm. tube; rotation 0.33° to the left). Although hydrolysis with alkali gave a negative result, one acetyl group was still present which could not be eliminated until the methylglycosidic group with which it is ultimately linked in the orthoester formation had been removed by acid; 0.2767 g. of the substance was dissolved in 10 cc. of water and 1 cc. of decinormal hydrochloric acid was added to the solution. After standing half an hour at room temperature, the solution was neutralized, after which it required 11 cc. of decinormal alkali, while the calculated value for one acetyl group is 11.7 cc.

Isolation of Schlubach's Methylfructoside Tetraacetate.—For the isolation of this compound it was not necessary to purify the sirup which was obtained from the original methyl alcoholic solution by the above procedure of (1) or (2). For each 5 g. of either sirup, 100 cc. of boiling water was used to produce a clear solution in fifteen minutes. From each 5 g. of the sirup of (1), there was obtained 0.9 g. of beautiful crystals of the fructoside, after the aqueous solution had been kept in the ice-box for one day. From the solution containing 5 g. of the sirup prepared by procedure (2), 1.7 g. of the same crystalline fructoside was isolated. From the mother liquors, by repeated extractions with chloroform, a large amount of pure β-tetraacetylfructose was obtained. Analyses, melting point and optical rotation of the crystalline fructoside agreed with the data recorded by Schlubach. In contrast with its isomeride possessing orthoester structure, this substance is stable toward dilute acids at room temperature.

Preparation of a New Crystalline Ethylfructoside Tetraacetate.—Twenty eight grams of β-chloroacetylfructose was added to 60 cc. of absolute ethyl alcohol containing 40 g. of commercial silver oxide. After shaking for two hours at room temperature, the mixture was filtered from the silver salts, and the filtrate was concentrated *in vacuo* to a sirup. On shaking at room temperature with 150 cc. of water containing two drops of concentrated hydrochloric acid to decompose the orthoester, the sirup gradually dissolved, and suddenly a crystalline mass precipitated. The dried substance (15 g.) showed $[\alpha]^{20}D$ −62.3° in chloroform, while pure β-tetraacetylfructose has $[\alpha]^{20}D$ −92.3° in the same solvent. From the mother liquor 5 g. of crystalline material separated at 0°, showing $[\alpha]^{20}D$ −82.3° in chloroform. From the mother liquor of this substance, by repeated extractions with chloroform, 5 g. of pure β-tetraacetylfructose was recovered. The first two substances were united (20 g.), dissolved in 30 cc. of warm chloroform, and to the solution 80 cc. of ether was added. Pure β-tetraacetylfructose (16 g.) separated out in the cold. The filtrate was concentrated *in vacuo* to a sirup, which was dissolved in 25 cc. of boiling water by addition of a few cc. of alcohol. On cooling, the solution deposited 2 g. of the new ethylfructoside tetraacetate in the form of beautiful prismatic needles. The substance did not reduce Fehling's solution; it melted at 103–104°; $[\alpha]^{20}D$ 51.6°; $[\alpha]^{20}C$ 40.8° and $[\alpha]^{20}_{Hg_I}$ 61.0° in chloroform solution (0.1801 g. of substance, 10 cc. of solution, 2-dm. semi-micro tube; rotations 1.86, 1.47, 2.20° to the right, respectively). Recrystallization from dilute alcohol did not change the rotatory power or melting point; found, ethoxyl, 11.72; calcd., 11.97. In an acetyl estimation 0.2500 g. of the substance required 26.6 cc. of decinormal alkali; calcd. for four acetyls, 26.6 cc. Beside this new crystalline fructoside, the original sirup contained a large amount (about 90%) of a new tetraacetyl-β-ethylfructoside <2,6>, which showed all the properties characteristic of glycosides with orthoester structure.

Summary

1. It has been found that the reaction between β-acetochlorofructose <2,6> and methyl alcohol does not give rise exclusively to the methylfructoside tetraacetate of Schlubach. This fructoside is merely the product of a side reaction, the main reaction being the formation, in 64–80% yield, of a new β-methylfructoside tetraacetate <2,6> possessing orthoester structure.

2. From β-chloroacetylfructose and ethyl alcohol, a new crystalline ethylfructoside tetraacetate with m. p. 103–104°, and $[\alpha]^{20}D$ 51.6° in chloroform solution, has been prepared. This again has been found to be only a by-product, the main product of the reaction being a new β-ethylfructoside tetraacetate <2,6> with orthoester structure.

3. A simplified method of preparation and a convenient means of isolating Schlubach's fructoside has been described.

4. The significance of the formation of the above orthoesters from β-chloroacetylfructose has been discussed.

PRINCETON, NEW JERSEY RECEIVED JANUARY 28, 1935