

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 191]

## The Oxidation of Certain Glycosides by Lead Tetraacetate<sup>1</sup>

BY R. C. HOCKETT AND W. S. McCLENAHAN<sup>2</sup>

In a previous paper<sup>3</sup> we stated that a number of methyl pyranosides, when dissolved in certain non-aqueous solvents, rapidly consume two molecular equivalents of lead tetraacetate. Evidence was presented that the two stages of the oxidation are (1) cleavage of a carbon-carbon bond between two adjacent, free carbinol groups with formation of a dialdehyde (II) and (2) subsequent elimination of one carbon atom to produce a second dialdehyde (IV).

Since the pyranosides all contain three adjacent unprotected carbinol groups (I), there are obviously two alternative positions in each compound at which the initial cleavage may occur. The isolated final products of the reaction do not, of course, by their structure provide any information regarding the position of initial attack (IV). Criegee,<sup>4</sup> however, has accumulated considerable evidence to the effect that *cis* glycols are oxidized more rapidly than *trans* glycols. Among the glycosides under investigation there may exist three possible types of configuration since the three carbinol groups inside the ring may be considered as forming two overlapping pairs: these types may be designated *cis-cis*, *cis-trans* (I), or *trans-trans*. No compounds of the first type were available during this study, but several *cis-trans* and *trans-trans* glycosides have been investigated. If Criegee's observation with respect to rates of oxidation is of general application it would be predicted that all those glycosides which contain no *cis* glycol configuration would consume their first mole of lead tetraacetate less rapidly than those which contain at least one *cis* pair of hydroxyls.<sup>5</sup> This relation has been verified in all the cases studied. Figure 1 shows

(1) This paper was read before the Division of Organic Chemistry at the meeting of the American Chemical Society in Milwaukee, Wisconsin, September, 1938.

(2) The material presented in this paper is taken from a thesis submitted by W. S. McClenahan to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy in June, 1938. Mr. McClenahan was Louis Francisco Verges Fellow in Chemistry in 1936-1937 and 1937-1938.

(3) *THIS JOURNAL*, **60**, 2061 (1938).

(4) Criegee, (a) *Ber.*, **64**, 260 (1931); (b) *ibid.*, **65**, 1770 (1932); (c) *Ann.*, **507**, 159 (1933).

(5) Similar considerations have been employed by Freudenberg and Rogers, *THIS JOURNAL*, **59**, 1602 (1937), in establishing the configurations of the anhydrohexitols, styracitol and polygalitol.

a significant gap between the curve representing the oxidation of the slowest *cis-trans* glycoside ( $\alpha$ -methyl-1-fucopyranoside) and that of the fastest *trans-trans* glycoside ( $\beta$ -methyl-*d*-xylopyranoside). The correlation between configurations and rates suggests that the *cis* positions are those initially attacked.

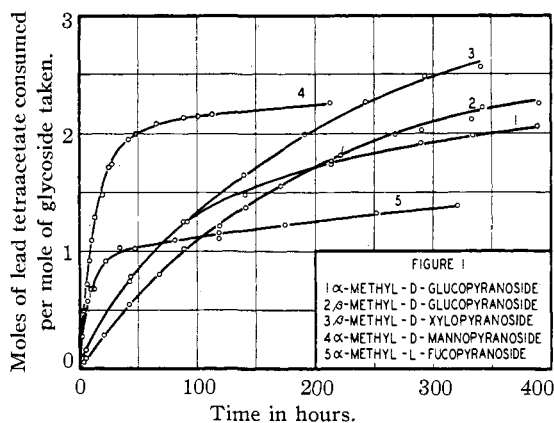


Fig. 1.

The second objective of the present study was to discover what effect upon the rates of oxidation would result from changing the substituent upon the reducing group from methyl to benzyl. In the two cases examined ( $\alpha$ -methyl- and  $\alpha$ -benzyl-fructofuranoside,  $\beta$ -methyl- and  $\beta$ -benzyl-fructopyranoside,<sup>6(a)</sup> this alteration in structure was found to have very little effect (Fig. 2).

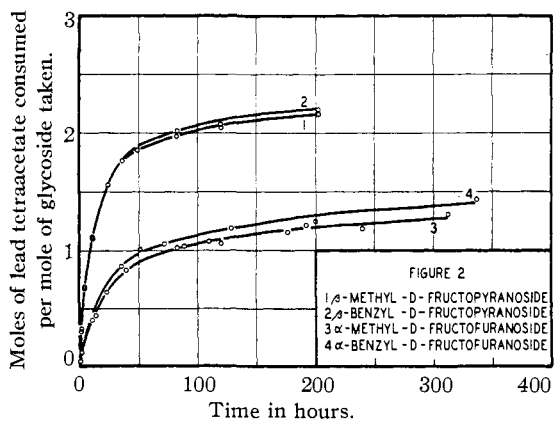


Fig. 2.

(6) (a) Purves and Hudson, *THIS JOURNAL*, **59**, 49, 1170 (1937); (b) Pacsu, *ibid.*, **57**, 745 (1935).

A third objective was to learn whether reversing the configuration of the groups about the reducing carbon would alter the oxidation rates. In the few cases where an  $\alpha$ - and  $\beta$ -pair were available for testing, their curves belonged to the same family (Figs. 3 and 4).

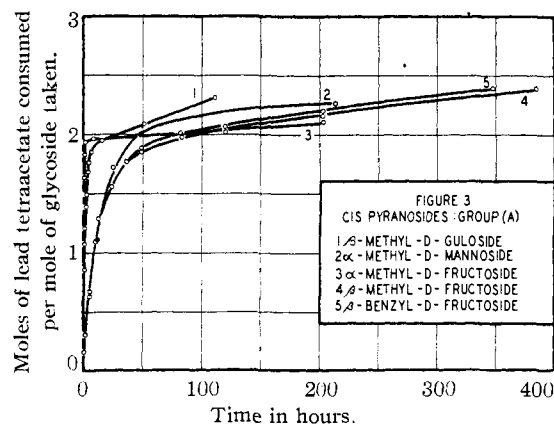


Fig. 3.

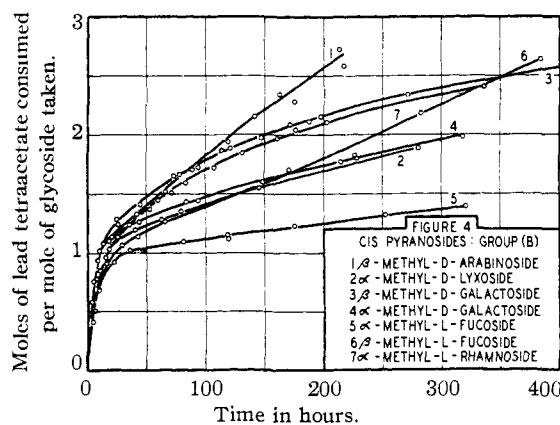
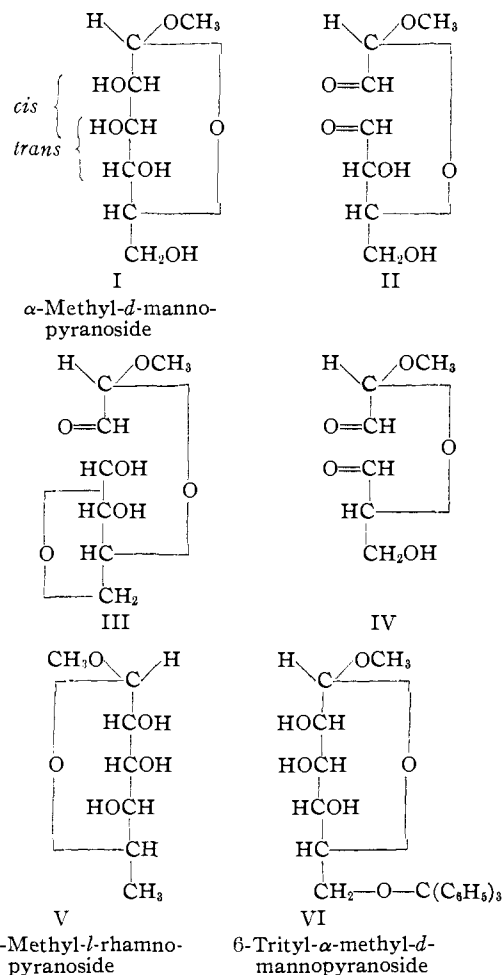


Fig. 4.

The fourth objective was to gain some information concerning the rates of consumption of the second mole of oxidant. The observation of Criegee<sup>7</sup> that glycerol consumes two moles of lead tetraacetate is presumptive evidence that hydroxyaldehydes are attacked by this reagent since glycolaldehyde should be the product of oxidation by the first mole. We found experimentally that the *cis* glycosides studied can be divided sharply into two groups according to whether (A) (Fig. 3) the consumption of oxidant slows down significantly only after the absorption of two moles or whether (B) (Fig. 4) it slows down after use of one mole. It has been found possible to correlate these differences by means of a simple

(7) Criegee, *Ann.*, **495**, 211 (1932).

hypothesis. All the glycosides of the first type (A) are so constituted that after initial fission at the *cis* glycol position, the resulting product would be a  $\gamma$ -hydroxyaldehyde (*e. g.*, II). According to the observations of Helferich,<sup>8</sup> hydroxyaldehydes of this nature readily form cyclic hemiacetals; such rearrangement would produce a five-membered ring structure (III) containing a new pair of adjacent carbinol groups which presumably would be attacked readily by the oxidant.<sup>9</sup> The gly-

(8) Helferich, *Ber.*, **64**, 104 (1931).(9) (a) More exactly, the dialdehyde probably would be in equilibrium with two cyclic hemiacetals in which the new glycol groups would be *cis* and *trans*, respectively. Criegee<sup>1b,c</sup> has shown that *cis* glycols in a five-membered ring system frequently are oxidized very rapidly; the concentration of the *cis* form would tend to maintain itself through a shift in the equilibrium.(b) Oxidation of such a hemiacetal should yield a formic acid ester similar to that formulated by Felton and Freudenberg, *This Journal*, **57**, 1637 (1935).(c) A similar hypothesis was advanced by Criegee<sup>7</sup> to explain why  $\alpha$ -methyl-mannofuranoside and 1-mannono- $\gamma$ -lactone produced little formaldehyde when oxidized by lead tetraacetate. In these cases, if initial fission occurs between carbons two and three, cyclic hemiacetal formation would destroy the remaining glycol structure and prevent further oxidation (VII, VIII and IX).

cosides of type (B) if initially cleaved at the *cis* position yield products whose structures are unfavorable to hemiacetal formation (unless bimolecularly) and hence may be expected to react further less readily.

The most striking case of this difference is represented by the pair:  $\alpha$ -methyl-*d*-mannopyranoside (I) and  $\alpha$ -methyl-*l*-rhamnopyranoside (V). These substances would be enantiomorphs save for the lack of oxygen on carbon six of the latter. The former rapidly consumes *two* moles of lead tetraacetate while the latter, although initially attacked at nearly the same rate, slows down a great deal after use of one mole. To gain additional evidence concerning the function of the sixth hydroxyl in promoting the second stage of the reaction, through hemiacetalization, the behavior of 6-trityl- $\alpha$ -methyl-*d*-mannoside (VI) was studied. It was first ascertained that this substituent was stable toward the reaction medium (glacial acetic acid) and then it was found that the rate of oxidation closely paralleled that of the methyl rhamnoside (Fig. 5).

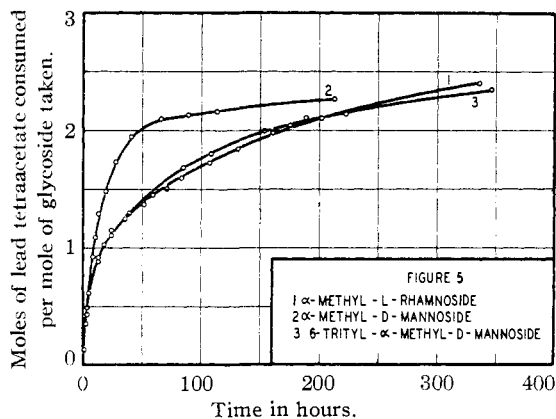
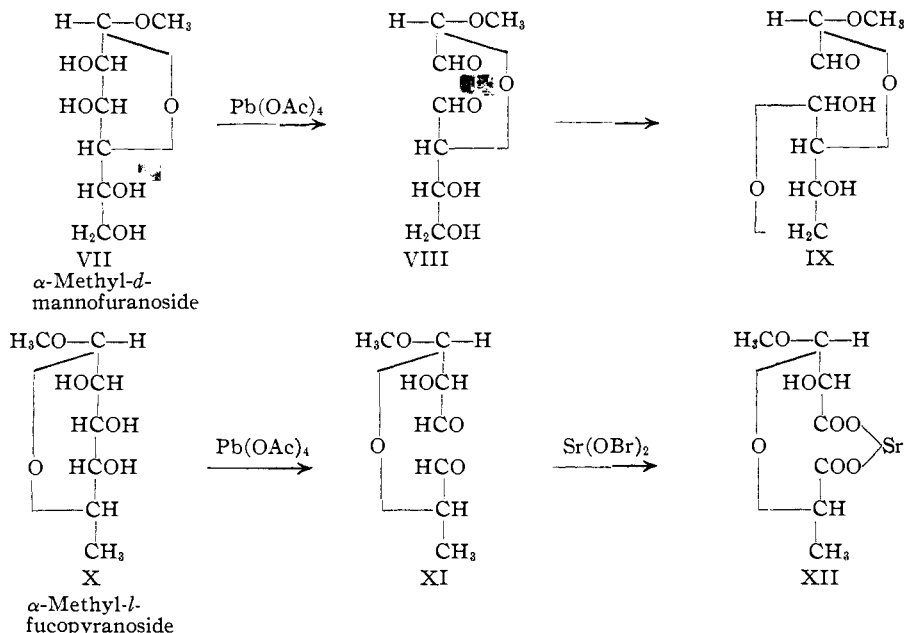


Fig. 5.

previous publication.<sup>3</sup> There was isolated, as its strontium salt, a dibasic acid which seems to contain all the original carbon of the glycoside and therefore probably is represented correctly by formula XII.

The consumption of only one mole of oxidant by this glycoside would have suggested the presence of a furanoside structure but for the rate of



It was also noted from the rate curve that  $\alpha$ -methyl-*l*-fucoside (of rotation<sup>10</sup>  $-197^\circ$ ) is only slowly attacked after oxidation by one mole of oxidant. A sample of this glycoside was therefore treated with an equimolar quantity of lead tetraacetate by the technique described in the

(10) All rotations stated in this paper refer to specific rotations of sodium light at  $20^\circ$ .

this reaction which is characteristic of a *cis*-hydroxyl pair. That  $\alpha$ -methyl-*d*-fucoside ( $-197^\circ$ ) is a pyranoside has been established beyond question by Maclay, Hann and Hudson<sup>11</sup> through oxidation by periodic acid. Hence the very low rate of attack of the dialdehyde initially formed appears attributable to the unfavorable structure

(11) Maclay, Hann and Hudson, *THIS JOURNAL*, **61**, 1660 (1939).

of this substance in accordance with the hypothesis given. The data obtained for several miscellaneous compounds are illustrated in Fig. 6. From this it appears that the oxygen bridge in fructose is stable even after cleavage of the carbon chain has occurred.

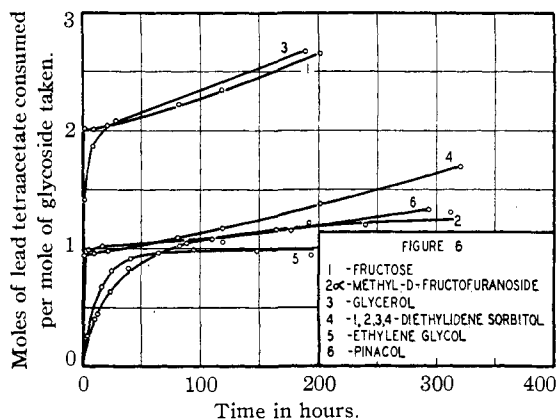


Fig. 6.

In the rate studies the molar concentrations of the glycosides were uniform throughout. A ratio of six and one-half moles of oxidant to one of glycoside was used. That this was virtually equivalent to an infinite excess is indicated by the observation that doubling the ratio in certain cases caused practically no change in rate.

We wish cordially to thank Professor C. B. Purves of this Laboratory for the fructosides employed, Dr. H. S. Isbell of the National Bureau of Standards for samples of  $\alpha$ - and  $\beta$ -methyl-*d*-gulopyranosides, and Dr. Paul Arthur, Jr., of this Laboratory for valuable suggestions in the interpretation of the data.

### Experimental

**Standard Lead Tetraacetate Solution.**—The salt prepared as previously described<sup>3</sup> was recrystallized from glacial acetic acid and was made up to a normality of 0.1315 in aldehyde-free acetic acid (29 g. per liter) by dissolving the requisite weight in hot acid, pouring the solution into cool acid and filtering the mixture. The solution was standardized under the conditions used in the rate determinations. It was found to deteriorate gradually over a period of several months.

**Rate Determinations.**—To 49 cc. of aldehyde-free acetic acid in a 100-cc. glass-stoppered volumetric flask was added 0.0005 mole (0.001 equivalent) of the dry glycoside which had been purified until its rotation agreed with recorded values. Warming on the steam-bath was necessary in a few cases. After cooling the solution to 20°, the time was noted and 50 cc. of standard lead tetraacetate solution at 20° was added from a pipet. The mixture was made up rapidly to 100 cc., mixed and placed in a

constant temperature room maintained at 20–21°. At noted intervals, 10-cc. samples were withdrawn and run into 20 cc. of aqueous buffer solution containing 20 g. of reagent sodium or potassium iodide and 250 g. of sodium acetate per liter; the liberated iodine<sup>12</sup> was titrated with 0.02 *N* sodium thiosulfate solution.

The method was employed successfully upon as little as 0.000125 mole (24 mg.) of glycoside by making proportionate reductions in all the quantities given above.

**$\alpha$ -Methyl-*l*-rhamnopyranoside.**—A 3-g. sample of triacetyl- $\alpha$ -methyl-*l*-rhamnopyranoside melting at 86–87° (corr.), showing a rotation of  $-54.65^\circ$  in acetylene tetrachloride (*c*, 3.2112; *l*, 4) and  $-60.34^\circ$  in chloroform (*c*, 3.2100; *l*, 4) was deacetylated with barium methylate.<sup>13</sup> The concentration of the resulting aqueous solution was calculated from its optical rotation, the solvent was removed by distillation under reduced pressure and remaining traces of water by several redistillations in the presence of glacial acetic acid. The sirup was made up to 250 cc. with acetic acid and aliquots containing 0.0005 mole of methyl rhamnoside were withdrawn for oxidation experiments.

**6 - Trityl -  $\alpha$  - methyl - *d* - mannopyranoside.**—This substance, prepared by the method of Watters, Hockett and Hudson,<sup>14</sup> who also proved the structure, rotated  $+22.1^\circ$  (*c*, 1.4680; *l*, 2; CHCl<sub>3</sub>) after drying to constant weight *in vacuo* at 65°.

**$\alpha$ - and  $\beta$ -Methyl-*l*-fucosides.**—Fucose, extracted from *Ascophyllum nodosum*, was converted to the glycosides as described by Hockett, Phelps and Hudson,<sup>15</sup> using precipitation with potassium acetate to separate the  $\beta$ -isomer from the predominating  $\alpha$ -form.<sup>16</sup>

**Oxidation of  $\alpha$ -Methyl-*l*-fucopyranoside.**—Two grams (0.011 mole) of the fucoside was oxidized in 150 cc. of chloroform with 5 g. (0.011 mole) of lead tetraacetate according to the method previously described.<sup>3</sup> After removing lead and acetic acid, the rotation of an aqueous solution was observed, and a specific rotation of approximately  $-80^\circ$  was calculated assuming that the oxidation had been complete and that only one product had been formed. A titration by the Cajori<sup>17</sup> method revealed that approximately two equivalents of aldehyde had been formed per mole of lead tetraacetate consumed. In a two-stage oxidation, the same quantity of aldehyde would be produced by two moles of oxidant. After oxidation with strontium hypobromite, 2.5 g. (71%) of very fine crystals of a strontium salt was obtained. The rotation was unchanged by recrystallization after a value of  $+29.80^\circ$  in water (*c*, 0.6924; *l*, 4) was reached. The free acid liberated by an equivalent quantity of hydrochloric acid rotated  $-13.2^\circ$  (*c*, 0.2650; *l*, 4); after adding 3 drops more of concd. hydrochloric acid,  $-16.8^\circ$ .

(12) An experiment was made which indicated that the aldehydes formed in the oxidation of the glycosides probably do not react appreciably with the liberated iodine in the *acid* solution: 5-cc. of standard lead tetraacetate solution was added to a mixture of 5 cc. of acetic acid and 20 cc. of buffer solution. Then 0.5 g. of glucose was added. After five minutes, the titer with sodium thiosulfate was found to be the same as with a blank.

(13) Isbell, *Bur. Standards J. Research*, **5**, 1185 (1930).

(14) Watters, Hockett and Hudson, *THIS JOURNAL*, **61**, 1528 (1939).

(15) Hockett, Phelps and Hudson, *ibid.*, **61**, 1658 (1939).

(16) Watters, Hockett and Hudson, *ibid.*, **56**, 2199 (1934).

(17) Cajori, *J. Biol. Chem.*, **54**, 622 (1922).

*Anal.* Calcd. for  $C_7H_{10}O_7Sr \cdot 2H_2O$ :  $H_2O$ , 10.93. Found: loss in wt. at  $105^\circ$ , *in vacuo*, 10.18, 11.0. Calcd. for  $C_7H_{10}O_7Sr$ : Sr, 29.84. Found: 29.40, 29.25. Calcd. for  $C_6H_8O_6Sr$ : Sr, 33.23.<sup>18</sup>

### Summary

1. The rates of oxidation of a number of glycosides by lead tetraacetate in glacial acetic acid have been measured.

2. All the glycosides which contain a *cis* glycol structure consumed the first mole of lead tetraacetate much more rapidly than those which contain only *trans* glycol structures, suggesting that the initial attack is at the *cis* position when such is present.

3. In two cases, substitution of benzyl for methyl on the first carbon has no effect upon the oxidation rates.

4. In several cases,  $\alpha$ - and  $\beta$ -isomers have been

(18) The physical properties of our salt also differ markedly from those of the strontium salt obtained by Maclay and Hudson (ref. 11) which contains one carbinol group less.

found to show a general similarity in the oxidation experiments.

5. The glycosides containing glycol structures have been separated by experimental study into two groups: (A) those which consume a second mole of oxidant with a speed comparable to that at which the first is consumed, and those (B) which consume the second mole at a distinctly lower rate, and a hypothesis has been proposed to explain this difference.

6. The substitution of a trityl radical at carbon six of  $\alpha$ -methyl-*d*-mannopyranoside is shown to shift this glycoside from group (A) to group (B) in accord with the prediction of the hypothesis.

7.  $\alpha$ -Methyl-*l*-fucoside ( $-197^\circ$ ) has been oxidized by one mole of lead tetraacetate in chloroform solution and by strontium hypobromite to a dibasic acid containing all the carbon of the original substance.

CAMBRIDGE, MASS.

RECEIVED APRIL 5, 1939

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

## Glycofuranosides and Thioglycofuranosides. VI. Preparation of Dimethyl Acetal and Methylfuranosides from *d*-Fructosedithylmercaptal

BY EUGENE PACSU

In a preliminary communication<sup>1</sup> it was reported that the application of the furanoside synthesis developed<sup>2</sup> in this Laboratory to *d*-fructosedithylmercaptal had resulted in the unexpected formation of *d*-fructosedimethylacetal. This was the second observed case where a sugar acetal had been formed from a starting material that contained all of its hydroxyl groups unprotected, the first case being that of the *l*-rhamnosediethylacetal.<sup>2e</sup> The starting material, fructosedithylmercaptal, could not be obtained directly from fructose and mercaptan. Since Emil Fischer showed<sup>3</sup> that his general method for the preparation of sugar mercaptals had failed in the case of fructose and sorbose, it appeared as though the ketose mercaptals could not exist at all. However, Brigl and Schinle found<sup>4</sup> that the benzoyl analog of pentaacetyl-*keto*-fructose, for which the open-chain structure with a free carbonyl

group was previously established<sup>5</sup> by Pacsu and Rich, gave readily a mercaptal derivative on treatment of the substance with ethyl mercaptan and dry hydrogen chloride. Subsequently, Wolfrom and Thompson reported<sup>6</sup> the formation of pentaacetyl fructosedithylmercaptal from pentaacetyl-*keto*-fructose and ethyl mercaptan in the presence of zinc chloride. From the acetylated mercaptal, on deacetylation with ammonia in methyl alcoholic solution, the authors obtained fructosedithylmercaptal in about 78% yield. It has now been found that the yield of the latter compound can be increased almost to that required by the theory, if the deacetylation be carried out at room temperature in methyl alcoholic solution in the presence of a small quantity of barium methylate.

The reaction between sugar mercaptals and mercuric chloride in neutral alcoholic solution was hitherto believed<sup>2b</sup> only to proceed through the following two stages

(5) Pacsu and Rich, *THIS JOURNAL*, **54**, 1697 (1932); **55**, 3018 (1933).

(6) Wolfrom and Thompson, *ibid.*, **56**, 880 (1934).

(1) Pacsu, *THIS JOURNAL*, **60**, 2277 (1938).

(2) (a) Pacsu and Green, *ibid.*, **58**, 1823 (1936); (b) Green and Pacsu, *ibid.*, **59**, 1205 (1937); (c) Green and Pacsu, *ibid.*, **59**, 2569 (1937); (d) Green and Pacsu, *ibid.*, **60**, 2056 (1938); (e) Green and Pacsu, *ibid.*, **60**, 2288 (1938); (f) Pacsu and Scattergood, *ibid.*, **61**, 534 (1939).

(3) Fischer, *Ber.*, **27**, 673 (1894).

(4) Brigl and Schinle, *ibid.*, **66**, 325 (1933).