

APPLICATION OF THE FLUORATING PROCESS TO FRUCTOSE

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ABSTRACT

The prolonged action of hydrofluoric acid on fructose acetate involves both the reducing carbon (the second) and the first carbon, which is not asymmetric; whereas, former work has shown that for cellobiose acetate it involves both the reducing carbon (the first) and the second carbon, which is asymmetric and is reversed by this action. The prolonged action of hydrofluoric acid on fructose acetate is similar to the action of phenylhydrazine on fructose, which also spreads from the second to the first carbon. It seems probable that the nonasymmetry of the carbon is essential for explaining this behavior.

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I. INTRODUCTION

Previous investigation has shown that *brief* action of water-free hydrofluoric acid on acetylated sugars yields mono-fluor derivatives in which the acetyl group of the reducing carbon is replaced by fluorine. Thus crystalline fluoro derivatives of acetylated arabinose, xylose, glucose, fructose, cellobiose, gentiobiose, melibiose, and maltose have been prepared.¹

Prolonged action of hydrofluoric acid on cellobiose octa-acetate caused a peculiar change, as not only the acetyl group of the reducing carbon was replaced by fluorine, but the acetyl group of the next carbon was split off and the resulting OH group reversed. A derivative of another sugar was formed, fluor-hexa-acetyl glucosidomannose.²

II. PROLONGED ACTION OF HYDROFLUORIC ACID ON ACETYLATED FRUCTOSE

The present communication deals with the prolonged action of hydrofluoric acid on acetylated fructose. A crystalline compound³

¹ D. H. Brauns, J. Am. Chem. Soc., 45, pp. 833, 2388; 1923; 46, p. 1485; 1924; 49, p. 3173; 1927; 51, p. 1826; 1929. The series on optical rotation and atomic dimension will be continued separately.

² D. H. Brauns, J. Am. Chem. Soc., 48, p. 2785; 1926.

³ This compound has been prepared in small amount before (J. Am. Chem. Soc., 48, p. 2780; 1926), but not investigated.

was separated, which was found by analysis to be a fluor-triacetyl hexose, one acetyl group being saponified (just as in cellobiose acetate) by the prolonged action of hydrofluoric acid. In this case, however, no reversion of an asymmetric group had occurred (as in the cellobiose derivative), since fluor-tetra-acetyl fructose was obtained on reacetylating, and was identified by the constants described for that compound.⁴ We have further found, as described in detail below, that it is the acetyl group of the first or nonasymmetric carbon atom which has been saponified; hence, a reversion could not take place.

This difference in behavior of fructose and cellobiose may be explained in the following manner: In the case of fructose there are two dissimilar carbon atoms attached to the reducing carbon. One of these (the third) is asymmetric, but the other (the first) is not. Assuming that the groups attached to an asymmetric carbon have a more rigid configuration than those of a nonasymmetric carbon,⁵ it will be found plausible that in case the arrangement of the asymmetric groups is not favorable a preference would exist for the non-asymmetric group. This spreading of a reaction to the first (non-asymmetric) carbon for fructose does not stand alone. It is similar to the action of phenylhydrazine on fructose yielding fructose (glucose) phenylosazone with fructose phenylhydrazone as an intermediate.

The following experimental results proved that the acetyl group of the first carbon was split off. The fluor-triacetyl fructose, which will be designated fluor-triacetyl fructose I, was methylated, yielding a new crystalline fructose derivative, fluor-methyl-triacetyl fructose I. The position of the methoxyl group in this compound was established as follows: The fluor-methyl triacetyl fructose I was saponified with barium hydroxide in the cold, by which not only the acetyl group, but also the fluorine atom was split off,⁶ yielding a monomethyl fructose. This compound could not be obtained in crystalline form. A methoxyl determination showed the sirup to be a monomethyl fructose, and it did not give a phenylosazone under conditions which give for fructose an osazone with good yield. Of the two methyl fructoses (1-methyl and 2-methyl) which obviously could not form an osazone,⁷ only 1-methyl fructose is possible here (since fluorine was attached to carbon 2 when fluor-triacetyl fructose was methylated). We conclude, therefore, that the compounds under investigation have the constitution 1-methyl-2-fluor-triacetyl fructose and 1-unsubs.-2-fluor-triacetyl fructose.⁸

Since it was suspected at first that the acetyl group of the third carbon had been saponified during prolonged fluoration, an attempt was made to prepare fluor-methyl-triacetyl fructose I, using 3-methyl fructose⁹ as the starting product.

⁴ See footnote 1, p. 449.

⁵ There are at least two identical atoms or groups of atoms attached to a nonasymmetric carbon. This identity would make a deformation of the tetrahedral orientation of the valences easier than for an asymmetric carbon where tension must exist by the interference of the affinities of the four different atoms or groups.

⁶ Exceptional behavior on the part of fructose. See experimental part.

⁷ The figures indicate the carbon atom. 2-Methyl fructose would, therefore, be identical with methyl fructoside. Irvine and Hynd (J. Chem. Soc., **95**, p. 1224; 1909) easily obtained a crystalline methyl fructose osazone from 3-methyl fructose, which preparation they recommend for the identification of 3-methyl fructose.

⁸ "1-Unsubs." means that the hydroxyl group of the first carbon atom has not been replaced.

⁹ Concerning the constitution of 3-methyl fructose and α - and β -diacetone fructose, see Anderson, Charlton, Haworth, and Nicholson, J. Chem. Soc., p. 1337; 1929.

3-Methyl fructose was prepared according to the methods of Irvine and Hynd¹⁰ and Ohle and Koller,¹¹ following the procedure: Fructose $\longrightarrow$ α -diacetone fructose $\longrightarrow$ 3-methyl-diacetone fructose $\longrightarrow$ 3-methyl fructose.

The 3-methyl fructose was acetylated with acetic anhydride and zinc chloride in the cold, yielding a new crystalline fructose derivative, 2-unsubs-3-methyl-triacetyl fructose.¹² This compound was fluorated, giving the new crystalline derivative, 2-fluor-3-methyl-triacetyl fructose, or fluor-methyl triacetyl fructose II. The melting points and specific rotations in chloroform of the two similar compounds are compared below:

Fluor-methyl-triacetyl fructose I, m. p. 94°, $[\alpha]_D^{20} = -116.30$.

Fluor-methyl-triacetyl fructose II, m. p. 113–114°, $[\alpha]_D^{20} = -88.70$.

It follows from the quoted constants that the two fluor-methyl-triacetyl fructose derivatives are not identical. This is due to the fact¹³ (later established by the saponification with barium hydroxide), that the methoxyl group in fluor-methyl triacetyl fructose I is situated at carbon 1, whereas in fluor-methyl triacetyl fructose II it is at carbon 3.

Table 1 gives the specific and molecular rotations in chloroform of the four new fructose derivatives. The rotations in chloroform of α -diacetone fructose and its methyl derivative, which are included in Table 1, have not been recorded previously in the literature.

TABLE 1.—Specific and molecular rotations of investigated compounds

	Molecular weight	Specific rotation	Molecular rotation
1-Unsubs.-2-fluor-triacetyl fructose.....	308	-128.8	-396.7
1-Methyl-2-fluor-triacetyl fructose.....	322	-116.3	-374.5
α -Diacetone fructose.....	260	-146.6	-381.2
3-Methyl-diacetone fructose.....	274	-134.7	-369.1
2-Unsubs.-3-methyl-triacetyl fructose ¹	320	-84.1	-269.1
2-Fluor-3-methyl-triacetyl fructose.....	322	-88.7	-285.6

¹ It is obvious that 2-unsubs.-3-methyl triacetyl fructose would be an excellent starting material for the preparation of a number of new compounds, such as α - and β -3-methyl tetra-acetyl fructose, 2-3 dimethyl triacetyl fructose and 2-3 dimethyl fructose. The methods have been described for the preparation of the analogous compounds: α - and β -penta-acetyl fructose, β -methyl tetra-acetyl fructose, and β -methyl fructose (C. S. Hudson and D. H. Brauns, J. Am. Chem. Soc., 37; p. 2736; 1915; 38; p. 1216; 1916).

III. EXPERIMENTAL

General remarks.—The saccharimeter degrees (S) are converted to circular degrees by multiplication by the factor 0.3462. Unless otherwise stated, volume of flask = 24.9784, length of tube = 4 dm.

1. 1-UNSUBS.-2-FLUOR-TRIACETYL FRUCTOSE

This compound may be prepared from β -penta-acetyl or β -tetra-acetyl fructose by the prolonged action of hydrofluoric acid. How-

¹⁰ Irvine and Hynd, J. Chem. Soc., 95; p. 1224; 1909.

¹¹ Ohle and Koller, Ber., 57; p. 1571; 1924.

¹² Since fluorine attacks the reducing carbon first, and during the fluoration of this compound none of the acetyl groups was found to be removed, it follows that the hydroxyl group in 3-methyl-triacetyl fructose must be on the second carbon atom. The ring structure of the newly described derivative is probably the same as that of tetra-acetyl fructose, since the method of acetylation of 3-methyl fructose and of fructose is exactly the same. However, the particular ring structure of the compounds is not given as it does not affect the conclusions drawn.

¹³ Concerning different ring structures, see footnote 12.

ever, since the yield is small and fluor-tetra-acetyl fructose is formed as an intermediate, it is advantageous to use the latter compound as a starting product. The receiver of the hydrofluoric acid still contained 15 g of powdered fluor-tetra-acetyl fructose and was cooled in ice and salt. After about 30 g of water-free hydrofluoric acid had been distilled, the receiver was well stoppered and immersed in brine, the temperature of which was allowed to rise gradually from -11° to -7° during a period of 26 hours. The receiver and brine were contained in a 1-gallon thermos jar which was kept in the refrigerator. These conditions were found the most advantageous for obtaining a maximum yield. The reaction product was worked up as previously described¹⁴ and gave a light yellow sirup. Ether was added, the product evaporated to dryness, more ether added, and the mixture kept at 0° for 12 hours or more before filtering. The yield by this method was better and the product more nearly pure than when the mixture was filtered immediately and at room temperature. The compound was recrystallized four times from ether. The yield of pure substance was 10 per cent.

Rotation.—*Second recrystallization:* Subs., 0.5547; $\alpha = -32.65$ S; volume of flask, 24.9767 cc; $[\alpha]_D^{20} = -127.24$. *Third recrystallization:* Subs., 0.6024; 0.6131; $\alpha = -35.85$ S; -36.50 S; $[\alpha]_D^{20} = -128.66$; -128.70 . *Fourth recrystallization:* Subs., 0.6175; $\alpha = -36.80$ S; volume of flask, 24.9784 cc; $[\alpha]_D^{20} = -128.83$. The specific rotation of the pure substance is taken as -128.8 . The pure product crystallizes in well-defined prisms, is stable, colorless, and has a bitter taste. It is very soluble in most solvents except water, benzene, and petroleum ether. M. P. 134° to 135° . *Analyses:* Subs., 0.1881; CO_2 , 0.3243; H_2O , 0.0937. Subs., 1.0135; CaF_2 , 0.1190. Acetyl determination: Subs., 0.5000: 86.53 cc of 0.25 *N* H_2SO_4 , 282.14 cc of 0.1 *N* NaOH . Molecular weight: Subs., 0.0816, 0.0855, 0.0048: Camphor, 0.1000. ΔT , 10.5° , 12.0° , 6.0° . *Calculated* for $\text{C}_6\text{H}_7\text{O}(\text{C}_2\text{H}_3\text{O}_2)_3$ OH F: C, 46.73; H, 5.56; F, 6.16; 64.9 cc of 0.1 *N* NaOH for $\text{AcOH} + \text{F}$; mol. wt., 308. *Found:* C, 47.02; H, 5.57; F, 5.71; 65.8 cc of 0.1 *N* NaOH ; mol. wt., 311, 285, 319.

2. CONVERSION OF 1-UNSUBS. 2-FLUOR-TRIACETYL FRUCTOSE TO 2-FLUOR-TETRA-ACETYL FRUCTOSE

This conversion is important for proving that the prolonged fluorination has not reversed an asymmetric center in the molecule or caused any other change which would destroy the fructose structure.

One gram of powdered fluor-triacetyl fructose was added to a hot solution of 0.5 g of anhydrous sodium acetate in 8 cc of acetic anhydride and the mixture boiled for 10 minutes. The reaction product was poured into 100 cc of ice water and soon solidified to crystalline mass. It was separated on a suction filter and recrystallized from methyl alcohol. The determination of the specific rotation in chloroform gave the following results: *Rotation:* Subs., 0.5717; $\alpha = -24.20$ S; $[\alpha]_D^{20} = -91.60$. After recrystallization from ether the following results were obtained: Subs., 0.4075; $\alpha = -17.10$ S; $[\alpha]_D^{20} = -90.72$; m. p., 112° . When mixed with pure fluoro-tetra-acetyl fructose ($[\alpha]_D^{20} = -90.43$ in chloroform), the melting point was likewise 112° . These experiments prove that the prepared fluor-triacetyl compound is a fructose derivative.

¹⁴ See footnote 1, p. 449.

3. 1-METHYL-2-FLUOR-TRiacetyl FRUCTOSE FROM 1-UNSUBS.-2-FLUOR-TRiacetyl FRUCTOSE

Two grams of powdered and dried fluor-triacetyl fructose was boiled for about five hours under reflux with 25 cc of methyl iodide, and 12 g of silver oxide was added gradually. The reaction product was diluted with ether, filtered by suction, and the precipitate washed with ether. The filtrate was evaporated in air and gave about 1.9 g of sirup, which solidified after being kept in a vacuum desiccator for two days and stirred with petroleum ether. The 1.7 g of impure crystals were dissolved in 1.5 liters of petroleum ether (b. p. 30° to 55°), filtered, and the filtrate allowed to evaporate in a beaker in air. As evaporation progressed the solution was transferred to smaller and smaller beakers. Impure crystals separated at the top, and were kept separate from those of the bottom and the lower part of the walls. Further recrystallizations were performed by allowing ether solutions to evaporate in air. The crystals were washed with 50 per cent ether-petroleum ether. The determination of the specific rotation in chloroform solution gave the following results: Subs., 0.6021: $\alpha = -29.50$ S; volume of flask, 24.9767 cc; $[\alpha]_D^{20} = -105.91$. *First recrystallization*: Subs., 0.5436: $\alpha = -28.65$ S; volume of flask, 24.9767; $[\alpha]_D^{20} = -113.90$. *Second recrystallization*: Subs., 0.4332: $\alpha = -23.30$ S; volume of flask, 24.9767 cc; $[\alpha]_D^{20} = -116.26$. *Third recrystallization*: Subs., 0.3950: $\alpha = -25.25$ S; volume of flask, 24.9767; $[\alpha]_D^{20} = -116.30$. The specific rotation of the pure substance is taken as -116.3 ; m. p., 94°. The pure product crystallizes in short prisms or plates and is very soluble in the ordinary solvents except water and petroleum ether. *Analyses*: Subs., 0.1894: CO₂, 0.3377; H₂O, 0.1029; OCH₃ determination: Subs., 0.2200: AgI, 0.1623. Acetyl determination: Subs., 0.4563: 96.49 cc of 0.25 N H₂SO₄, 296.79 cc of 0.1 N NaOH. *Calculated* for C₆H₇O (C₂H₃O₂) OCH₃F: C, 48.42; H, 5.94; OCH₃, 9.63; 56.64 cc of 0.1 N NaOH for AcOH + F. *Found*: C, 48.63; H, 6.08; OCH₃, 9.75; 55.57 cc of 0.1 N NaOH. A positive qualitative test for fluorine was obtained.

4. SAPONIFICATION OF 1-METHYL-2-FLUOR-TRiacetyl FRUCTOSE AND PROOF OF THE POSITION OF THE METHYL GROUP

One and three-fourths grams of crystalline barium hydroxide was dissolved in 25 cc of water on the steam bath and filtered into an Erlenmeyer flask with glass stopper. The solution was cooled with ice to about 5°, and 0.5 g of powdered methyl fluor-triacetyl fructose was added and shaken until dissolved. The solution was kept 1 hour longer in ice, then saturated with carbon dioxide and filtered. Sulphuric acid (0.25 N) was added until all barium was precipitated, but care was taken not to add an excess of the acid. Filtration was performed through a Gooch filter and the solution concentrated in vacuo. By dissolving in methyl alcohol, filtering, and evaporating, a thick, slightly yellowish sirup was obtained which was kept in a vacuum desiccator. A qualitative test for fluorine was negative.¹⁵ A methoxyl determination proved the sirup to be a mono-methyl fructose. OCH₃ determination: Subs., 0.1412: AgI, 0.1752.

¹⁵ It is remarkable that this method of saponification does not affect the fluorine in fluor-acetyl derivatives of the aldoses, but removes it from this derivative of fructose, and also from fluor-tetra-acetyl fructose.

Found: OCH_3 , 16.4 per cent. Calculated for $\text{C}_6\text{H}_{11}\text{O}_5 (\text{OCH}_3)$, 15.98 per cent.

The following experiment proves that the monomethyl fructose does not form an osazone:

Thirty milligrams of the sirup obtained from the described saponification was dissolved in 3 cc of water. A solution of 0.4 g of freshly prepared phenylhydrazine in 0.3 cc of acetic acid and 3 cc of water was added, and the resulting solution heated in a steam bath. The heating was continued for 45 minutes but no crystals separated even on cooling the solution. Thirty milligrams of fructose when treated in the same manner gave a nearly quantitative yield of pure osazone.

5. 3-METHYL TRIACETYL FRUCTOSE

α -Diacetone fructose (1-2, 4-5 diacetone fructose) was prepared according to the method of Ohle and Koller.¹⁶ The specific rotation of the chloroform solution gave the following results: *Second recrystallization*: Subs., 0.5685: $\alpha = -38.40$ S; $[\alpha]_D^{20} = -146.70$. *Third recrystallization*: Subs., 0.5373: $\alpha = -36.43$; $[\alpha]_D^{20} = -146.57$. *Fourth recrystallization*: Subs., 0.5767: $\alpha = -39.10$ S; $[\alpha]_D^{20} = -146.57$. The specific rotation of the pure substance in chloroform is taken as -146.6 ; m. p., 118° to 119° (Fischer, 119° to 120°).

The specific rotation of the pure substance in water was -160.5 (Fischer, $[\alpha]_D^{20} = -161.3$ in water).

3-Methyl diacetone fructose was prepared according to Irvine and Hynd.¹⁷ We did not have the difficulties which these authors report in obtaining a good yield of pure product (50 per cent) if amounts larger than 10 g of α -diacetone fructose were worked with at one time. We have methylated quantities of 35 g and 45 g of fructose diacetone and obtained 52 per cent yield of pure 3-methyl-diacetone fructose. It may be that the silver oxide which we dried at 80° in a vacuum of less than 1 mm of mercury was more active than that used by Irvine and Hynd.

The substance was recrystallized from dilute methyl alcohol (3 alcohol:1 water). The determination of the specific rotation in chloroform gave the following results: *First crystallization* of the crude product of $[\alpha]_D^{20} = -136.0$. Subs., 0.5023, 0.5896: $\alpha = -31.25$ S, -36.75 S; $[\alpha]_D^{20} = -134.52$, -134.75 . *Second recrystallization*: Subs., 0.6173, 0.6547: $\alpha = -38.45$ S, -40.80 S; $[\alpha]_D^{20} = -134.65$, -134.73 . The specific rotation in chloroform is taken as -134.7 . Our values for the specific rotation of the pure substance in acetone, and the melting point (115°) agree with those obtained by Irvine and Hynd.

The method of Irvine and Hynd¹⁸ was followed by hydrolyzing 3-methyl diacetone fructose with 0.1 per cent hydrochloric acid. However, a product was obtained which was only partially hydrolyzed, as was found by methoxyl content and specific rotation. Twice the strength of the acid (0.2 per cent HCl) gave complete hydrolysis of the acetone groups. The 3-methyl fructose was recrystallized from ethyl acetate containing about 5 per cent methyl alcohol.

3-methyl triacetyl fructose was prepared from 3-methyl fructose by the same method used for the preparation of tetra-acetyl fructose

¹⁶ See footnote 11, p. 451.

¹⁷ See footnote 10, p. 451.

¹⁸ See footnote 10, p. 451.

from fructose. Four grams of finely powdered 3-methyl fructose was added gradually to a cold solution of 0.35 g. of zinc chloride in 20 cc. of acetic anhydride. The mixture was cooled in ice and vigorously shaken until only a small part of the 3-methyl fructose remained undissolved (about 30 minutes). The cold solution was then poured into 30 cc. of ice water in a flat porcelain dish, 20 g. of sodium bicarbonate was added and the mixture allowed to stand for 30 minutes. The excess of sodium bicarbonate was filtered off by suction and washed with chloroform. The filtrate was shaken out with chloroform, the chloroform solution dried with sodium sulfate, and evaporated in a current of air. The crystals which separated were stirred with ether, and filtered off by suction. The crude product (0.9 g.) was recrystallized from ether containing a little absolute alcohol. Yield of pure substance, 20 per cent. In working up larger amounts than 4 g. of 3-methyl fructose, the yield became relatively smaller. *Rotation*: Subs., 0.6182: $\alpha = -23.05$ S; $[\alpha]_D^{20} = -80.61$. *First recrystallization*: Subs., 0.6237: $\alpha = -24.25$ S; $[\alpha]_D^{20} = -84.05$. *Second, recrystallization*: Subs., 0.5989: $\alpha = -23.30$ S; $[\alpha]_D^{20} = -84.11$. The specific rotation of the pure substance in chloroform is taken as -84.1 . The compound crystallizes in needles and is bitter; m. p., $156-157^\circ$. It is stable and soluble in ordinary solvents, fairly soluble in ether and slightly in water and petroleum ether. *Analyses*: Subs., 0.2102: CO_2 , 0.3765; H_2O , 0.1188. OCH_3 determination: Subs., 0.2091: AgI , 0.1546. Acetyl determination: Subs., 0.5012: 96.49 cc. of 0.25 H_2SO_4 , 287.99 cc. of 0.1 N NaOH. *Calculated* for $\text{C}_6\text{H}_8\text{O}_2(\text{C}_2\text{H}_3\text{O}_2)_3$ OCH_3 : C, 48.72; H, 6.30; OCH_3 , 9.70; AcOH , 56.25. *Found*: C, 48.85; H, 6.32; OCH_3 , 9.78; AcOH , 56.02.

6. 2-FLUOR-3-METHYL TRIACETYL FRUCTOSE

The method of fluorating 3-methyl triacetyl fructose is the same as described for fluorating the acetylated sugars.¹⁹ The receiver contained 4 g. of powdered 3-methyl triacetyl fructose and the still about 40 g. of potassium bifluoride. The distillation was finished in about 45 minutes and the reaction product was worked up directly. After evaporation of the chloroform, the residue crystallized when stirred with ether. The yield of crude product separated by suction was 2.7 g. Upon recrystallization from ether two fractions were obtained; one contained fluorine, the other did not. They differed considerably in melting point and specific rotation. The fluor-containing compound was recrystallized until a constant specific rotation (in chloroform) was reached. The amount of the other compound (which probably was not the original methyl-triacetyl fructose) was too small for purification. *Rotation*: First recrystallization: Subs., 0.5861: $\alpha = -24.15$ S; $[\alpha]_D^{20} = -89.08$. Second recrystallization, first, second, and third fraction, respectively: Subs., 0.5996, 0.5711, 0.4080: $\alpha = -24.60$ S, -23.40 S, -16.75 S; $[\alpha]_D^{20} = -88.70$, -88.57 , -88.75 . The specific rotation of the pure substance in chloroform was taken as -88.7 ; m. p., 113° to 114° . The pure substance crystallizes in needles or small prisms and has a bitter taste. It is very soluble in ordinary solvents except petroleum ether and water. *Analyses*: Subs., 0.2099: CO_2 , 0.3717; H_2O , 0.1120.

¹⁹ See footnote 1, p. 449.

Subs., 0.5000: CaF_2 , 0.0525. OCH_3 determination: Subs., 0.2008: AgI , 0.1499. *Acetyl determination*: Subs., 0.5008: 96.08 cc. of 0.25 N H_2SO_4 , 302.35 cc. of 0.1 N NaOH . *Calculated* for $\text{C}_6\text{H}_7\text{O}_2\text{F}$. OCH_3 ($\text{C}_2\text{H}_3\text{O}_2$)₃: C, 48.42; H, 5.94; F, 5.90; OCH_3 , 9.63; 62.16 cc. of 0.1 N NaOH for $\text{AcOH} + \text{F}$. *Found*: C, 48.30; H, 5.97; F, 5.12; OCH_3 , 9.87; 62.15 cc. of 0.1 N NaOH .

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