

into a bicyclo-octadiene (XI), which is converted by hydrolysis into hydroquinone-acetic acid (homogentisic acid).

Both dibenzalacetone and benzalacetophenone react with one equivalent of ketene acetal to produce 1,1-diethoxy-2-cinnamoyl(or benzoyl)-3-phenyl-cyclobutane. Each of these products may

be hydrolyzed to the known β -phenyl- γ -cinnamoyl(or benzoyl)butyric acid.

Neither dimethylmaleic anhydride nor phorone reacts with ketene acetal under conditions that caused satisfactory reactions with the other α,β -unsaturated carbonyl compounds.

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RECEIVED OCTOBER 27, 1941

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

The Transformation of Tetramethylglucoseen-1,2 into 5-(Methoxymethyl)-2-furaldehyde

BY M. L. WOLFROM, E. G. WALLACE AND E. A. METCALF

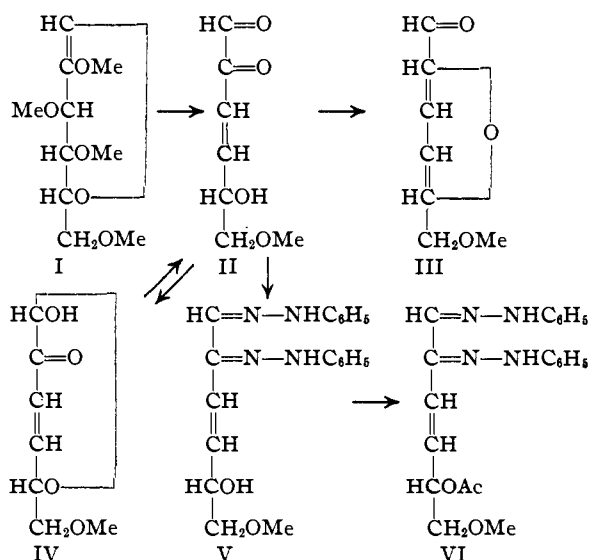
Raymond¹ has made the very reasonable and stimulating suggestion that 2,3,4,6-tetramethyl-*d*-glucoseen-1,2 (I) may be the intermediate in the interconversion of tetramethylglucose and tetramethylmannose in dilute alkali. This interconversion has been investigated by Lewis and his students.² Tetramethylglucoseen was then synthesized in crystalline condition in this Laboratory.³ It was found that this substance was not oxidized by Fehling solution and was thus not alkali-sensitive. Lewis and co-workers² noted that the equilibrated alkaline solution of tetramethylglucose exhibited an abnormally high hypiodite consumption which was brought to a normal value by acid treatment. Tetramethylglucoseen was found³ to consume four atoms of iodine per mole, or a value of 200% "apparent tetramethylaldehyde."

The behavior of tetramethylglucoseen in acid media was then of interest. It was soon found that it did not form a mixture of tetramethylmannose and tetramethylglucose and was thus not an intermediate in the interconversion of these two sugars. Its behavior in acid media was nevertheless of interest and a report of this study is the subject of the present communication.

The final product of the acid treatment of tetramethylglucoseen has been found to be 5-(methoxymethyl)-2-furaldehyde (III). This was identified by freezing point (-8°), analysis, and by its behavior with Fehling solution and with acid resorcinol. Further confirmation of identity

was afforded by the preparation of three crystalline derivatives and comparison of two of these with authentic specimens prepared by other methods. These derivatives were the oxime (m. p. $97-98^\circ$), semicarbazone (m. p. $163.5-164.5^\circ$) and acid (5-(methoxymethyl)-2-furoic acid of m. p. $67.5-68.6^\circ$). This aldehyde (III) is also the product obtained on the acid treatment of tetramethylfructofuranose⁴ and it is of interest to note that the methylated pentoses produce furaldehyde on treatment with mineral acids.⁵

The conversion of tetramethylglucoseen into 5-(methoxymethyl)-2-furaldehyde by mineral acidity is, however, a complex reaction and some information was obtained regarding its course.



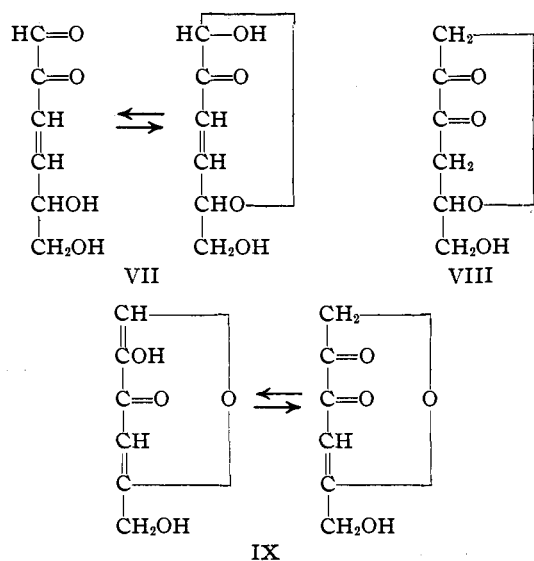
(1) A. L. Raymond in Gilman, "Organic Chemistry," John Wiley and Sons, New York, N. Y., 1938, Vol. II, p. 1512.

(2) M. L. Wolfrom with W. Lee Lewis, *THIS JOURNAL*, **50**, 837 (1928); R. D. Greene with W. Lee Lewis, *ibid.*, **50**, 2813 (1928); cf. J. H. Simons and H. C. Struck, *ibid.*, **56**, 1947 (1934).

(3) M. L. Wolfrom and D. R. Husted, *ibid.*, **59**, 2559 (1937).

(4) W. N. Haworth, E. L. Hirst and V. S. Nicholson, *J. Chem. Soc.*, 1513 (1927).

(5) C. E. Gross with W. Lee Lewis, *THIS JOURNAL*, **53**, 2772 (1931); H. T. Neher with W. Lee Lewis, *ibid.*, **53**, 4411 (1931); H. G. Bott and E. L. Hirst, *J. Chem. Soc.*, 2621 (1932).



It was found that a 5% solution of tetramethylglucoseen in 3 *N* hydrochloric acid at 25° were favorable conditions for following the course of this reaction. Polarimetrically (curve A of Fig. 1) the reaction was found to consist of a very rapid reaction producing a levorotatory substance followed by a slower reaction reaching optical inactivity in about eight hours. A minimum in the polarimetric curve was reached at about sixty-five minutes. The copper reduction curve (curve B of Fig. 1) followed the initial faster reaction whereas the hypiodite consumption curve (curve C of Fig. 1) paralleled the slower reaction. The

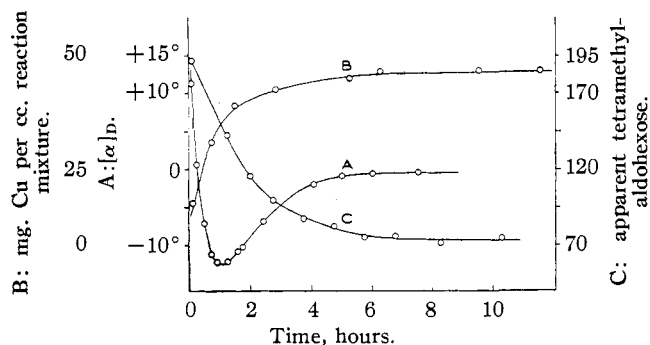
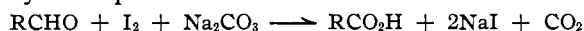


Fig. 1.—Rate of change of 2,3,4,6-tetramethyl-*D*-glucoseen-1,2 (5%) in 3.00 *N* hydrochloric acid at 25° as followed by polarimetry (A), copper reduction (B) and hypiodite consumption (C).

latter began with an iodine consumption of four atoms of iodine per mole of starting tetramethylglucoseen and dropped to a value of about 70% of that required for an iodine consumption of two atoms per mole of tetramethylglucoseen monoaldehydic conversion product (70% "apparent

tetramethylaldehyde"). The reaction between an aldehyde and hypiodite, under the conditions of the Cajori⁶ procedure employed, is represented by the equation



The reaction of tetramethylglucoseen with 3 *N* hydrochloric acid at 25° was interrupted at the sixty-five minute stage, which was the point of minimum in the polarimetric curve. A low yield of final product, 5-(methoxymethyl)-2-furaldehyde, was obtained at this point by isolation as the semicarbazone. A crystalline phenylosazone, not isolable at the completion of the reaction, was obtained. This substance (m. p. 120.5–121.5°) was optically active (spec. rot. -9°, D line, CHCl_3) and analyzed for a monomethyl phenylosazone of the parent structure $\text{C}_6\text{H}_8\text{O}_4$. Bergmann and Zervas⁷ had obtained a phenylosazone of the same parent structure by the direct treatment of glucoseen-1,2 tetraacetate (oxyglucal tetraacetate) with phenylhydrazine and subsequent deacetylation, a monoacetate (very probably on carbon six, being obtained initially. The same substance was produced by these workers from galactoseen-1,2 tetraacetate. For the parent structure, $\text{C}_6\text{H}_8\text{O}_4$, Bergmann and Zervas proposed two formulas (VII and VIII), favoring the latter (VIII), mainly on the basis that their monoacetate was recovered unchanged on further mild acetylation. Formula VIII is a dihydro derivative of kojic acid

(IX) and some additional, but not definitive, support for this structure has been obtained in studies of the phenylosazones of certain racemic reduction products of kojic acid.⁸

These two fundamental structures (VII and VIII, but with a methoxyl group on the terminal primary carbon atom) also come into consideration in allocating a structure to the parent substance of the phenyloszone isolated in our work. Of these, we favor the acyclic tautomer of (VII) for the parent body of our isolated monomethyl phenyloszone (V) because this osazone could be further acetylated and the acetate introduced (VI) was O-acetyl as judged by the fact that it could be saponified by the Kunz procedure.⁹ The experience of this Laboratory has been that the N-acetyl deriva-

(6) F. A. Cajori, *J. Biol. Chem.*, **54**, 617 (1922).

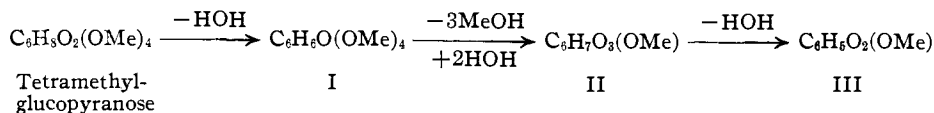
(7) M. Bergmann and L. Zervas, *Ber.*, **64B**, 1434 (1931).

(8) K. Maurer, *ibid.*, **64B**, 2358 (1931); J. W. Armit and T. J. Nolan, *J. Chem. Soc.*, 3023 (1931).

(9) A. Kunz and C. S. Hudson, *This Journal*, **48**, 1982 (1926).

tives of sugar nitrogen carbonyl condensation products are not saponified by this procedure.¹⁰ Our osazone could not be obtained directly from the tetramethylglucoseen but this observation cannot be correlated with the circumstance that glucoseen tetraacetate formed an osazone directly, since the acetate groups are undoubtedly more labile under these conditions than are the corresponding methoxyl groups.

As Bergmann and Zervas⁷ have noted, these transformations of the very sensitive glucoseens can be considered as intramolecular dismutation reactions involving the elimination of water or, in our case, of methanol. This can be represented schematically as follows.



In the course of this work, the preparation of the tetramethylglucoseen was improved, although the previously recorded constants were verified. We also record the crystalline 1-acetate of tetramethylmannopyranose.

Experimental

Preparation of 2,3,4,6-Tetramethyl-*d*-glucoseen-1,2.—The procedure of Wolfrom and Husted³ was modified. In the preparation of the 1-bromo derivative from the 1-acetate of tetramethylglucopyranose, the chloroform was replaced by toluene and the final solvent removal was effected at room temperature or lower, at a pressure of 3–4 mm. After the ether-dioxane solution of the crude tetramethylglucoseen had been filtered from inorganic salts, the sirup obtained on solvent removal under reduced pressure was dissolved in six parts of water, filtered and extracted repeatedly (eight times) with ether. The extracted material was then distilled in a Hickman pot still¹¹ at 10⁻³ mm.; m. p. 13° (by cooling curve method), spec. rot. +15° (32°, *c* 3.8, H₂O).¹² The constants previously recorded³ for this substance were: m. p. 12°, spec. rot. +15° (30°, *c* 2, H₂O). The compound is best stored at the temperature of solid carbon dioxide-acetone, coloration being noted in four to five days at 0°.

Isolation of the Phenylsazone of the Intermediate Product.—2,3,4,6-Tetramethyl-*d*-glucoseen-1,2 (0.25 g.) was dissolved in 5 cc. of 3 *N* hydrochloric acid at 25° and maintained at that temperature for sixty-five minutes. These conditions of acidity and temperature were selected after preliminary experimentation, which showed that the reaction rate increased with temperature and with acid concentration. At the end of this period, the solution

was treated with an excess of barium carbonate, and filtered. To the filtrate was added a filtered solution (5 cc.) containing phenylhydrazine hydrochloride (0.5 g.) and potassium acetate (0.8 g.). The oily solid that separated was removed by decantation, washed with water by decantation and crystallized from ethanol (decolorizing charcoal) by the addition of water; m. p. 118–119.5°. Pure material was obtained on crystallization from acetone-water or ethanol-water; m. p. 120.5–121.5°, spec. rot. -9° (21°, *c* 2.9, U. S. P.¹³ CHCl₃). The substance crystallized in the form of long, yellow needles.

Anal. Calcd. for C₁₈H₁₈ON₄-OCH₃: C, 67.43; H, 6.55; N, 16.56; OCH₃, 9.17. Found: C, 67.43; H, 6.55; N, 16.29; OCH₃, 8.89.

No reaction was noted when tetramethylglucoseen was treated with phenylhydrazine acetate under the above conditions (or at 98° for twenty minutes) but with omission of the 3 *N* acid treatment. This phenylsazone could

not be isolated, even on nucleation, from the oily phenylhydrazine reaction product obtained from the neutralized solution after the completion of the reaction (eight hours at 25°) between tetramethylglucoseen and 3 *N* hydrochloric acid.

Phenylsazone Monoacetate of the Intermediate Product.—The above-described phenylsazone (100 mg.) of the intermediate product was acetylated overnight at 15° with pyridine (2 cc.) and acetic anhydride (0.5 cc.). The crude solid (100 mg.) obtained on pouring the reaction mixture into ice and water was purified from 60% ethanol; m. p. 131–132°. The substance formed flaky, golden crystals and was dextrorotatory in chloroform solution but the amount of material available was insufficient for an evaluation of this constant.

Anal. Calcd. for C₁₈H₁₈ON₄-OCH₃-COCH₃: C, 66.30; H, 6.36; N, 14.73; CH₃CO, 2.43 cc. 0.1 *N* NaOH per 100 mg. Found: C, 66.23; H, 6.33; N, 14.68; O-Ac, 10.261 cc.

5-(Methoxymethyl)-2-furaldehyde from 2,3,4,6-Tetramethyl-*d*-glucoseen-1,2.—2,3,4,6-Tetramethylglucoseen-1,2 (5.45 g.) was brought to a volume of 100 cc. in 3 *N* hydrochloric acid at 25° and maintained at that temperature for eight hours. At the end of this period the solution was neutralized with barium carbonate, filtered and extracted with chloroform. The sirup obtained on solvent removal from the dried chloroform (decolorizing charcoal) extract was distilled in the Hickman pot still at 10⁻³ mm.; yield 2.82 g. (81%). The distillate was not pure for it was slightly optically active. It was purified through the semicarbazone.

The above distillate (2.82 g.) was dissolved in the least amount of hot water. Semicarbazide hydrochloride (2.82 g., 1.25 moles) and sodium acetate (2.5 g., 1.5 moles) were dissolved in a small amount of hot water and added to the above hot solution. The product crystallized on cooling; yield 3.00 g. (76%), m. p. 153.5–154.5°.

(10) M. L. Wolfrom, M. Konigsberg and S. Soltzberg, *This Journal*, **58**, 490 (1936).

(11) K. C. D. Hickman and C. R. Sanford, *J. Phys. Chem.*, **34**, 637 (1930).

(12) All rotations are recorded to the D line of sodium light, 32° is the temperature *c* is the concentration in grams per 100 cc. soln.

(13) United States Pharmacopoeia.

This material was of sufficient purity for the succeeding step but for identification purposes a portion was purified to constant melting point from absolute ethanol; m. p. 163.5–164.5° (uncor.), unchanged on admixture with a specimen of 5-(methoxymethyl)-2-furaldehyde semicarbazone (m. p. 163.5–164.5°) prepared from tetramethylfructofuranose according to the procedure of Haworth, Hirst and Nicholson.⁴ Haworth and co-workers record the melting point of 166–167° for this substance and Middendorp¹⁴ records 170°. We were unable to verify these higher melting points. When the semicarbazone was recrystallized from ethyl acetate–heptane, the maximum melting point was found to be 156–157° but when such a preparation was ground in a mortar the melting point of 163.5–164.5° was obtained.

Anal. Calcd. for $C_7H_9O_2N_3OCH_3$: C, 48.72; H, 5.62; N, 21.31; OCH_3 , 15.74. Found: C, 48.78; H, 5.45; N, 21.64; OCH_3 , 16.13.

This semicarbazone also was isolated, but in low yield, from the neutralized solution obtained after a sixty-five minute reaction period between tetramethylglucoseen and 3 *N* hydrochloric acid at 25°.

The aldehyde was regenerated from the semicarbazone according to the general procedure of Wolfrom, Georges and Soltzberg.¹⁵ The above semicarbazone (3.00 g.) was dissolved in 225 cc. of water at 60° in a flask fitted with an aspirator (nitrogen dioxide fumes) and a mechanical stirrer. A solution of 18 g. of sodium nitrite in 90 cc. of water was added. Then 50 cc. of hydrochloric acid (1:1) was added dropwise. After a three-minute interval, 14.4 g. of sodium nitrite was added slowly, followed after two minutes by the dropwise addition of 28.8 cc. of hydrochloric acid (1:1). After a three-minute interval a like amount of sodium nitrite was added slowly, followed, after a two-minute interval, by a like amount of the acid. After a three-minute interval an equal amount of sodium nitrite was added and stirring (decolorizing charcoal) continued until the evolution of oxides of nitrogen ceased. The filtered solution was extracted with chloroform and the sirup obtained on solvent removal from the dried (decolorizing charcoal) extract was twice distilled from a Hickman pot still at 10^{-3} mm.; yield 1.77 g. (83%), optically inactive, m. p. –8° (by cooling curve). Middendorp¹⁴ records a melting point of –9° for 5-(methoxymethyl)-2-furaldehyde.

Anal. Calcd. for $C_7H_9O_3$: C, 60.00; H, 5.71. Found: C, 59.24; H, 5.62.

The substance had a pleasant, coumarin-like odor, reduced hot Fehling solution and gave a brick-red precipitate on heating a solution made from a drop of the material, 3 cc. of hydrochloric acid (1:2) and a few drops of a 5% resorcinol solution.

The substance formed an oxime which was purified from low boiling petroleum ether–ether; m. p. 97–98° (uncor.) unchanged on admixture with a specimen of 5-(methoxymethyl)-2-furaldehyde oxime (m. p. 97–98°) prepared from tetramethylfructofuranose according to the procedure of Haworth, Hirst and Nicholson.⁴ Haworth and co-

workers⁴ record the melting point of 103–104° for this substance.

For further confirmation of the identity of 5-(methoxymethyl)-2-furaldehyde, the distilled liquid (1.00 g.) was oxidized to the corresponding acid with alkaline permanganate according to the procedure of Franklin and Aston¹⁶ for the preparation of furoic acid from furaldehyde except that the reaction product was isolated in a different manner. The filtrate from the manganese dioxide separation was concentrated to dryness under reduced pressure at 45°, dissolved in a small amount of dilute hydrochloric acid, concentrated under reduced pressure to one-third its volume, acetone added and concentration continued. The crystalline product so obtained was purified from petroleum ether–ether; yield 0.43 g., m. p. 67.5–68.5° (uncor.). Haworth and co-workers⁴ record a melting point of 72–73°, with softening at 69°, for 5-(methoxymethyl)-2-furoic acid and Cooper and Nuttall¹⁷ record 67.5–68.5°.

Tetramethyl-*d*-mannopyranose-1(α)-acetate.—Crystalline tetramethylmannopyranose (100 g.) was acetylated at the temperature of the boiling water-bath for three hours (mechanical stirring) with acetic anhydride (500 cc.) and twice-fused sodium acetate (15 g.). The cooled solution was filtered from undissolved sodium acetate, which was washed with toluene. To the filtrate was added toluene (200 cc.) and anhydrous ether (200 cc.) and the acetic anhydride removed under reduced pressure at 40–50°, more of the toluene and ether being added to the residue and again distilled, to effect complete removal of the acetic anhydride. The resultant sirup was dissolved in anhydrous ether and filtered (decolorizing charcoal) from the sodium acetate. The sirup obtained on ether removal under reduced pressure was crystallized by cooling in a solid carbon dioxide–acetone bath, warming in an ice-bath and stirring with anhydrous ether; yield 52 g. Pure material was obtained on further crystallization from anhydrous ether; m. p. 48.5–49.5°, spec. rot. +63° (21°, *c* 4.6, absolute chloroform), +56° (27°, *c* 3.1, water). The substance was soluble in the common organic solvents and was appreciably soluble in water.

Anal. Calcd. for $C_{10}H_{19}O_6(COCH_3)$: CH_3CO , 3.59 cc. 0.1 *N* NaOH per 100 mg. Found: CH_3CO , 3.62 cc.

We are indebted to Mr. E. Grilly (NYA Project O. S. U.) and to Mr. Arthur D. Evans, Jr., for assistance in the experimental work.

Summary

- 2,3,4,6-Tetramethyl-*d*-glucoseen-1,2 is transformed into 5-(methoxymethyl)-2-furaldehyde by hydrochloric acid.
- The rates of change in optical rotation, copper reduction and alkaline iodine consumption have been followed throughout the course of the reaction.
- An intermediate product has been isolated as a phenylosazone, further characterized as a monoacetate, and a structure (II) proposed for it.

(14) J. A. Middendorp, *Rec. trav. chim.*, **38**, 25 (1919).

(15) M. L. Wolfrom, L. W. Georges and S. Soltzberg, *This Journal*, **56**, 1794 (1934).

(16) P. F. Franklin and F. W. Aston, *J. Chem. Soc.*, **70**, 515 (1901).

(17) W. E. Cooper and W. H. Nuttall, *ibid.*, **99**, 1199 (1911).

