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

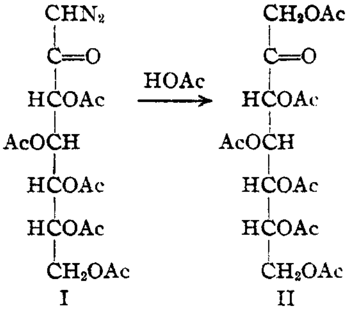
The Action of Diazomethane upon Acyclic Sugar Derivatives. III.[1] A New Synthesis of Ketoses and of their Open Chain (*keto*) Acetates

BY M. L. WOLFROM, S. W. WAISBROT AND ROBERT L. BROWN

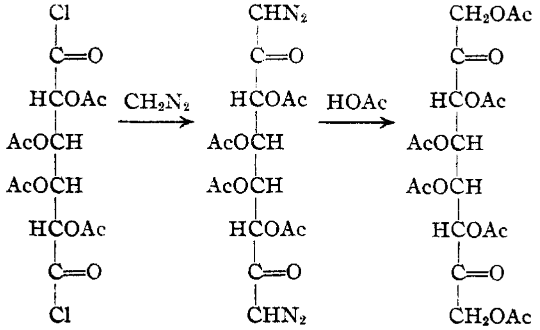
Bradley and Robinson[2] described the reaction of a diazomethyl ketone with acetic acid to produce an acetoxymethyl ketone, although analogous reactions for the acylation of diazoacetic ester had been noted earlier by Staudinger and coworkers.[3] The recent availability of the diazomethyl ketones in the sugar series[4] makes feasible the application of this reaction to the synthesis of ketoses in their open chain or *keto*-acetate structure.

The reaction was first established for the known fructose derivative and the diazomethyl ketone obtained[1] from *d*-arabonyl chloride tetraacetate and diazomethane was found to react smoothly with glacial acetic acid to produce the open chain or *keto*-form of *d*-fructose pentaacetate, a derivative that had been synthesized by Hudson and Brauns[5] by direct acetylation procedures and whose open-chain structure is established.[6] Reaction of I, designated 1-diazo-1-desoxy-*keto*-*d*-glucoheptulose pentaacetate,[4] with acetic acid produced *keto*-*d*-glucoheptulose hexaacetate (II), isomeric with and convertible (by saponification and reacetylation) to the one known cyclic hexaacetate of *d*-glucoheptulose.[7]

Utilizing the acetolysis procedure of Tambor and Du Bois,[8] 1-bromo-1-desoxy-*d*-glucoheptulose pentaacetate[1] was converted into II in somewhat lower yield than from the diazomethyl ketone I and acetic acid. This new acyclic derivative (II) exhibited no mutarotation in either chloroform or methanol solution and its ultraviolet absorption spectrum in U. S. P. chloroform revealed a pronounced absorption maximum at 2830 Å. (log $\epsilon_{\max.} = 1.60$ at 2830 Å.) which corresponds closely to the value reported by Baldwin, Wolfrom and Lowry[9] for *keto*-*d*-fructose pentaacetate (log $\epsilon_{\max.} = 1.59$ at 2830 Å.) and by Khouvine and Arragon[10] for *keto*-*l*-sorbose pentaacetate (absorption maximum at about 2800 Å.). Inasmuch as it has been shown that the cyclic acetates do not exhibit an absorption maximum in the region of that for the ketonic carbonyl group,[10] these data constitute proof that no ring closure has occurred during the series of reactions leading to the formation of the new derivatives and confirm the assignment of the acyclic or *keto* structure to our compound.



I II



III IV V

The series of reactions recorded above provide a general method for the synthesis of acyclic ketose acetates and represent a transformation of an aldose to the next higher ketose. It was then of interest to apply these reactions to a dibasic sugar acid and for this purpose the long-known mucyl dichloride tetraacetate (III)[11] was selected. From III the bisdiazomethyl ketone IV was obtained. Treatment of IV with hydrogen chloride yielded

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[1] Previous publication in this series: M. L. Wolfrom, S. W. Waisbrot and Robert L. Brown, THIS JOURNAL, **64**, 1701 (1942).

[2] W. Bradley and R. Robinson, *J. Chem. Soc.*, 1310 (1928); *ibid.*, 1545.

[3] H. Staudinger and C. Mächling, *Ber.*, **49**, 1973 (1916); H. S. Staudinger, J. Becker and H. Hirzel, *ibid.*, 1978.

[4] M. L. Wolfrom, D. I. Weisblat, W. H. Zophy and S. W. Waisbrot, THIS JOURNAL, **63**, 201 (1941).

[5] C. S. Hudson and D. H. Brauns, *ibid.*, **37**, 2736 (1915).

[6] E. Pacsu and F. V. Rich, *ibid.*, **55**, 3018 (1933); M. L. Wolfrom and A. Thompson, *ibid.*, **56**, 880 (1934).

[7] W. C. Austin, *ibid.*, **54**, 1925 (1932); M. L. Wolfrom and A. Thompson, *ibid.*, **56**, 1804 (1934).

[8] J. Tambor and E. M. Du Bois, *Ber.*, **51**, 748 (1918).

[9] W. C. G. Baldwin, M. L. Wolfrom and T. M. Lowry, *J. Chem. Soc.*, 696 (1935).

[10] Yvonne Khouvine and G. Arragon, *Bull. soc. chim.*, [5] **5**, 1404 (1938).

[11] E. Jacoby, Inaugural Dissertation, Berlin, 1907; O. Diels and F. Löflund, *Ber.*, **47**, 2351 (1914); J. Müller, *ibid.*, **47**, 2654 (1914).

the dichloro derivative and treatment with acetic acid produced the well-crystallized diketose acetate V, designated 1,8-dihydroxy-mucyldimethane hexaacetate. This is an open chain acetate of a diketose, a new type of derivative in the sugar field.

Extension of this work is in progress in this Laboratory.

Experimental

***keto-d*-Fructose Pentaacetate.**—1-Diazo-1-desoxy-*keto-d*-fructose tetraacetate[1] (1 g.) was dissolved in glacial acetic acid (25 cc.) and refluxed for one hour. The dark brown solution was poured on crushed ice, and the resulting solution was extracted with three 25-cc. portions of chloroform. The combined extracts were washed free of acetic acid with water and the solution dried. Upon solvent removal under reduced pressure, a dark sirup was obtained which was dissolved in 20 cc. of absolute ethanol, decolorized repeatedly with charcoal and concentrated under reduced pressure to 8 cc. Upon standing in the ice-chest the concentrate yielded 0.5 g. of pale yellow crystals; m. p. 63–67°. Several recrystallizations from ethanol yielded a pure product identified by melting point, mixed melting point and rotation as *keto-d*-fructose pentaacetate for which Hudson and Brauns[5] record the constants; m. p. 69–70°, spec. rot.[12] +35° ($CHCl_3$).

***keto-d*-Glucoheptulose Hexaacetate (II).**—1-Diazo-1-desoxy-*keto-d*-glucoheptulose pentaacetate[4] (I, 5.0 g.) was dissolved in glacial acetic acid (100 cc.) and the solution refluxed to the cessation of nitrogen evolution (ten to fifteen minutes; delivery tube from condenser top placed in water as indicator). The hot reaction mixture was poured on crushed ice (400 g.) and the resulting solution extracted with four 50-cc. portions of chloroform. The extract was washed free of acetic acid with water, dried over Drierite and decolorized (Darco). Upon solvent removal under reduced pressure the product crystallized spontaneously as light yellow needles. The crystalline mass was dissolved in 60 cc. of hot 1:4 ethanol–water, decolorized and diluted with an equal volume of warm water. Upon cooling, the product separated as long, white prismatic needles; yield 3.7 g. (70%), m. p. 103.5–105°, spec. rot. +18° (abs. $CHCl_3$). Three additional crystallizations were effected by solution in 15 parts of hot 1:4 ethanol–water and dilution with an equal volume of water to yield pure *keto-d*-glucoheptulose hexaacetate; m. p. 104–105°, spec. rot. +18.7° (22°, *c* 2.7, U. S. P. or abs. $CHCl_3$). These constants remained unchanged on further crystallization from aqueous ethanol or acetone–petroleum ether.

The substance was soluble in ethanol, acetone, acetic acid and warm ether but was insoluble in water and petroleum ether. The compound exhibited no detectable mutarotation in either chloroform or methanol solution. An absorption spectrum analysis[13] of the substance in chloroform (U. S. P.) solution (0.0377 molar) revealed an absorption maximum at 2830 Å. (log $\epsilon_{\max.}$ = 1.60 at 2830 Å.).

Anal. Calcd. for $C_7H_8O_7(CH_3CO)_6$: C, 49.35; H, 5.67; CH_3CO, 12.97 cc. 0.1 *N* NaOH per 100 mg. Found: C, 49.33; H, 5.53; CH_3CO, 12.90 cc.

keto-d-Glucoheptulose hexaacetate could also be prepared from 1-bromo-*keto-d*-glucoheptulose pentaacetate[1] by the general acetolysis procedure of Tambor and Du Bois.[8] The bromo derivative (2 g.) was dissolved in acetic anhydride (10 cc.) containing fused potassium acetate (3 g.). After shaking for five minutes the mixture was heated for thirty minutes at 70° and then allowed to stand overnight. The crystals obtained on pouring the reaction mixture into ice and water were removed by filtration and washed with a small amount of cold ether; yield 0.9 g., m. p. 102°, spec. rot. +17° ($CHCl_3$). Further purification yielded pure material identified by melting point, mixed melting point and rotation as *keto-d*-glucoheptulose hexaacetate.

The nature of the sugar portion in the above compound was verified by transformation into the one known cyclic hexaacetate of *d*-glucoheptulose.[7] *keto-d*-Glucoheptulose hexaacetate (1.0 g.) was treated for an hour at 0° with a dry methanol solution of anhydrous ammonia. The sirup obtained on solvent removal under reduced pressure was acetylated at 100° with acetic anhydride and sodium acetate, and the product obtained on pouring the cooled reaction mixture into water was recrystallized (decolorizing charcoal) from 75% ethanol; yield 0.2 g., m. p. 114.5–115.5°, spec. rot. +86° (23°, *c* 3, U. S. P. $CHCl_3$). A mixed melting point with an authentic specimen of *d*-glucoheptulose hexaacetate (m. p. 114.5–115°) was unchanged. Austin[7] recorded the following constants for *d*-glucoheptulose hexaacetate: m. p. 112°, spec. rot. +87° ($CHCl_3$). Wolfrom and Thompson[7] found the constants: m. p. 115–116°, spec. rot. +87° ($CHCl_3$). The present product is therefore identified as the *d*-glucoheptulose hexaacetate of Austin.

1,8-Bisdiazo-mucyldimethane Tetraacetate (IV).—Mucyl dichloride tetraacetate[11] (III, 4 g.) was suspended in anhydrous ether and added slowly with continuous stirring to a solution of diazomethane (4 g.) in 200 cc. of anhydrous ether, previously cooled in an ice–salt bath. The reaction was maintained at the temperature of the ice–salt bath for two hours, whereupon the product was removed by filtration and washed with ether. Pure material was obtained on further crystallization from ethanol; yield 3.5 g., m. p. 179–180° (dec.). The crystals were soluble in acetone, chloroform and dioxane.

Anal. Calcd. for $C_{16}H_{18}O_{10}N_4$: C, 45.07; H, 4.25; N, 13.14. Found: C, 45.13; H, 4.31; N, 12.82.

1,8-Dichloro-mucyldimethane Tetraacetate.—1,8-Bisdiazomucyldimethane tetraacetate (IV, 1 g.) was suspended in ether (40 cc.) and treated, under cooling, for thirty minutes with a stream of dry hydrogen chloride, whereupon the chloro compound formed was removed by filtration and purified by crystallization from ether; yield practically quantitative, m. p. 174–175°.

Anal. Calcd. for $C_{16}H_{20}O_{10}Cl_2$: C, 43.35; H, 4.55; Cl, 16.0. Found: C, 43.47; H, 4.67; Cl, 15.4.

1,8-Dihydroxy-mucyldimethane Hexaacetate (V).—1,8-Bisdiazo-mucyldimethane tetraacetate (IV, 1 g.) was refluxed for thirty minutes with glacial acetic acid (10 cc.),

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[12] All rotations are recorded to the D-line of sodium light.

[13] We are indebted to Professor W. R. Brode and Mr. John Patterson of this Laboratory for this analysis.

whereupon the cooled solution was poured on ice (25 g.) and the separated solid removed by filtration and purified by crystallization from ethanol; m. p. 193–195° (dec.).

Anal. Calcd. for $C_{20}H_{26}O_{14}$: C, 48.98; H, 5.34. Found: C, 48.76; H, 5.31.

We acknowledge the assistance rendered in a portion of this work by Messrs. Ralph S. Klopper and Stephen Olin.

Summary

1. The known *keto-d*-fructose pentaacetate has been synthesized by the reaction between acetic acid and 1-diazo-1-desoxy-*keto-d*-fructose tetraacetate.

2. Acetic acid was reacted with 1-diazo-1-desoxy-*keto-d*-glucoheptulose pentaacetate (I) to produce *keto-d*-glucoheptulose hexaacetate (II), also obtainable by the acetylation of 1-bromo-*keto-d*-glucoheptulose pentaacetate.

3. Mucyl dichloride tetraacetate (III) was treated with diazomethane to produce the bisdiazomethyl ketone (IV) from which the 1,8-dichloride and the 1,8-diacetoxy (V) derivatives were formed. The latter is an acetate of a diketose, a new type of structure in the sugar field.

4. The above reactions establish a new synthesis of *keto*-acetates from aldose derivatives of lower (one or two carbon atoms) carbon content.

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[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Structure of the Dextrins Isolated from Corn Sirup[1]

BY MELVIN LEVINE, JOSEPH F. FOSTER AND R. M. HIXON

The structural differences between the different starches and starch fractions, especially with regard to the questions of branching and non-reducing fractions, would appear to be somewhat clarified by a more complete study of the structure of the low molecular weight products of hydrolysis. In the older literature Brown[2] concluded that these products consist essentially of maltose and a "stable dextrin" of definite molecular size (about 40 glucose units) with a specific rotation of about 196° and a reducing power equivalent to 5.5% maltose, or about the value which would be expected for a molecule of this size if it terminated in a reducing glucose molecule. These results have been partially accepted in the corn sirup industry where "dextrin" is considered to be a definite substance having the rotation reported by Brown, but considered to be non-reducing.[3] From a theoretical standpoint these degradation products would be expected to consist of a mixture of glucose polymers of varying chain length, and with reducing power and specific rotation[4] depending on the chain length. If the original starch contains branching, as the present evidence indicates, these molecules might be expected to be further complicated.

The method which we are reporting in this paper for isolating the dextrins from corn sirup was developed primarily to make these materials available in relatively large quantities for physiological investigations. The availability of such dextrins together with the theoretical importance of a more complete knowledge of their structure has encouraged a rather detailed investigation of these materials, especially with regard to the questions of branching and the presence of any non-reducing fractions.

Experimental

Isolation of Crude Dextrins from Corn Sirup.—The conditions used for the isolation of the dextrins were selected after a study of the solubilities of glucose and maltose in aqueous alcohol (Fig. 1). Fifteen pounds of corn sirup[5] was weighed into a five-gallon container. Enough absolute methyl alcohol to bring the concentration to 80–85% was added, the mixture heated to 55° in a water-bath and stirred thoroughly until a homogeneous mixture was obtained, which was allowed to stand at approximately 45° until the supernatant alcoholic extract was clear (twenty-four to forty-eight hours) and was then decanted. The residual heavy sirup was again extracted with approximately three volumes of 80% alcohol by stirring at 55°, allowing to settle at 40°, and decanting the clear supernatant liquor. This extraction process was repeated four times.

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(1) Journal Paper No. J-1007 of the Iowa Agricultural Experiment Station, Ames, Iowa; Projects No. 688 and 516. Supported in part by a grant from the Corn Industries Research Foundation.

(2) Brown and Millar, *J. Chem. Soc.*, **75**, 315 (1899).

(3) For one method of analysis and a review of the general methods in use see Fetzer, Evans and Longnecker, *Ind. Eng. Chem.*, *Anal. Ed.*, **5**, 81 (1933).

(4) Freudenberg, Friedrich and Bumann, *Ann.*, **494**, 41 (1932).

(5) The corn sirup used was Amaizo Crystal White, 41 purity, 43° Bé., furnished by the American Maize Products Company, Roby, Ind.