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

The Action of Diazomethane upon Acyclic Sugar Derivatives. I

BY M. L. WOLFROM, D. I. WEISBLAT, W. H. ZOPHY AND S. W. WAISBROT

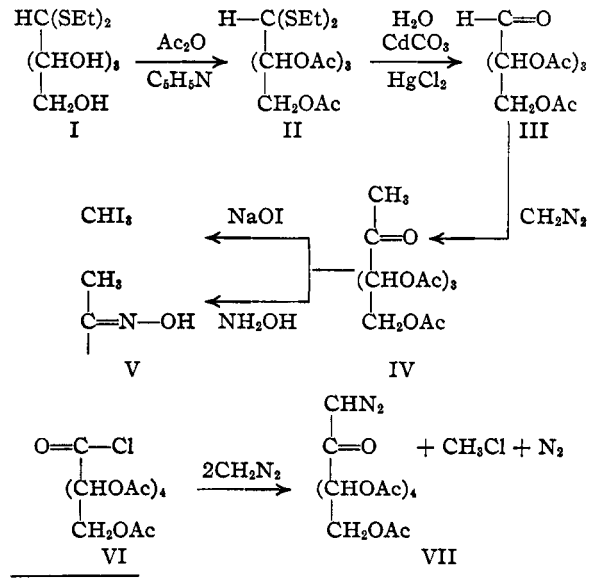
A characteristic reaction of an aldehyde, discovered by Meyer[1] and more closely investigated by Schlotterbeck,[2] is its conversion to the corresponding methyl ketone by the action of diazomethane. Brigl and co-workers[3] applied this reaction to *aldehydo-d*-glucose 3,4,5,6-tetrabenzoate in their proof of structure of this substance. They obtained a crystalline product which exhibited the analysis expected for a methyl ketone but for which no complete proof of structure was offered.

In the work herein reported we have studied the action of diazomethane upon *aldehydo-l*-arabinose tetraacetate[4] (III) and have found that a crystalline product is obtained which has been characterized as the methyl ketone and may be designated 1-desoxy-*keto-l*-fructose tetraacetate (IV). This reaction is of considerable interest to the carbohydrate chemist since it provides a means of converting an aldose into a ketose. As a *d*-fructose derivative is of more immediate interest than is a derivative of the *l*-variety, the enantiomorphic methyl ketone was prepared from *aldehydo-d*-arabinose tetraacetate (III), which latter substance was prepared from *d*-arabinose by the procedure used for the synthesis of its enantimorph. The diazomethane reaction product (IV) (m. p. 77–78°, spec. rot. +55.5° in abs. $CHCl_3$) was proved to be the expected 1-desoxy-*keto-d*-fructose tetraacetate (IV) by analysis; by formation of a crystalline oxime; and by the fact that it gave positive iodoform, Seliwanoff (ketose) and Fehling reduction reactions.

The reaction of diazomethane with an aldehyde is not always simple and products other than the methyl ketone may be formed. A general mechanism for this process has been proposed by Arndt.[5] In accordance with this viewpoint, a second product has been found in our reaction mixture which is still under further investigation but which undoubtedly will be interpretable on the basis of the Arndt mechanism. For purposes of contemplated further work, however, the methyl ketone was the desired product.

The action of diazomethane upon an acid chloride was studied by Clibbens and Nierenstein,[6] who obtained α-chloroacetophenone from benzoyl chloride. Arndt and co-workers[7] showed that such a reaction may follow a different course and obtained diazomethyl ketones from a number of acid chlorides.

In the sugar field, Gätzi and Reichstein[8] obtained a sirupy diazomethyl ketone by the action of diazomethane upon diethylidene-*l*-xylonyl chloride and Iwadare[9] obtained a sirupy diazomethyl ketone from isopropylidene-*d*-glyceryl chloride and diazomethane. In the work herein reported, we have studied the action of diazomethane upon *d*-gluconyl chloride pentaacetate[10] (VI) and have obtained a crystalline product which showed Fehling reduction and which by analysis was characterized as the diazomethyl ketone and may be designated 1-diazo-1-desoxy-*keto-d*-glucoheptulose pentaacetate (VII). Evidence for the formation of a chlorine-containing compound, prob-



(1) H. Meyer, *Monatsh.*, **26**, 1295 (1905).
(2) F. Schlotterbeck, *Ber.*, **40**, 479 (1907).
(3) P. Brigl, H. Mühlschlegel and R. Schinle, *ibid.*, **64**, 2921 (1931).
(4) M. L. Wolfrom and Mildred R. Newlin, THIS JOURNAL, **52**, 3619 (1930).
(5) F. Arndt and B. Eistert, *Ber.*, **68**, 196 (1935); *cf.* H. H. Lewis, M. Nierenstein and E. M. Rich, THIS JOURNAL, **47**, 1728 (1925).
(6) D. A. Clibbens and M. Nierenstein, *J. Chem. Soc.*, 1491 (1915).
(7) F. Arndt, B. Eistert and W. Partale, *Ber.*, **60**, 1364 (1927); F. Arndt and J. Amende, *ibid.*, **61**, 1122 (1928).
(8) K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **21**, 186 (1938).
(9) K. Iwadare, *Bull. Chem. Soc. Japan*, **14**, 131 (1939).
(10) R. T. Major and E. W. Cook, THIS JOURNAL, **58**, 2477 (1936).

ably the chloromethyl ketone, was also obtained but further investigation will be required to characterize this substance in pure form. It is probable that this by-product is produced by the action on the diazomethyl ketone of hydrogen chloride formed in the reaction mixture by traces of moisture.

Further work is in progress in this Laboratory.

Experimental

***d*-Arabinose Diethyl Mercaptal (I).**—This substance was prepared from *d*-arabinose[11] (80 g.) according to the procedure described by Fischer[12] for the *l*-modification; yield 100 g., m. p. 125–126°, spec. rot. 0° (23°, *c* 3.0, pyridine).[13] The substance was soluble in warm water and was practically insoluble in cold water, alcohol and ether. For the enantiomorph, Fischer recorded similar solubilities and a melting point of 124–126°.

Anal. Calcd. for $C_9H_{20}O_4S_2$: S, 24.97. Found: S, 25.16.

***d*-Arabinose Diethyl Mercaptal Tetraacetate (II).**—This substance was prepared according to the procedure described by Wolfrom and Newlin[4] for *l*-arabinose diethyl mercaptal tetraacetate; yield practically quantitative; m. p. 80°, spec. rot. +30° (23°, *c* 4.2, U. S. P. $CHCl_3$). For the enantiomorph, Wolfrom and Newlin recorded the constants: m. p. 80°, spec. rot. −30° ($CHCl_3$).

Anal. Calcd. for $C_5H_6O_4(CH_3CO)_4(SC_2H_5)_2$: CH_3CO, 9.43 cc. 0.1 *N* NaOH per 100 mg. Found: CH_3CO, 9.50 cc.

aldehydo-d-**Arabinose Tetraacetate (III).**—The improved demercaptalation procedure of Wolfrom and Konigsberg[14] was used in removing the thioacetal groups from *d*-arabinose diethyl mercaptal tetraacetate. To 100 g. of *d*-arabinose diethyl mercaptal tetraacetate dissolved in 360 cc. of acetone was added 200 g. of finely powdered cadmium carbonate and 40 cc. of water. To this was added with vigorous stirring 236 g. of mercuric chloride dissolved in 360 cc. of acetone. The vigorous mechanical stirring was maintained for twenty hours at room temperature. The mixture was filtered into a flask containing 20 g. of cadmium carbonate. The residue on the filter was washed thoroughly with acetone and the combined solvent removed under reduced pressure (45–50°) in the presence of the cadmium carbonate.

The residue was extracted with several portions of warm chloroform (U. S. P.) and the extract washed with an aqueous solution of potassium iodide and then with water until free of halides. The dried, decolorized, chloroform solution was concentrated to a thick sirup under reduced pressure (45–50°). The product crystallized from an acetone–ether–petroleum ether mixture (2:1:3); yield 38 g., m. p. 112–114°. Pure material was obtained on two more crystallizations from the same solvent mixture; m. p. 113–115°, spec. rot. +65° (23°, *c* 4.1, abs. $CHCl_3$). The solubility behavior, crystalline form, and reducing character were the same as have been reported for *aldehydo-l*-arabinose tetraacetate for which Wolfrom and Newlin[4] recorded the constants: m. p. 113–115°, spec. rot. −66° (abs. $CHCl_3$).

Anal. Calcd. for $C_5H_6O_5(CH_3CO)_4$: C, 49.04; H, 5.69; CH_3CO, 12.6 cc. 0.1 *N* NaOH per 100 mg. Found: C, 49.33; H, 5.67; CH_3CO, 12.6 cc.

aldehydo-d-**Arabinose Semicarbazone Tetraacetate.**—The semicarbazone was prepared in a manner analogous to that used by Wolfrom and Newlin[4] for its enantiomorph; yield practically quantitative, m. p. 183–185°, spec. rot. −72.0° (30°, *c* 1.2, abs. $CHCl_3$). Wolfrom and Newlin recorded for the enantiomorph: m. p. 184–187°.

Anal. Calcd. for $C_6H_9O_5N_3(CH_3CO)_4$: CH_3CO, 10.7 cc. 0.1 *N* NaOH per 100 mg.; N, 11.20. Found: CH_3CO, 10.7 cc.; N, 11.29.

1-Desoxy-*keto-d*-**fructose Tetraacetate (IV).**—The diazomethane used in this work was generated by the action of methyl alcoholic potassium hydroxide on ethyl N-methyl-N-nitroso-carbamate according to the procedure of von Pechmann.[15]

The diazomethane generated by the decomposition of 20 cc. of the urethan was distilled in an ether stream directly into an absolute chloroform solution of 24 g. of *aldehydo-d*-arabinose tetraacetate cooled to 0–5°. There was a steady, vigorous evolution of nitrogen as the reaction proceeded. The yellow color of the diazomethane was discharged very quickly until about three-fourths of the total quantity had been added. The solution then acquired a permanent yellow tinge indicative of an excess of diazomethane. Upon standing overnight at room temperature the reaction mixture was again colorless. The amorphous precipitate of polymethylenes was removed by filtration and the solvent removed by concentration. The sirup was taken up in 50 cc. of absolute ethanol and the solution made opalescent by the addition of petroleum ether. The product crystallized slowly, in beautiful cubic crystals, on standing in an ice-box; yield 15.4 g. (two crops, 62% of theory), m. p. 75–77°. Pure material was obtained after four recrystallizations from 95% ethanol; m. p. 77–78°, spec. rot. +55.5° (30°, *c* 3.3, abs. $CHCl_3$), +58.3° (22°, *c* 3.0, methanol, no mutarotation).

The substance reduced Fehling solution very readily. It was insoluble in cold and warm water, and in petroleum ether, but was readily soluble in methanol, warm ethanol, acetone, chloroform and warm ether. The product gave a deep yellow color with cold alcoholic potassium hydroxide. Under the conditions of the Seliwanoff[16] reaction the substance first gave a yellow color which changed to the cherry red characteristic of ketoses, after standing for about one hour. *keto-d*-Fructose pentaacetate produced the color in fifteen minutes. Under these same conditions acetone gave a permanent yellow color and *aldehydo-d*-arabinose tetraacetate produced no color whatsoever. The Kiliani[17] color test for 2-desoxy sugars was negative.

Anal. Calcd. for $C_6H_5O_5(CH_3CO)_4$: C, 50.59; H, 6.08;

(11) R. C. Hockett and C. S. Hudson, THIS JOURNAL, **56**, 1632 (1934).

(12) E. Fischer, *Ber.*, **27**, 673 (1894).

(13) All rotations are recorded to the D-line of sodium light; 23° is the temperature; *c* is the concentration in g. per 100 cc. of soln.

(14) M. L. Wolfrom and M. Konigsberg, THIS JOURNAL, **61**, 574 (1939).

(15) H. von Pechmann, *Ber.*, **28**, 855 (1895).

(16) T. Seliwanoff, *ibid.*, **20**, 181 (1887).

(17) H. Kiliani, *Arch. Pharm.*, **234**, 276 (1896); **251**, 576 (1913).

CH_3CO, 12.0 cc. 0.1 *N* NaOH per 100 mg. Found: C, 50.41; H, 6.12; CH_3CO, 12.1 cc. (Freudenberg method[18]).

On working up the mother liquor material from the above compound from ethanol–water followed by chloroform–alcohol there was obtained a crystalline substance (m. p. 162–164° with dec., spec. rot. +41° in abs. $CHCl_3$) which is under further investigation.

1-Desoxy-*keto*-*l*-fructose Tetraacetate (IV).—*aldehydo*-*l*-Arabinose tetraacetate was treated with diazomethane and the product isolated as described above for its enantiomorph; m. p. 77–78°, spec. rot. +55° (25°, *c* 3.9, abs. $CHCl_3$).

The substance reduced Fehling solution and displayed the same solubility and reactivity as its enantiomorph.

Anal. Calcd. for $C_{14}H_{20}O_9$; C, 50.59; H, 6.08. Found: C, 50.72; H, 6.04.

On working up the mother liquor material from the above compound as described for its enantiomorph, there was obtained a crystalline substance (m. p. 162–164° with dec., spec. rot. −41° in abs. $CHCl_3$).

1-Desoxy-*keto*-*d,l*-fructose Tetraacetate (IV).—An amount of 100 mg. of 1-desoxy-*keto*-*d*-fructose tetraacetate, m. p. 77–78°, and 100 mg. of 1-desoxy-*keto*-*l*-fructose tetraacetate, m. p. 77–78°, was dissolved in 1 cc. of 95% ethanol. The racemate crystallized in clusters of small irregular plates; yield 0.18 g., m. p. 95–97°, spec. rot. 0° (32°, *c* 3.9, abs. $CHCl_3$)

1-Desoxy-*keto*-*d*-fructose Oxime Tetraacetate (V).—An amount of 0.45 g. (1 mole) of 1-desoxy-*keto*-*d*-fructose tetraacetate was dissolved in 10 cc. of absolute ethanol. A solution of 0.20 g. (2 moles) of hydroxylamine hydrochloride and 0.40 g. (3 moles) of potassium acetate in 5 cc. of aqueous alcohol (1:1) was added and the mixture shaken vigorously. After standing for three hours at room temperature the solvent was removed by a stream of dry air and the oxime extracted from the inorganic material with several portions of warm methanol. The methanol solution was concentrated to approximately 1 cc. and 3 cc. of water added. Upon standing in the ice-box, the oxime crystallized in beautiful, transparent, four-sided plates; yield 0.25 g., m. p. 102–107°. Pure material was obtained on three recrystallizations from the same solvent; m. p. 112–113°, spec. rot. +8.7° (33°, *c* 2.8, abs. $CHCl_3$). The substance was moderately soluble in methanol, ethanol and chloroform and was practically insoluble in water and petroleum ether.

Anal. Calcd. for $C_6H_9O_5N(CH_3CO)_4$: C, 48.41; H, 6.10; N, 4.03. Found: C, 48.61; H, 6.28; N, 3.98.

Conversion of 1-Desoxy-*keto*-*d*-fructose Tetraacetate into Iodoform.—The procedure employed was that of Fuson and Tullock[19] for water-insoluble substances. 1-Desoxy-*keto*-*d*-fructose tetraacetate (1 g.) was dissolved in 3 cc. of dioxane; 1 cc. of 10% sodium hydroxide solution was added and the mixture shaken. An iodine solution (10 g. of iodine and 20 g. of potassium iodide in 80 cc. of water) was then added in small portions until a definite excess was present. The mixture was warmed for several minutes in a water-bath at 60°; the excess iodine was removed by the addition of the necessary amount of the 10% base and then diluted with water. A yellow precipitate of iodoform crystallized upon standing; yield 50 mg.; m. p. 120–121° (mixed m. p. with an authentic sample of iodoform showed no depression). Blanks on the reagents and on *aldehydo*-*d*-arabinose tetraacetate yielded no iodoform.

1-Diazo-1-desoxy-*keto*-*d*-glucoheptulose Pentaacetate[20] (VII).—To a solution of 2.1 g. (2.3 moles) of diazomethane dissolved in anhydrous ether at 0°, was added slowly with stirring 5 g. (1 mole) of *d*-gluconyl chloride pentaacetate[10] dissolved in 50 cc. of anhydrous ether. The solution stood at room temperature for three hours. The ether was then removed by a stream of dry air. The residue was dissolved in warm ether and upon cooling the product crystallized. Pure material was obtained on several recrystallizations from ether; yield 2.5 g., m. p. 106–106.5°; spec. rot. +65.8° (30°, *c* 4, abs. $CHCl_3$).

The product crystallized in rosets of needles. The substance was soluble in acetone, chloroform, alcohol and warm ether. It was insoluble in water, ligroin and cold ether. Fehling solution was reduced upon heating at the boiling point for a few minutes.

Anal. Calcd. for $C_{17}H_{22}O_{11}N_2$: C, 47.44; H, 5.15; N, 6.51. Found: C, 47.58; H, 5.13; N, 6.62.

On ethanol recrystallization of the mother liquor material from the above compound there was obtained a chlorine-containing crystalline substance (m. p. 86°) which is under further investigation.

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Summary

1. *d*-Arabinose diethyl mercaptal (I) (and its tetraacetate) has been synthesized.

2. *aldehydo*-*d*-Arabinose tetraacetate (III) (and its semicarbazone) has been synthesized from *d*-arabinose diethyl mercaptal tetraacetate.

3. The action of diazomethane upon *aldehydo*-*d*-arabinose tetraacetate (and *aldehydo*-*l*-arabinose tetraacetate) produced a crystalline substance which is designated 1-desoxy-*keto*-*d*-fructose tetraacetate (IV) (and 1-desoxy-*keto*-*l*-fructose tetraacetate) and its stucture is made probable by its ability to yield an oxime; to undergo the iodoform reaction; and to give a positive Seliwanoff reaction.

4. The action of diazomethane upon *d*-gluconyl chloride pentaacetate produced a crystalline substance designated 1-diazo-1-desoxy-*keto*-*d*-glucoheptulose pentaacetate (VII).

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(18) K. Freudenberg and M. Harder, *Ann.*, **433**, 230 (1923).

(19) R. C. Fuson and C. W. Tullock, THIS JOURNAL, **56**, 1638 (1934).

(20) Experimental work by S. W. Waisbrot.