from gramine methiodide and potassium silver cyanide.

The tertiary amine (gramine) reacts with malonic ester in the presence of a small amount of the sodium derivative of the ester to yield ethyl α-carbethoxy-β-(3-indole)-propionate. However, the yield of alkylation product obtained from the amine is inferior to that obtained from the amine methiodide.

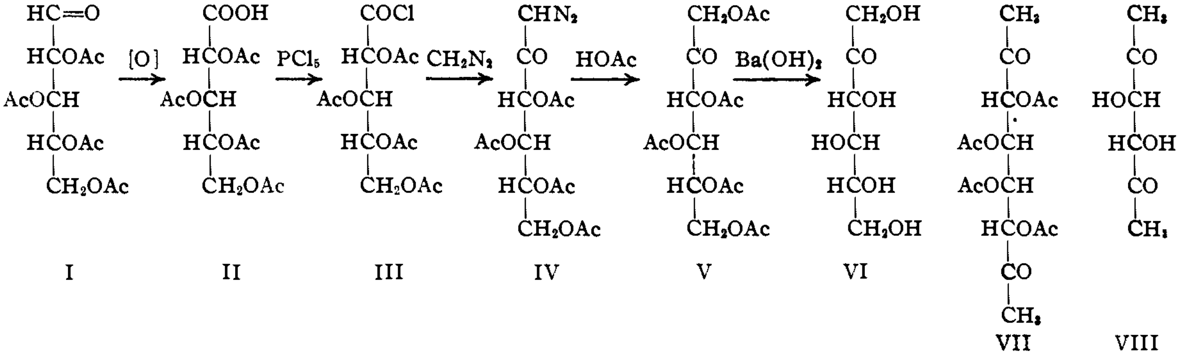
URBANA, ILLINOIS RECEIVED OCTOBER 2, 1943

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

The Action of Diazomethane upon Acyclic Sugar Derivatives. VI.[1] D-Sorbose[2]

BY M. L. WOLFROM, S. M. OLIN AND EVAN F. EVANS[3]

In continuation of our work upon the action of diazomethane upon acyclic sugar derivatives, we have synthesized 1-desoxy-1-diazo-*keto*-D-sorbose tetraacetate (IV) from D-xylonyl chloride tetraacetate (III). D-Xylonic acid tetraacetate (II) was prepared by the oxidation of *aldehydo*-D-xylose tetraacetate (I) according to the procedure reported by Major and Cook.[4] We describe an improved preparation of *aldehydo*-D-xylose tetraacetate[5] from D-xylose diethyl mercaptal tetraacetate, utilizing the general techniques of Wolfrom and Konigsberg.[6] The constants of Major and Cook[4] for I (m. p. 90–91°, spec. rot. +22.5° in absolute chloroform, for the L-form) have been verified. The rotation value differs appreciably from that previously reported[5] (m. p. 87–89°, spec. rot. −16° in chloroform, for the D-form). D-Xylonyl chloride tetraacetate has apparently not been recorded, although Major and Cook[7] described the D,L form.



I II III IV V VI VII VIII

Treatment of the diazomethyl ketone IV with acetic acid yielded *keto*-D-sorbose pentaacetate, enantiomorphic with the substance prepared by Arragon[8] and, nearly simultaneously, by Schlubach and Vorwerk[9] through the direct acetylation of L-sorbose. The acyclic nature of *keto*-L-sorbose pentaacetate was demonstrated by Cramer and Pacsu[10] and shortly later by Arragon.[11] We report herein a crystalline oxime of *keto*-L-sorbose pentaacetate. To our knowledge, this is the first nitrogen condensation product obtained for an acyclic or *keto* form of a ketohexose pentaacetate, previous attempts[10,12] having been unsuccessful. We record also the D,L form of *keto*-sorbose pentaacetate.

Careful saponification of *keto*-D-sorbose pentaacetate led to the synthesis of D-sorbose. Previous saponifications of the enantiomorphic derivative have been recorded by Schlubach and Vorwerk[9] and by Arragon.[11] This synthesis of D-sorbose from D-xylose compares with the synthesis of L-sorbose reported by Gätzi and Reichstein.[13] These workers oxidized diethylidene-(*levo*)-sorbitol to diethylidene-L-xylonic acid. From the crystalline acid chloride of the latter substance a sirupy diazomethyl ketone was obtained which on acid hydrolysis yielded crystalline L-sorbose. D-Sorbose (earlier psuedo-tagatose, *l*-sorbose) was first synthesized by Lobry de Bruyn and Alberda van Ekenstein[14] by the action of dilute aqueous alkali upon D-galactose. It was later formed from D-gulose and D-idose

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[1] Previous publication in this series: M. L. Wolfrom and Robert L. Brown, THIS JOURNAL, **65**, 1516 (1943).

[2] Presented before the Division of Sugar Chemistry and Technology at the 106th meeting of the American Chemical Society, Pittsburgh, Pennsylvania, September 7, 1943.

[3] Allied Chemical and Dye Corporation Fellow, 1942–1943.

[4] R. T. Major and E. W. Cook, THIS JOURNAL, **58**, 2474 (1936).

[5] M. L. Wolfrom and Mildred R. Newlin, *ibid.*, **53**, 4379 (1931).

[6] M. L. Wolfrom and M. Konigsberg, *ibid.*, **61**, 574 (1939).

[7] R. T. Major and E. W. Cook, *ibid.*, **58**, 2477 (1936).

[8] G. Arragon, *Compt. rend.*, **196**, 1733 (1933).

[9] H. H. Schlubach and J. Vorwerk, *Ber.*, **66B**, 1251 (1933).

[10] F. B. Cramer and E. Pacsu, THIS JOURNAL, **59**, 1467 (1937).

[11] G. Arragon, *Compt. rend.*, **205**, 735 (1937).

[12] M. L. Wolfrom and A. Thompson, THIS JOURNAL, **56**, 880 (1934).

[13] K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **21**, 186 (1938).

[14] C. A. Lobry de Bruyn and W. Alberda van Ekenstein, *Rec. trav. chim.*, **16**, 262 (1897); **19**, 1 (1900); J. U. Nef, *Ann.*, **403**, 342 (1914).

by aqueous alkali[15] and by pyridine.[16] Fischer and Baer[17] have demonstrated the formation of D-sorbose (and D-fructose) by the action of dilute alkali upon D-glyceraldehyde.

We include herein the synthesis of a derivative of a dicarbonyl-octose. The diazomethyl ketone obtained[18] from mucyl dichloride tetraacetate and designated 1,8-bisdiazomucyldimethane tetraacetate, was reduced with hydriodic acid according to the procedure of Wolfrom and Brown,[19] yielding the crystalline substance VII, designated mucyldimethane tetraacetate. In the C_6 series, a dicarbonyl hexose of a similar type has been isolated in crystalline form by Micheel,[20] who employed an entirely different method of synthesis. In this excellent work, the long-known 1,6-dichloro-D-mannitol[21] was converted through a series of crystalline intermediates into D-(*levo*)-tartaryldimethane, VIII, designated 1,4-dimethyl-1,4-diketo-tetrose by Micheel and Horn.

All compounds described herein were obtained in crystalline form.

Experimental

Improved Preparation of *aldehydo*-D-Xylose Tetraacetate (I).[22]—To a solution of 40 g. of mercuric chloride in 100 cc. of acetone in a 1-liter 3-necked flask was added 5 cc. of water and 25 g. of powdered cadmium carbonate and the mixture was stirred vigorously for ten minutes. To this was added a solution of 15 g. of D-xylose diethyl mercaptal tetraacetate[5] in 100 cc. of acetone and the resulting mixture was maintained at room temperature and under vigorous mechanical stirring for twelve hours, whereupon it was filtered and the solvent removed from the filtrate under reduced pressure and in the presence of a little fresh cadmium carbonate. The residual cake was extracted thrice with 75-cc. portions of warm chloroform and the combined extracts washed with 10% aqueous potassium iodide (to the disappearance of the red complex first formed) and then with water (to a negligible halide test with silver nitrate). The sirup obtained on solvent removal (reduced pressure) from the washed and dried extract was crystallized from anhydrous ether; yield 6 g. (3 crops), m. p.[23] 87–89°, spec. rot. −22.5° (20°, *c* 2.5, abs. $CHCl_3$, D line). Further purification from anhydrous ether yielded pure *aldeydo*-D-xylose tetraacetate; m. p. 90–91°, spec. rot. −23.3° (22°, *c* 4, abs. $CHCl_3$, D line). These constants are in agreement with those reported by Major and Cook[4] (m. p. 90–91°, spec. rot. +22.5° in abs. $CHCl_3$ for the enantiomorph) but differ in rotation from those reported[5] previously from this Laboratory (m. p. 88–89°, spec. rot. −16° in $CHCl_3$). The melting point of 90–91° and the specific rotation of −23° ($CHCl_3$) may then be accepted for *aldehydo*-D-xylose tetraacetate.

Anal. Calcd. for $C_5H_6O_5(CH_3CO)_4$: CH_3CO, 12.6 cc. 0.1 *N* NaOH per 100 mg. Found: CH_3CO, 12.5 cc.

D-Xylonyl Chloride Tetraacetate (III).[24]—D-Xylonic acid tetraacetate (3.0 g.), prepared by the oxidation of *aldehydo*-D-xylose tetraacetate according to the procedure of Major and Cook,[4] was shaken for one hour in ether (160 cc.) and phosphorus pentachloride (2.0 g.). The product (2.0 g.) crystallized from the filtered reaction mixture on standing overnight at icebox temperature and a further quantity (0.6 g.) was obtained from the mother liquor on addition of petroleum ether; total yield 2.6 g. (89%). Pure material was obtained on recrystallization from anhydrous ether; m. p. 72–73°, spec. rot. −14° (25°, *c* 5, abs. $CHCl_3$, D line). The substance crystallized in prismatic crystals.

Anal. Calcd. for $C_5H_5O_5Cl(CH_3CO)_4$: Cl, 10.05; saponification value (5 equiv.), 14.2 cc. 0.1 *N* NaOH per 100 mg. Found: Cl, 9.80; saponification value, 14.0 cc.

1-Desoxy-1-diazo-*keto*-D-sorbose Tetraacetate (IV).[24]—The diazomethane used in this work was prepared by the method of Werner[25] as modified by Arndt.[26] The ethereal solution of diazomethane was dried over potassium hydroxide pellets and was used at concentrations of 0.015–0.025 g. of diazomethane per cc. of solution. The concentration was determined by titration against benzoic acid.[27]

A solution of D-xylonyl chloride tetraacetate (8.3 g.) in sodium-dried ether (30 cc.) was poured slowly with stirring into 100 cc. of a dry, ether solution of diazomethane containing 2.3 g. of diazomethane. There was a vigorous evolution of nitrogen gas during the addition, and the crystallization of the reaction product, which began almost immediately after the addition of the acid chloride was complete, was allowed to complete itself at icebox temperature; yield 7.7 g. (92%), m. p. 122–124°, spec. rot. +43° (25°, *c* 5, abs. $CHCl_3$, D line). Pure material was obtained on recrystallization from five parts of acetone by the addition of like volumes each of ether and petroleum ether; m. p. 124.5–125.5°, spec. rot. +44.5° (25°, *c* 5, abs. $CHCl_3$, D line).

This diazomethyl ketone formed individual canary-yellow crystals that were insoluble in ether and petroleum ether but were very soluble in acetone, chloroform and alcohol.

Anal. Calcd. for $C_{14}H_{18}O_9N_2$: C, 46.93; H, 5.06; N, 7.82. Found: C, 46.94; H, 5.09; N, 7.33.

***keto*-D-Sorbose Pentaacetate (V).**[24]—A solution of 1-desoxy-1-diazo-*keto*-D-sorbose pentaacetate (2.0 g.) in glacial acetic acid (25 cc.) was refluxed until the cessation of nitrogen evolution (*ca.* twenty minutes). The crystalline solid obtained on pouring the cooled solution onto a mixture of ice and water and partially neutralizing the acetic acid with sodium bicarbonate, was removed by filtration and washed with water; yield 1.6 g. (73%), m. p. 91–94°, spec. rot. −1.9° (25°, *c* 4, abs. $CHCl_3$, D line). Pure material (elongated prisms) was obtained on recrystallization from methanol (decolorizing carbon)–water; m. p. 97.5–98.5°, spec. rot. −2.5° (25°, *c* 4, abs. $CHCl_3$, D line). For the enantiomorph, the following constants are reported: m. p. 99°, spec. rot. +2.8° (20°, $CHCl_3$, 5780 Å.)[8,11]; m. p. 96.5–97.5°, spec. rot. +2.9° (20°, *c* 2, $CHCl_3$, D line).[9]

Anal. Calcd. for $C_6H_7O_6(CH_3CO)_5$: C, 49.23; H, 5.68; CH_3CO, 12.8 cc. 0.1 *N* NaOH per 100 mg. Found: C, 49.16; H, 5.66; CH_3CO, 12.8 cc.

***keto*-D,L-Sorbose Pentaacetate.**[24]—Equal weights (1.0 g. of each) of *keto*-D-sorbose pentaacetate and *keto*-L-sorbose pentaacetate[8,9] were crystallized from methanol (15 cc.) and water (25 cc.); yield 1.8 g. (90%), m. p. 83–84° (unchanged on further crystallization), spec. rot. 0° (25°, *c* 2, abs. $CHCl_3$, D line).

Anal. Calcd. for $C_6H_7O_6(CH_3CO)_5$: C, 49.23; H, 5.68; CH_3CO, 12.8 cc. 0.1 *N* NaOH per 100 mg. Found: C, 49.16; H, 5.70; CH_3CO, 12.9 cc.

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(15) W. Alberda van Ekenstein and J. J. Blanksma, *Rec. trav chim.*, **27**, 1 (1908).

(16) K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **21**, 456 (1938).

(17) H. O. L. Fischer and E. Baer, *ibid.*, **19**, 519 (1936).

(18) M. L. Wolfrom, S. W. Waisbrot and R. L. Brown, THIS JOURNAL, **64**, 2329 (1942).

(19) M. L. Wolfrom and Robert L. Brown, *ibid.*, **65**, 1516 (1943).

(20) F. Micheel, *Ann.*, **496**, 77 (1932); F. Micheel and K. Horn, *ibid.*, **515**, 1 (1934).

(21) G. Bouchardat, *Ann. chim. phys.*, [5] **6**, 100 (1875).

(22) Experimental work by Mr. Robert L. Brown of this Laboratory.

(23) All melting points herein reported were taken in Pyrex melting point tubes.

(24) Experimental work by Mr. S. M. Olin.

(25) E. A. Werner, *J. Chem. Soc.*, **115**, 1093 (1919).

(26) F. Arndt, *Org. Syntheses*, **15**, 3, 48 (1935).

(27) E. K. Marshall, Jr., and S. F. Acree, *Ber.*, **43**, 2323 (1910).

Oxime of *keto*-L-Sorbose Pentaacetate.[28]—An amount of 5 g. of *keto*-L-sorbose pentaacetate[8,9] was dissolved in 250 cc. of boiling water. Hydroxylamine hydrochloride (2.5 g.) and potassium acetate (5 g.) were added to the hot solution which was then allowed to cool slowly to room temperature. Upon cooling to 0° and scratching the sides of the flask, the product crystallized; yield 1.3 g., m. p. 113–114°, spec. rot. −42° (23°, *c* 3, abs. $CHCl_3$, D line). An additional 0.4 g. was obtained by extraction of the mother liquor with chloroform. The constants were unaltered after recrystallization from solution in acetone–ether by the addition of petroleum ether.

Anal. Calcd. for $C_6H_8O_6N(CH_3CO)_5$: C, 47.41; H, 5.72; N, 3.46; CH_3CO, 12.3 cc. 0.1 *N* NaOH per 100 mg. Calcd. for $C_6H_9O_6N(CH_3CO)_4$: C, 46.28; H, 5.83; N, 3.86; CH_3CO, 11.0 cc. Found: C, 47.40; H, 5.88; N, 3.68; CH_3CO (O-acetyl[29]), 12.1 cc.

D-Sorbose (VI) from *keto*-D-Sorbose Pentaacetate.[28]—An amount of 2.43 g. of *keto*-D-sorbose pentaacetate was added to 100 cc. of 0.6 *N* barium hydroxide solution, previously cooled to *ca.* 5°. With occasional shaking, the crystals dissolved in about thirty minutes. The solution was kept for one hour longer at *ca.* 5° and then was saturated with carbon dioxide and the precipitated barium carbonate was removed by filtration. A slight excess of 2 *N* sulfuric acid was added slowly and the barium sulfate removed by filtration through a bed of Super-Cel (Johns–Manville). The excess sulfuric acid was then removed exactly with barium hydrate and the filtered solution was concentrated under reduced pressure at 40° to a sirup which crystallized spontaneously. The crystalline mass was stirred with 10 cc. of ethanol for filtration; yield 0.90 g. (80%), m. p. 158–160°, spec. rot. +40.5° (26°, *c* 3, H_2O, D line). Pure material was obtained on one recrystallization from water by the addition of absolute ethanol; m. p. 160–162°, spec. rot. +43 (24°, *c* 3, H_2O, D line, no significant mutarotation). For D-sorbose, Alberda van Ekenstein and Blanksma[15] reported the constants: m. p. 165°, spec. rot. +43° (*c* 1, H_2O, D line). For the enantiomorphic L-sorbose, Schlubach and Vorwerk[9] have recorded the constants: m. p. 159–161°, spec. rot. −43° (20°, *c* 2, H_2O, D line). Pigman and Isbell[30] record a small, complex mutarotation for L-sorbose.

Mucyldimethane Tetraacetate (VII).[24]—To a chloroform (40 cc.) solution of 1,8-bisdiazomucyldimethane tetraacetate[18] (2.00 g.), in a separatory funnel, was added 8 cc. of 47% hydriodic acid. The mixture was shaken until cessation of nitrogen evolution, diluted with water (40 cc.) and the chloroform layer removed and washed successively with water, aqueous sodium thiosulfate and water. A white crystalline solid was obtained on solvent removal from the dried chloroform solution; yield 1.60 g., m. p. 200–204°. Pure material was obtained on recrystallization from acetone by the addition of absolute ethanol; yield 1.35 g. (78%), m. p. 204–206°. The substance gave a positive iodoform test (iodoform identified by m. p. and mixed m. p.).

Anal. Calcd. for $C_{16}H_{22}O_{10}$: C, 51.21; H, 5.91. Found: C, 51.25; H, 5.85.

Summary

1. An improved demercaptalation procedure for *aldehydo*-D-xylose tetraacetate (I) is described.
2. The tetraacetates of D-xylonyl chloride (III) and of 1-desoxy-1-diazo-*keto*-D-sorbose (IV) have been synthesized. Reaction of the latter with acetic acid led to the synthesis of *keto*-D-sorbose pentaacetate (V), from which D-sorbose (VI) was obtained on saponification.
3. An oxime of *keto*-L-sorbose pentaacetate has been obtained.
4. *keto*-D,L-Sorbose pentaacetate is described.
5. Hydriodic acid reduction of 1,8-bisdiazomucyldimethane tetraacetate yielded mucyldimethane tetraacetate (VII).

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[28] Experimental work by Mr. Evan F. Evans.

[29] M. L. Wolfrom, M. Konigsberg and S. Soltzberg, THIS JOURNAL, **58**, 490 (1936).

[30] W. W. Pigman and H. S. Isbell, *J. Research Natl. Bur. Standards*, **19**, 443 (1937).

COLUMBUS, OHIO RECEIVED SEPTEMBER 29, 1943

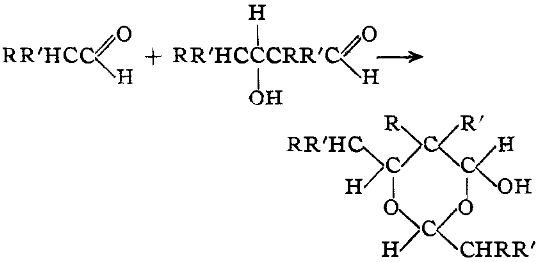
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF ILLINOIS INSTITUTE OF TECHNOLOGY]

The Aldol Condensation. III. Aldol-aldehyde Addition Products and their Derivatives

BY ROBERT H. SAUNDERS AND M. J. MURRAY

Späth, Lorenz and Freund[1] and Hanschke[2] have recently independently reported the isolation of an addition product of acetaldehyde to aldol, together with the acetate and benzoate of this compound. While this work was still unknown to us, we reported an analogous compound formed by the reaction of isobutyraldehyde with its aldol.[3] Under the circumstances we are reporting the results of our research to date and are concluding our work on this phase of the problem.

The following equation shows the addition of aldehyde to its aldol to form a 1,3-dioxane derivative



I.

By acetylating the crude reaction mixtures of aldolized aldehydes related to acetaldehyde, propionaldehyde, *n*- and isobutyraldehydes we obtained the 6-acetoxy-1,3-dioxanes in about 70% yields. In one instance, namely, that from isobutyraldehyde, we also prepared the 6-methoxy-1,3-dioxane. Physical properties for

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[1] Späth, Lorenz and Freund, *Ber.*, **76B**, 57–68 (1943); *C. A.*, **37**, 4695 (1943).

[2] Hanschke, *Ber.*, **76B**, 180 (1943); *C. A.*, **37**, 5374 (1943).

[3] Saunders, Murray and Cleveland, THIS JOURNAL, **65**, 1714 (1943).