[Contribution from the Department of Chemistry of The Ohio State University]

Acyclic Acetates of Dialdoses[1]

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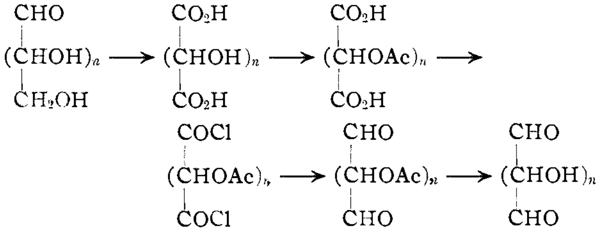
The preparation of *dialdehydo-galacto*-dialdohexose tetraacetate (I) from tetra-O-acetylmucyl dichloride is detailed. 1,6-Dibromogalactitol hexaacetate (II) was prepared from I. No conditions were found for the cyclization of I or II to inositol derivatives. Acylation of zinc xylarate (III) yielded tri-O-acetylxylaric anhydride (IV; and the tribenzoate V) from which tri-O-acetylxylaric acid (VI) was obtained. No conditions were found to form the bis-(acyl chloride) of VI without cyclization to IV. *dialdehydo-(meso-glycero-gulo)*-Dialdoheptose pentaacetate (IX) and penta-O-acetyl-*meso-(glycero-gulo)*-heptaric anhydride are described.

Polyhydroxy dialdehydes and their derivatives are little known. Crystalline *erythro*-dialdotetrose (*meso*-tartaraldehyde) and derivatives of it and of the isomeric DL-*threo*-dialdotetrose have been reported by Wohl and Mylo[2] and by others.[3–5] The crystalline bis-(phenylhydrazone) and other derivatives of *xylo*-dialdopentose[6] are known. The amino substituted dialdohexoses obtained through the glycol cleavage of N,N-dibenzoylstreptamine[7] and of its deoxy derivative[8] are crystalline substances. Dangschat and Fischer[9] have prepared the tetraacetates of *dialdehydo-galacto*-dialdohexose (I), *dialdehydo-allo*-dialdohexose and DL-*ido*-dialdohexose (the latter characterized as crystalline dihydrazones) through the glycol cleavage of substituted inositols obtained from conduritol and *myo*-inositol. An extension of this technique has been made by Ballou and Fischer,[10] who have reported the crystalline 2,3:4,5-diisopropylidene-*dialdehydo*-D-*manno*-dialdohexose from (+)-inositol.

A route to the synthesis of sugar dialdehydes (dialdoses) presents itself through the sequence



$$\begin{array}{c}\text{CHO}\\ |\\ (\text{CHOH})_n\\ |\\ \text{CH}_2\text{OH}\end{array}\longrightarrow\begin{array}{c}\text{CO}_2\text{H}\\ |\\ (\text{CHOH})_n\\ |\\ \text{CO}_2\text{H}\end{array}\longrightarrow\begin{array}{c}\text{CO}_2\text{H}\\ |\\ (\text{CHOAc})_n\\ |\\ \text{CO}_2\text{H}\end{array}\longrightarrow$$

$$\begin{array}{c}\text{COCl}\\ |\\ (\text{CHOAc})_n\\ |\\ \text{COCl}\end{array}\longrightarrow\begin{array}{c}\text{CHO}\\ |\\ (\text{CHOAc})_n\\ |\\ \text{CHO}\end{array}\longrightarrow\begin{array}{c}\text{CHO}\\ |\\ (\text{CHOH})_n\\ |\\ \text{CHO}\end{array}$$

The crystalline tetraacetate of *dialdehydo-galacto*-dialdohexose (I) has been reported[11] as having been so synthesized, but no details are available in the journal literature. The acid-catalyzed direct acetylation of mucic (galactaric) acid leads to the formation of its crystalline tetraacetate in good yield[12–14] from which the crystalline bis-(acyl chloride)[15] is readily obtained. Conditions are herein reported for the catalytic reduction of this halide, by the Rosenmund procedure, to yield the crystalline *dialdehydo-galacto*-dialdohexose tetraacetate (I) with properties in agreement with those reported by Dangschat and Fischer.[9] This substance was further characterized as its bis-(acetyl bromide) carbonyl addition compound (II) herein designated 1,6-dibromogalactitol hexaacetate. This substance was isolated in only one crystalline form, although stereochemical theory would predict that a *meso* and a DL product could arise. Conditions could not be found to cyclize this derivative or its parent dialdehyde tetraacetate to an inositol.

In the aldopentaric acid series, acylation of zinc xylarate (III) led to the crystalline cyclic anhydride triacetate (IV; and tribenzoate V) from which tri-O-acetylxylaric acid (VI) could be obtained. No conditions were found for transforming the latter to its bis-(acyl chloride) without recyclization to the anhydride.

The acid-catalyzed acetylation of salts of aldonic acids generally leads to the production of the fully acetylated acid.[16] This procedure has been adapted to the aldaric acid series by Adelman and Breckenridge,[17] who have recorded penta-O-acetyl-*meso-(glycero-gulo)*-heptaric acid (VII). In a repetition of their preparation, a small amount of the acetylated eight-membered cyclic anhydride of this dibasic acid was obtained. The bis-(acyl chloride) of the aldoheptaric acid (VIII), although a very unstable substance that was not characterized, could be reduced to give, in low yield, the crystalline *dialdehydo-meso-(glycero-gulo)*-dialdoheptose pentaacetate (IX), the first recorded example of this type of substance in the aldoheptose series.

Experimental

Preparation of *dialdehydo-galacto*-Dialdohexose Tetraacetate (I).—This compound has been reported in an unpublished German university dissertation[11] and in a preliminary publication by Dangschat and Fischer,[9] but no details have been communicated to the journal literature. Mucic acid was acetylated with acetic anhydride and sul-

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[1] Preliminary work on this problem was carried out in this Laboratory by Vera Rudin Usdin. Dr. Kimiko Anno assisted in the preparation of the manuscript for publication.

[2] A. Wohl and B. Mylo, *Ber.*, **45**, 332 (1912).

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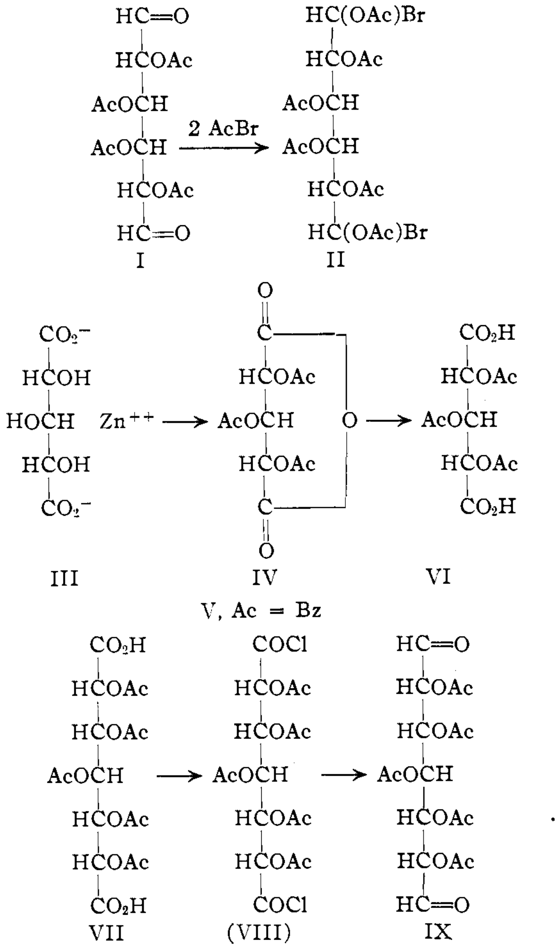

I II

III IV VI

V, Ac = Bz

VII (VIII) IX

furic acid as described by Skraup,[13] and the crystalline tetra-O-acetylmucic acid (m.p. 245–248° from 96% ethanol) obtained was converted to the crystalline tetra-O-acetylmucyl dichloride (m.p. 177–178° from benzene) with phosphorus pentachloride in acetyl chloride according to Diels and Löflund.[15]

Anal. Calcd. for $C_{14}H_{16}O_{10}Cl_2$: C, 40.50; H, 3.88. Found: C, 40.61; H, 3.73.

An all-glass apparatus consisting of a three-necked flask equipped with a mercury-sealed stirrer, a guarded condenser and a gas entry tube equipped with a plunger (to clear any solid formed) was employed. All glassware was dried at 100° before use. Tetra-O-acetylmucyl dichloride (20 g.), 800 ml. of xylene (distilled from sodium) and 5 g. of freshly prepared palladium (on barium sulfate) catalyst[18] were stirred in this apparatus under reflux while passing in a stream of dry hydrogen gas. The hydrogen chloride produced was absorbed in standard alkali and its quantity was measured. After several hours the reaction, while incomplete, had slowed down considerably. Addition of fresh catalyst did not increase the rate of reaction. The hydrogen stream was then replaced by dry nitrogen gas to remove hydrogen chloride and the hot solution was filtered. Crystallization occurred on cooling and a further quantity was obtained on solvent concentration to one-half volume under reduced pressure, yield 4.5 g., m.p. 172–175°. Pure material was obtained on recrystallization from 100% ethanol or ethyl acetate (free of ethanol, acetic acid and water[19]); m.p. 184° (dec.) in agreement with Dangschat and Fischer.[9] The substance crystallized in elongated six-sided plates.

1,6-Dibromogalactitol Hexaacetate (II).—An amount of 475 mg. of *dialdehydo-galacto*-dialdohexose tetraacetate (I) was dissolved at room temperature in 12 ml. of acetyl bromide and the solution was maintained at room temperature for 2 hr., whereupon it was added dropwise under stirring to an excess of ice and water. The solid that formed was removed by filtration and was recrystallized from benzene–petroleum ether (b.p. 30–60°) and chloroform–petroleum ether; yield 610–690 mg. (75–85%), m.p. 161–163°. No evidence of more than one separable product was obtained.

Anal. Calcd. for $C_{18}H_{24}O_{12}Br_2$: C, 36.50; H, 4.08; Br, 26.99. Found: C, 36.56; H, 4.08; Br, 27.29.

Attempted Cyclization.—No conditions were found that yielded a reaction mixture giving the Scherer inositol test[20]: on treating 1,6-dibromogalactitol hexaacetate with silver, zinc, magnesium, calcium or sodium; or on attempted cyclic aldolization of *dialdehydo-galacto*-dialdohexose tetraacetate with alkali or cyanide ion.

Tri-O-acetylxylaric Anhydride (IV).—D-Xylose (300 g.) was oxidized with nitric acid according to Chalov.[21] The reaction mixture was concentrated to a sirup at 50–55° under reduced pressure followed by adding water and again concentrating under reduced pressure to a sirup. The residue was extracted with ether (room temperature) to remove the oxalic acid. The sirupy product crystallized on standing and was recrystallized from hot ether; m.p. 151–152° (recorded[22] 152°).

The acid was neutralized in dilute (33%) aqueous solution with zinc acetate dihydrate and from this the crystalline zinc salt (III) separated; yield 260 g. (53.5%).

Anal. Calcd. for $C_5H_6O_7Zn$: Zn, 26.84. Found: Zn, 26.75.

Using a modification of the procedure of Adelman and Breckenridge,[17] the zinc salt was cautiously treated under reflux with 2 ml. (for each gram of salt) of acetyl chloride and maintained under reflux for 1 hr. The cooled reaction mixture was filtered to remove a precipitate which was combined with the residue obtained from the filtrate on solvent removal under reduced pressure. The solid was washed successively at room temperature with *N* hydrochloric acid and water. After drying in a desiccator, it was recrystallized from ethyl acetate (free of water, alcohol and acetic acid[19]), ethyl acetate–petroleum ether, isopropyl ether, or ether–petroleum ether; yield 80%, m.p. 146–147°. Tri-O-acetylxylaric anhydride was soluble in hot ethyl acetate, somewhat so in ethyl ether, and was insoluble in chloroform. Its initial solution in 75% ethanol was neutral in reaction.

Anal. Calcd. for $C_{11}H_{12}O_9$: C, 45.83; H, 4.19. Found: C, 45.96; H, 4.42.

Tri-O-acetylxylaric Acid (VI).—Tri-O-acetylxylaric anhydride (IV, 7.1 g.) was shaken with excess *N* sulfuric acid at room temperature until solution was effected (15–30 min.). This solution was extracted with several portions of ether and the dried (with sodium sulfate) extract was concentrated to low volume under reduced pressure. Crystallization in rosettes occurred on the addition of petroleum ether and standing at ice-box temperature. They were recrystallized from ether–petroleum ether; yield 4.0 g. (53%), m.p. 154° and 139–146° on admixture with tri-O-acetylxylaric anhydride of m.p. 146–147°.

Anal. Calcd. for $C_{11}H_{14}O_{10}$: C, 43.14; H, 4.61. Found: C, 43.50; H, 4.76.

In an attempt to prepare the acid chloride with phosphorus pentachloride in ether, following the general directions of Major and Cook,[23] the tri-O-acetylxylaric acid was recovered unchanged. Treatment with phosphorus pentachloride in acetyl chloride or xylene yielded the anhydride (identified by melting point and mixed melting point).

Tri-O-benzoylxylaric Anhydride (V).—Five grams of zinc xylarate (III, previously dried for 2 hr. at 110°) was refluxed for 2 hr. with 30 ml. of isopropyl ether and 125 ml. of benzoyl chloride. The cooled reaction mixture was filtered from the separated zinc chloride, and ethanol (100%) was added to the filtrate to convert unreacted benzoyl chloride to ethyl benzoate. The mixture was washed successively with dilute hydrochloric acid and water, dried over sodium sulfate and concentrated to a sirup at 50° under reduced pressure (8 mm.). Petroleum ether was added to the warm solution to incipient turbidity and on slow cooling

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globular clusters of crystals separated. These were recrystallized from ethyl acetate by the addition of petroleum ether; yield 2.5 g., m.p. 223–224°.

Anal. Calcd. for $C_{26}H_{18}O_9$: C, 65.82; H, 3.82. Found: C, 65.88; H, 3.69.

Penta-O-acetyl-*meso-(glycero-gulo)*-heptaric Anhydride.—The procedure of Adelman and Breckenridge[17] for acetylating amorphous zinc *meso-(glycero-gulo)*-heptarate with acetyl chloride (to produce penta-O-acetyl-*meso-(glycero-gulo)*-heptaric acid) was followed and the crude sirup obtained on solvent removal from the dried chloroform extract was maintained for several days in a vacuum desiccator. Crystals formed, in low yield, that were separated from adherent sirup by filtration and were recrystallized from ethyl acetate by the addition of petroleum ether; m.p. 189.5–190°. A solution of the substance in 75% ethanol was initially neutral.

Anal. Calcd. for $C_{17}H_{20}O_{13}$: C, 47.22; H, 4.66. Found: C, 47.04; H, 4.42.

***dialdehydo-meso-(glycero-gulo)*-Dialdoheptose Pentaacetate (IX).**—Penta-O-acetyl-*meso-(glycero-gulo)*-heptaric acid (VII, 800 mg., m.p. 122°)[17] was stirred at room temperature with an equal weight of phosphorus pentachloride and 25 ml. of acetyl chloride. The filtered reaction mixture was concentrated under reduced pressure to half-volume and again filtered. The residue obtained on complete solvent removal under reduced pressure was crystallized from ether–petroleum ether; yield 310 mg. m.p. 105°. This material, presumably the bis-(acid chloride) VIII, exhibited a strong halogen test with alcoholic silver nitrate but was too unstable for characterization.

An amount of 300 mg. of the above product was immediately reduced in xylene solution with palladium-on-barium sulfate as described above for the preparation of *dialdehydo-galacto*-dialdohexose tetraacetate and the product obtained after a 4-hr. reaction time was isolated in the same manner and was recrystallized from purified ethyl acetate; m.p. 133–134°. The substance exhibited a strong Fehling reduction and was halogen-free.

Anal. Calcd. for $C_{17}H_{22}O_{12}$: C, 48.80; H, 5.30. Found: C, 48.78; H, 5.44.

COLUMBUS 10, OHIO

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

The Preparation of Higher-carbon Sugars from D-Mannose Including Crystalline D-Manno-L-*manno*-octose

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D-Manno-L-*manno*-octose has been crystallized for the first time and characterized through its phenylosazone and phenylosotriazole derivatives. D-Manno-L-*manno*- and D-manno-L-*gluco*-octonic acids as well as a number of their derivatives have been prepared. The rotations of the amides, phenylhydrazides and benzimidazoles of both acids conform to their respective rules of rotation. Some compounds in the heptonic series were reinvestigated and new derivatives were prepared. D-Manno-D-*talo*-heptonic amide conforms to the amide rule.

The research described in the present communication is a continuation[3] of the synthesis of higher-carbon sugars and their intermediates from D-mannose. For this purpose barium D-manno-D-*gala*-heptonate described by Montgomery and Hudson[3] was again prepared and from the mother liquors barium D-manno-D-*talo*-heptonate was isolated. Purification of the acid from the latter salt was effected through the phenylhydrazide[4] which in turn was converted[5] to D-manno-D-*talo*-heptonic lactone.[6] From the pure lactone the crystalline cadmium salt and the amide were prepared for the first time. The negative rotation of the amide conformed to the amide rule.[7]

Barium D-manno-D-*gala*-heptonate was converted to the lactone in the customary way[8] and the latter substance reduced to D-manno-D-*gala*-heptose.[9] The physical constants of previously known substances in the heptonic series were verified and the [α]D value, previously recorded for barium D-manno-D-*gala*-heptonate,[3] was corrected. Crystalline cadmium D-manno-D-*gala*-heptonate was also prepared.

When hydrogen cyanide addition to D-manno-D-*gala*-heptose was carried out with sodium cyanide and calcium chloride,[10] the D-manno-L-*manno*-octonic acid was separated from its epimer through its less soluble calcium salt or phenylhydrazide and obtained in pure form as the lactone. The D-manno-L-*gluco*-octonic acid, which had not been isolated previously, was obtained pure either from the partially purified calcium salt or from the phenylhydrazide. Pure derivatives of the two epimeric acids, such as the epimeric phenylhydrazides and benzimidazoles, were prepared from D-manno-L-*manno*-octonic lactone and D-manno-L-*gluco*-octonic acid; the rotations of these derivatives conformed to the phenylhydrazide[11] and benzimidazole[12] rules, respectively. Crystalline sodium D-manno-L-*gluco*-octonate, D-manno-L-*gluco*-octonic amide and ethyl D-manno-L-*manno*-octonate are also described in the present work.

When hydrogen cyanide addition to D-manno-D-*gala*-heptose was carried out with sodium cyanide and ammonium chloride, a crystalline, nitrogen-containing compound was obtained in good yield

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[1] Blockson Chemical Company, Joliet, Illinois.

[2] Deceased: (a) April 30, 1949; (b) December 27, 1952.

[3] Edna M. Montgomery and C. S. Hudson, THIS JOURNAL, **64**, 247 (1942); *cf.* also C. S. Hudson, *Advances in Carbohydrate Chem.*, **1**, 5 (1945).

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