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

Aldehydo-d-Mannose Pentaacetate Ethyl Hemiacetal

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At various intervals over a period of years we have attempted unsuccessfully in this Laboratory to prepare *aldehydo-d*-mannose pentaacetate in crystalline form. We were inclined to attribute these failures to a lack of stability of an *aldehydo*-acetate possessing the *cis*-hydroxyl configuration on carbon atoms two and three, but the excellent results of Hann and Hudson[1] with *aldehydo-d-α*-galaheptose hexaacetate disposed of this postulation. Although the oxime and semicarbazone of *aldehydo*-mannose pentaacetate[2] were available in crystalline form, removal of the nitrogen groups from these derivatives with nitrous acid led only to sirups.

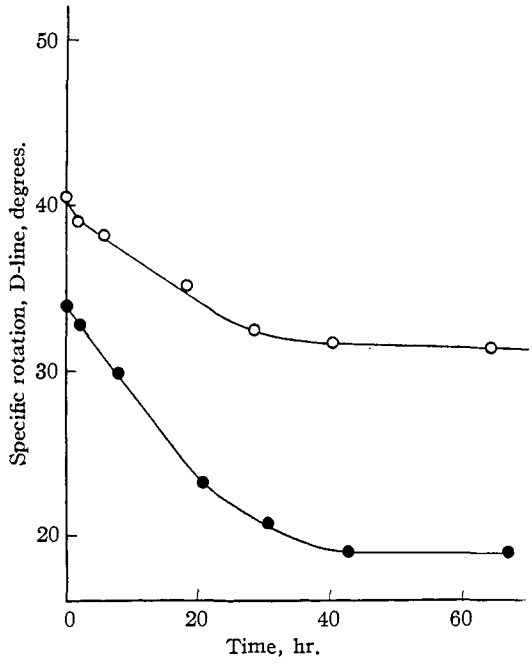
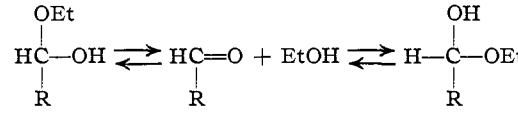


Fig. 1.—Mutarotation of *aldehydo-d*-mannose pentaacetate ethyl hemiacetal in absolute ethanol, ○, and in absolute chloroform, ●, 23°, *c* 5.0.

In the course of many preparations of the *aldehydo*-acetates of glucose and galactose by the controlled demercaptalation procedure[3] in this Laboratory, we have made some improvements in this general method. These improvements apparently are of a minor nature but are significant. They consist essentially in the use of larger quantities of cadmium carbonate, particularly during the removal of the acetone; in more efficient stirring of the reaction mixture, effected mainly through the use of larger quantities of acetone; and in more efficient removal of mercury compounds. Application of these improved procedures to mannose diethyl mercaptal pentaacetate led to the crystallization of *aldehydo*-mannose pentaacetate as its crystalline ethyl hemiacetal. The oxime and semicarbazone of this aldehyde were identical with those previously obtained by Wolfrom and Georges[2] by direct acetylation procedures.

aldehydo-Mannose pentaacetate ethyl hemiacetal showed a downward mutarotation in ethanol (Fig. 1). In chloroform solution it showed a downward mutarotation (Fig. 1) without passing through a minimum, as was the case with *aldehydo*-galactose pentaacetate ethyl hemiacetal.[4] It is probable that this does not represent a distinct difference in the nature of the two substances but simply a difference in the relative velocities of the two consecutive reactions which are definitely demonstrated for the galactose compound but which are probably common to both.



In the course of this work we had considered the possibility of applying to mannose the *aldehydo*-acetate synthesis reported by Cook and Major[5] and we had carried the procedure to the mannonic acid pentaacetate stage. In the deamination of the mannonamide pentaacetate we had employed nitrosyl chloride (or nitrosyl bromide) in place of the nitrous anhydride used by Hurd and Sowden.[6] Our original hope of obtaining the acid chloride directly by this procedure was not fulfilled, the acetylated acid being the reaction product. We are accordingly reporting the synthesis of mannonic acid penta-

(1) R. M. Hann and C. S. Hudson, THIS JOURNAL, **59**, 1898 (1937).
(2) M. L. Wolfrom and L. W. Georges, *ibid.*, **58**, 1781 (1936).
(3) M. L. Wolfrom, *ibid.*, **51**, 2188 (1929).
(4) M. L. Wolfrom, *ibid.*, **53**, 2275 (1931); M. L. Wolfrom and W. M. Morgan, *ibid.*, **54**, 3390 (1932).
(5) (a) E. W. Cook and R. T. Major, *ibid.*, **58**, 2410 (1936); (b) R. T. Major and E. W. Cook, *ibid.*, **58**, 2474 (1936).
(6) C. D. Hurd and J. C. Sowden, *ibid.*, **60**, 235 (1938).

TABLE I

ROTATIONS OF THE ANHYDROUS AND HYDRATED FORMS OF ACETYLATED GLUCONIC AND GALACTONIC ACIDS

	M. p., °C.	$[\alpha]_D$, $CHCl_3$ (alcohol free)	Temp., °C.	Molecular rotation
d-Gluconic acid pentaacetate	110–111	+11°	20	+4500°
d-Gluconic acid pentaacetate monohydrate	72–73	+10	23	+4200
d-Galactonic acid pentaacetate	131–132	+16	23	+6500
d-Galactonic acid pentaacetate monohydrate	100–101	+15	23	+6400

acetate by this procedure and also its extension to *d*-α-glucoheptonic acid hexaacetate. Good yields of the acetylated gluconic[5] and galactonic[6] acids can be obtained from the corresponding acetylated amides by this method. It is of interest to note that mucic acid tetraacetate[7] and the diacyl chloride of mucic acid tetraacetate[8] have long been known in crystalline form and the catalytic reduction of the latter to the sirupy dialdehyde tetraacetate is recorded by Kögl and Uenzelmann.[9]

We have noted the difference in chloroform rotation reported by Major and Cook[5b] for the anhydrous and monohydrate forms of gluconic acid pentaacetate. Hurd and Sowden[6] record only the anhydrous form of galactonic acid pentaacetate but from this substance the monohydrate is readily obtained. As rotation differences are definite proof of molecular constitutional differences, evidence might thus be established that these monohydrates are true orthoacids ($R—C(OH)_3$). A careful determination of the rotations in alcohol-free chloroform of these two pairs of compounds showed that two of the rotations recorded in the literature were slightly in error and that the anhydrous and monohydrate forms of each of the acetylated acids have essentially the same molecular rotation (Table I). This result indicates that the water is present in these compounds as water of hydration and is not constitutionally combined in an orthoacid structure. The lack of mutarotation exhibited by the monohydrates in chloroform solution also points to the same conclusion. We believe that this result is of some interest, as hydrates of optically active acids are generally not soluble in non-hydroxylated solvents. The compounds in hand had the requisite solubilities for determining the presence or absence of orthoacid structures.

By an extension to maltose diethyl mercaptal pentaacetate[10] of the improvements in the synthesis of *aldehydo*-acetates reported in this publication, we have recently obtained *aldehydo*-maltose octaacetate (m. p. 67–68°; spec. rot. + 85°, D-line, absolute $CHCl_3$, 21°) in crystalline form. This is the first crystalline *aldehydo*-acetate obtained in the disaccharide series. Details will be reported in a later publication.

(7) L. Maquenne, *Bull. soc. chim.*, [2] **48**, 719 (1887); Z. H. Skraup, *Monatsh.*, **14**, 488 (1893).

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

(9) Uenzelmann, Dissertation, Göttingen, 1931.

(10) M. L. Wolfrom and E. E. Stahly, THIS JOURNAL, **53**, 4379 (1931).

Experimental

***aldehydo-d*-Mannose Pentaacetate Ethyl Hemiacetyl.**[11] —An amount of 137 g. (5 mols) of mercuric chloride was dissolved in 500 cc. of acetone and placed in a 3-liter three-necked flask fitted with an efficient mechanical stirrer. Finely powdered cadmium carbonate (200 g.) and 20 cc. of water were added and the mixture stirred vigorously for fifteen minutes, whereupon 50 g. of *d*-mannose diethyl mercaptal pentaacetate[12] (1 mol) dissolved in 500 cc. of acetone was added slowly to the stirred mixture. The vigorous mechanical stirring was maintained for a period of approximately twenty hours at room temperature. The large volume of acetone employed greatly aids in obtaining efficient mechanical agitation.

The mixture was filtered into a flask containing 150 g. of finely powdered cadmium carbonate, the residue was well washed with acetone (500 cc.) and the solvent removed under reduced pressure (35–40°) 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 with water until free of halides. The dried chloroform extract was treated with decolorizing charcoal and the solvent removed under diminished pressure (35–40°). Absolute ethanol was added to the resultant sirup and when this was removed by concentration under reduced pressure, a partially crystalline mass resulted which could be recrystallized from absolute ethanol; yield 21.7 g. (three crops), m. p. 105–110°. Pure material was obtained on further recrystallization from absolute ethanol; m. p. 112–113°, spec. rot. +40.5 ⟶ +30° (23°; *c*, 5; absolute ethanol),[13] spec. rot. +34° ⟶ +20° (23°, *c*, 5; $CHCl_3$, dry and free of ethanol). At 23°, approximately seventy hours were required to attain equilibrium in ethanol. The time required to attain equilibrium in chloroform varied widely with different samples (from twelve to forty hours at 23°). Mutarotation data are diagrammed in Fig. 1.

aldehydo-d-Mannose pentaacetate ethyl hemiacetal crystallizes as small, individual plates of an octahedron-like

(11) Experimental work by Mr. M. Konigsberg.

(12) N. W. Pirie, *Biochem. J.*, **30**, 374 (1936).

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

TABLE II

PROPERTIES OF THE OXIME AND SEMICARBAZONE OF *aldehydo-d*-MANNOSE PENTAACETATE

Substance	M. p., °C.	$[\alpha]^{25}D$ (CHCl$_3$)	
aldehydo-d-Mannose	121–123	+15.6°	This work
oxime pentaacetate	120–123	+15.0	Wolfrom and Georges[2]
aldehydo-d-Mannose	180	+ 9.4	This work
semicarbazone pentaacetate	177–178	+ 9.2	Wolfrom and Georges[2]

structure and is soluble on warming in water, ether, heptane and toluene and is soluble in the other common organic solvents. The substance showed a positive Schiff aldehyde test and reduced Fehling's solution.

Anal. Calcd. for $C_6H_7O_6(COCH_3)_5(C_2H_5OH)$: OC_2H_5, 10.32; $COCH_3$, 11.46 cc. 0.1 *N* NaOH per 100 mg. Found: OC_2H_5, 10.51; $COCH_3$, 11.47 cc.; S, absent.

The crystalline material yielded a semicarbazone and an oxime identical with those described by Wolfrom and Georges.[2] These derivatives were prepared according to the directions of the latter and their properties are shown in Table II.

***d*-Mannonic Acid Pentaacetate Monohydrate.**[14]—An amount of 10 g. of *d*-mannonamide pentaacetate[15] was dissolved in 100 cc. of dry, alcohol-free chloroform and the solution was cooled to 0° and 15 cc. of nitrosyl chloride was added under mechanical stirring. The temperature of the solution was allowed to rise to room temperature over a period of about three hours and stirring was then maintained overnight. At the end of this period the solution was refluxed for one hour. The sirup obtained on solvent removal under reduced pressure was crystallized from alcohol by the addition of water; yield 7 g., m. p. 67–70°. Pure material was obtained on recrystallization from boiling water containing 2% ethanol; m. p. 68–70°; spec. rot. +23° (21°, *c*, 1.6; U. S. P. $CHCl_3$; no mutarotation).

Anal. Calcd. for $C_6H_7O_7(COCH_3)_5 \cdot H_2O$: saponification value, 14.1 cc. 0.1 *N* NaOH per 100 mg.; H_2O, 4.20. Found: saponification value, 14.0 cc.; H_2O,[16] 4.17.

Application of the above procedure to the acetylated amides of gluconic and galactonic acids produced the acetylated acids in good yield. Nitrosyl bromide may be substituted for the nitrosyl chloride.

Preparation of Nitrosyl Chloride.[14]—Nitrosyl chloride is not a readily available reagent and we will accordingly describe the method used in its preparation, although no originality is claimed for the procedure. Dry sulfur dioxide gas was passed into cold, fuming nitric acid until the contents of the flask became a pasty, crystalline mass. This was dried under reduced pressure over sulfuric acid. The nitrosylsulfuric acid so obtained was heated gently with an equivalent amount of dry sodium chloride and the nitrosyl chloride gas was liquefied by cooling the receiving flask with solid carbon dioxide.

***d*-α-Glucoheptonic Acid Hexaacetate Monohydrate.**[14]—*d*-α-Glucoheptonamide hexaacetate[17] (15 g.) was treated with nitrosyl chloride as described for the corresponding mannose compound. The sirup obtained on solvent removal crystallized on standing; yield 10.5 g.; m. p. 88–90°. Pure material was obtained on recrystallization from hot water containing 2% ethanol; m. p. 88–90°; spec. rot. +6° (26°, *c*, 2.0; U. S. P. $CHCl_3$; no mutarotation).

Anal. Calcd. for $C_7H_8O_6(COCH_3)_6 \cdot H_2O$: saponification value, 14.1 cc. 0.1 *N* NaOH per 100 mg.; H_2O, 3.63. Found: saponification value, 14.1 cc.; H_2O (16), 3.61.

***d*-Galactonic Acid Pentaacetate Monohydrate.**[14]—Crystallization of the anhydrous form[6] from water yielded the monohydrate of m. p. 100–101° and spec. rot. +15° (23°, *c*, 5.332; $CHCl_3$, alcohol free; *l*, 2-dm.; α, +1.60°; no mutarotation).

Anal. Calcd. for $C_6H_7O_7(COCH_3)_5 \cdot H_2O$: saponification value, 14.1 cc. 0.1 *N* NaOH per 100 mg. Found: 13.9 cc.

The rotations of highly purified samples of *d*-galactonic acid pentaacetate, *d*-gluconic acid pentaacetate and *d*-gluconic acid pentaacetate monohydrate were determined in chloroform (alcohol free) solution at concentrations of 5 g. per 100 cc. of solution and are recorded in Table I. The rotations therein recorded for galactonic acid pentaacetate and gluconic acid pentaacetate monohydrate represent new values for these substances. No mutarotation was exhibited by any of these compounds.

Summary

1. *aldehydo-d*-Mannose pentaacetate ethylhemiacetal has been synthesized in crystalline form and its mutarotation in chloroform and alcohol investigated.

2. The acyclic structures assigned by Wolfrom and Georges to the oxime and semicarbazone pentaacetates of *d*-mannose have been verified.

3. The use of nitrosyl chloride or bromide in the deamination of the acetylated aldonamides has been described.

4. *d*-Mannonic acid pentaacetate monohydrate and *d*-α-glucoheptonic acid hexaacetate monohydrate have been synthesized in crystalline form.

5. Evidence is given against the assignment of orthoacid structures to the monohydrates of *d*-gluconic acid pentaacetate and *d*-galactonic acid pentaacetate.

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(14) Experimental work by Mr. D. I. Weisblat.

(15) G. B. Robbins and F. W. Upson, THIS JOURNAL, **60**, 1789 (1938).

(16) Loss in weight on heating at 110° under reduced pressure over phosphorus pentoxide.

(17) G. Zemplén and D. Kiss, *Ber.*, **60**, 165 (1927).