

TABLE II
OSMOTIC AND ACTIVITY COEFFICIENTS FOR BARIUM AND STRONTIUM CHLORIDE SOLUTIONS

Weight molality (moles/1000 g. water)	Barium chloride ϕ (Osmotic coef- ficient)	Barium chloride γ (Activity coef- ficient)	Strontium chloride ϕ (Osmotic coef- ficient)	Strontium chloride γ (Activity coef- ficient)
0.05	0.860	(0.561)	0.892	0.572
.10	.844	.498	.871	.514
.20	.833	.440	.861	(.464)
.30	.834	.412	.865	.441
.40	.843	.396	.877	.430
.50	.857	.389	.894	.426
.60	.873	.386	.914	.427
.70	.888	.385	.936	.432
.80	.903	.385	.959	.438
.90	.919	.387	.983	.448
1.00	.934	.390	1.007	.458
1.10	.950	.394	1.032	.470
1.20	.965	.399	1.056	.484
1.30	.981	.405	1.080	.498
1.40	.997	.411		
1.50	1.013	.417		
1.60	1.030	.422		
1.70	1.048	.429		
1.80	1.067	.436		

accuracy of better than 1 part in 500, provided the reference activity coefficient is assumed correct.

The activity coefficients calculated in this investigation for barium chloride agree well with those of Robinson,⁶ of Tippetts and Newton⁴ and of Harned and Åkerlöf.¹⁷ The data of Scatchard and Tefft¹⁶ are in fair agreement, while the data of Lucasse,⁸ of Jones and Dole¹⁸ and Hepburn¹⁰ deviate more extensively.

The activity coefficients for strontium chloride, as calculated from the experimental data, agree quite well with those calculated by Harned and

(18) Jones and Dole, *THIS JOURNAL*, **51**, 1035, 1073 (1929).

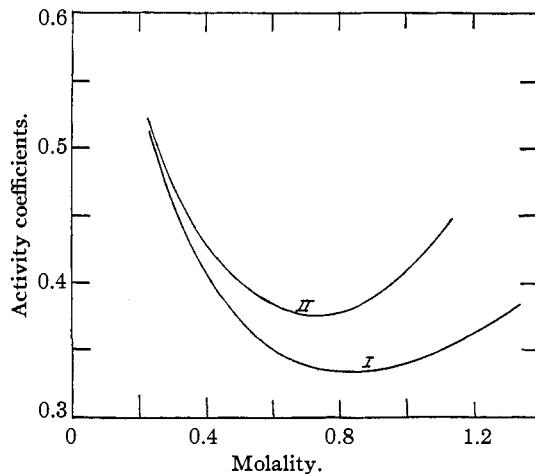


Fig. 3.—Activity coefficients of barium and strontium chlorides: I, BaCl₂; II, SrCl₂.

Åkerlöf,⁷ but they do not agree with those of Lucasse⁸ or of Hepburn.¹⁰

A series of determinations on calcium chloride has been made; however, the investigation is still in progress. The results will be reported at a later date.

Summary

1. Certain improvements in technique and in design of apparatus for the isopiestic method of determining activity coefficients have been described.

2. The activity coefficients have been determined for aqueous solutions of strontium chloride, using barium chloride as the reference standard. The values obtained are believed to have an accuracy better than 1 part in 500.

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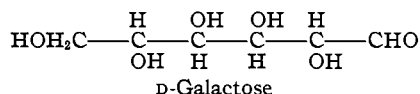
[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Crystalline Modifications of D-Manno-D-gala-heptose, and the Preparation of Some of Its Derivatives¹

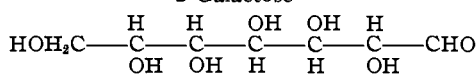
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D-Manno-D-gala-heptose, originally called *d*- α -mannoheptose by Emil Fischer,² who prepared it from D-mannose by the cyanohydrin synthesis, was shown by George Peirce³ to have the configuration of carbon atoms one to five like that of

D-galactose; because this heptose is related thus to D-mannose and to D-galactose, it has been termed D-manno-D-gala-heptose.⁴



D-Galactose



D-Manno-D-gala-heptose

(1) Publication authorized by the Surgeon General, U. S. Public Health Service. A preliminary report on the crystalline modifications of D-manno-D-gala-heptose was presented in part at the meeting of the National Academy of Sciences, Washington, D. C., April, 29, 1930. Not copyrighted.

(2) Fischer and Passmore, *Ber.*, **23**, 2226 (1890).

(3) Peirce, *J. Biol. Chem.*, **23**, 327 (1915).

(4) Hudson, *THIS JOURNAL*, **60**, 1537 (1938).

The research described in the present communication was undertaken in order to compare D-manno-D-gala-heptose and its derivatives with D-galactose and its derivatives.⁵ Meanwhile, the hydrate of the α -form and the hydrate of the β -form of the heptose have been described by Isbell.⁶

In Table I are listed, in the order of their decreasing extrapolated initial rotations⁷ in water, the several modifications of D-manno-D-gala-heptose reported by Fischer, by Isbell, and by the present authors. The heptose isolated by Fischer rotated initially $+85^\circ$. As suggested by Isbell,⁸ this is probably a double compound; a combination of our anhydrous α ($+124^\circ$) and β ($+43^\circ$) forms in equal proportions would be expected to have an initial rotation of $+83.5^\circ$, as compared with the value $+82.0^\circ$ now reported.

TABLE I
CRYSTALLINE MODIFICATIONS OF D-MANNO-D-GALA-
HEPTOSE

	M. p. °C.	Initial rotation in water, calcd. as anhydrous sugar	Mutarotation velocity, $k \times 10^3$
Second α -form, anhydrous	150	+144.0 ^c	13 \rightarrow 3.9
α -Heptose·CaCl ₂ ·4H ₂ O	141	149.8	16 \rightarrow 4.4
α -Monohydrate (Isbell ⁶)	107	130.3	6.1 \rightarrow 4.0
α -Monohydrate	115-120	123.8	4.2
α -Heptose, anhydrous	145	124.0	4.5
α -Heptose·CaCl ₂ ·3H ₂ O	158	122.2	1.2
α,β -Heptose (Fischer ⁵)	134	85.0	...
α,β -Heptose (Isbell ⁶)	...	85.0	...
α,β -Heptose	132	82.0	20.5 \rightarrow 5.2
β -Monohydrate	104	52.0	6.0 \rightarrow 4.2
β -Monohydrate (Isbell ⁶)	104	45.9	6.0 \rightarrow 3.7
β -Heptose, anhydrous	115	43.1	3.6

^a Isbell, Ref. 6. ^b Fischer and Passmore, Ref. 2. ^c Isbell, Ref. 6a, p. 529. ^d Calculated as a unimolecular reaction, in minutes and common logarithms.

Crystallization of the sugar from water at room temperature produced the monohydrate of the α -modification, with an extrapolated initial rotation of $+123.8^\circ$ calculated as the anhydrous heptose. The hydrate can be converted to an anhydrous α -form by drying at 40° *in vacuo*; its initial rotation of $+124.0^\circ$ agreed with the corresponding value calculated from the monohydrate. A third modification of the α -sugar was obtained in the form of a complex, C₇H₁₄O₇·CaCl₂·3H₂O, with an initial

(5) Similar comparisons between D-gala-L-manno-heptose and L-mannose, D-gala-L-gluco-heptose and L-glucose, and D-gala-L-gala-octose and L-galactose have been made by Hann, Merrill and Hudson, THIS JOURNAL, **57**, 2100 (1935); by Hann and Hudson, *ibid.*, **59**, 548 (1937); and by Maclay, Hann and Hudson, *ibid.*, **60**, 1035 (1938), respectively.

(6) (a) Isbell, *J. Res. Natl. Bur. Standards*, **18**, 527 (1937); (b) Isbell, *ibid.*, **20**, 106 (1938).

(7) Unless otherwise designated all rotations are specific rotations at 20° for sodium light; c represents the concentration in grams per 100 cc. of solution, and l the length of the tube in decimeters.

(8) Isbell, Ref. 6a, p. 527.

rotation $+122.2^\circ$ calculated for the heptose moiety. Each of these substances mutarotated in water to a value of about $+69.0^\circ$, calculated as heptose, and the course of mutarotation of each appeared to be unimolecular, and the velocity coefficients were identical in value.

A second anhydrous α -D-manno-D-gala-heptose has been isolated in small yields, by two methods which are described in the experimental section. An initial rotation of $+144.0^\circ$ characterizes this second form, together with a mutarotation curve showing decreasing coefficients. Confirmatory evidence for this second form was obtained in a calcium chloride complex, C₇H₁₄O₇·CaCl₂·4H₂O, which showed an initial rotation of $+140.8^\circ$ for the heptose moiety, and decreasing coefficients of similar values for its mutarotation. The α -monohydrate reported by Isbell, with initial rotation $+130.3^\circ$ calculated as the anhydrous heptose, appears to be intermediate between our two series of α -modifications.

Anhydrous β -D-manno-D-gala-heptose was obtained readily by the addition of glacial acetic acid to a sirup prepared by concentrating an aqueous solution of the sugar on the steam-bath. It had an extrapolated initial rotation of $+43.1^\circ$, a final rotation of $+69.1^\circ$, and mutarotated at a rate which corresponded to that of a unimolecular reaction.

A monohydrate of a β -modification was isolated in an attempt to recrystallize the α -heptose calcium chloride tetrahydrate. This β -hydrate showed an initial rotation, as heptose, of $+52.9^\circ$, with decreasing coefficients during mutarotation. The heptose portion of Isbell's β -monohydrate rotated $+45.9^\circ$, with increasing coefficients. Thus it appears probable that there are two β -modifications of rotations $+43.1^\circ$ and $+52.9^\circ$, respectively, just as there appear to be two distinct α -varieties, the experimental evidence for which is more certain; whether Isbell's β -monohydrate of $+45.9^\circ$ rotation represents a different or merely an intermediate form is not clear.

In addition to the several modifications of D-manno-D-gala-heptose, we have prepared, by the usual reactions, the acetochloro- and acetobromo-derivatives, the normal α - and β -methylglycosides and their acetates, and a β -methylglycofuranoside and its acetate. The specific and molecular rotations of these substances, together with those of a few derivatives described previously, are listed in Table II. The values for the corresponding

TABLE II
COMPARISON OF ROTATIONS OF SUBSTANCES IN THE D-GALACTOSE AND D-MANNO-D-GALA-HEPTOSE SERIES

	D-Galactose series, rotation		D-Manno-d-gala-heptose series, rotation		
	sp.	mol.	sp.	mol.	
Sugar	initial α	+150.7 ^a	+27,200	+124.0	+ 26,000
	initial β	+ 52.8 ^a	+ 9,500	+ 43.1	+ 9,100
	final	+ 80.2 ^a	+14,500	+ 68.9	+14,500
Aldonic acid amide	+ 30.2 ^b	+ 5,900	+ 28.0 ^b	+ 6,300	
Aldonic acid phenylhydrazide	+ 11.0 ^c	+ 3,100	+ 21 ⁱ	+ 6,600	
Aldonic acid lactone	- 77.6 ^d	-13,800	- 74.2 ^m	- 15,400	
Sugar acetate	α	+106.7 ^e	+41,700	+120.8 ⁿ	+ 55,800
	β	+ 25 ^e	+ 9,800	+ 34 ⁿ	+ 15,700
	aldehyde	- 25 ^f	- 9,800	- 34 ⁿ	- 15,700
Acetochloro α	+212 ^g	+77,800	+175	+ 76,800	
Acetobromo α	+236 ^h	+97,000	+208	+100,500	
Methylglycopyranoside	α	+196.1 ⁱ	+38,100	+178	+ 39,900
	β	+ 0.7 ⁱ	+ 100	- 5.1	- 1,100
Methylglycofuranoside β	- 97.2 ^j	-20,200 ^j	-111	- 24,600	
Methylglycopyranoside acetate	α	+133.0 ⁱ	+48,200	+149.5	+ 65,000
	β	- 14.0 ⁱ	- 5,100	+ 8.3	+ 3,600
Methylglycofuranoside acetate β	- 50.5 ^j	-19,000 ^j	- 43.5	- 18,900	

^a Isbell and Pigman, *J. Research Natl. Bur. Standards*, **18**, 158 (1937). ^b Hudson and Komatsu, *THIS JOURNAL*, **41**, 1141 (1919). ^c Nef, *Ann.*, **403**, 296 (1914). ^d Ruff and Franz, *Ber.*, **35**, 948 (1902). ^e Hudson and Parker, *THIS JOURNAL*, **37**, 1589 (1915). ^f Wolfrom, *ibid.*, **52**, 2464 (1930). ^g Skraup and Kremann, *Monatsh.*, **22**, 379 (1901). ^h Fischer and Armstrong, *Ber.*, **35**, 838 (1902). ⁱ Dale and Hudson, *THIS JOURNAL*, **52**, 2534 (1930). ^j Because the methylgalactofuranoside and its acetate are not crystalline, the specific and molecular rotations recorded here are for the ethylgalactofuranoside and its acetate, prepared by Schlubach and Meisenheimer, *Ber.*, **67**, 429 (1934). ^k Hudson and Monroe, *THIS JOURNAL*, **41**, 1140 (1919). ^l Hudson, *ibid.*, **39**, 468 (1917). ^m Fischer and Passmore, *Ber.*, **23**, 2226 (1890). ⁿ Montgomery and Hudson, *THIS JOURNAL*, **56**, 2463 (1934).

members of the D-galactose series are included for comparison. It may be noted that the molecular rotations of the anhydrous α (+124°) and β (+43°) D-manno-D-gala-heptose forms are in good agreement with the corresponding galactose pair, and that the aldonic acid derivatives agree fairly well. However the α -, the β - and the *aldehyde*-heptose hexaacetates have considerably higher rotations than the related hexose acetates. The acetobromo and acetochloro compounds and the α - and β -methylglycopyranosides are in good agreement, but the pyranoside acetates differ considerably from the heptose to the hexose series.

The methyl-D-manno-D-gala-heptoside of rotation -97.2° was assumed to be a furanoside because it had been prepared in the manner considered to be characteristic of furanoside formation, and because it was hydrolyzed by acid about twenty-five times as rapidly as the "normal" methyl-D-manno-D-gala-heptosides. A comparison of the molecular rotations of this glycoside and its acetate with the molecular rotations of the ethylgalactofuranoside and its acetate prepared by Schlubach and Meisenheimer⁹ serves to confirm the furanoside structure of our compounds. The

" β " designation is used because of their negative rotations.

The sugar D-manno-D-gala-heptose is exceptional in that it exhibits such a large number of definite crystalline modifications. Evidence has now been presented to indicate that there are two distinct forms of α -D-manno-D-gala-heptose rotating +124° and +144°, respectively; two β -forms also may occur. The form of rotation +82° is apparently a molecular combination. The very large negative rotation of the β -methyl furanoside appears to exclude the possibility that either of the strongly positive α -forms of the sugar can be a furanose. The α -form of rotation +124° could conceivably be a molecular combination of the +144° α -form with some one of the β -forms. Lastly, the existence of so many forms might be accounted for on the assumption that different ring conformations are possible¹⁰ and that such isomers of D-manno-D-gala-heptose have sufficient stability and crystallizing power to permit isolation of more than one form. An extension of this hypothesis might explain the lack of agreement between the molecular rota-

(10) Cf. Haworth, "The Constitution of Sugars," Edward Arnold and Co., London, 1929, p. 90; Pacsu, *THIS JOURNAL*, **61**, 2672 (1939); Hudson, *ibid.*, **61**, 2972 (1939); Scattergood and Pacsu, *ibid.*, **62**, 905 (1940).

(9) Schlubach and Meisenheimer, *Ber.*, **67**, 429 (1934).

tions of certain derivatives of this heptose and the molecular rotations of the corresponding derivatives of the configurationally related D-galactose.

Experimental

The Preparation of D-Manno-D-gala-heptose.—A smooth paste was obtained by stirring slowly 200 g. of powdered vegetable ivory into 140 cc. of 85% sulfuric acid in a 1-liter porcelain casserole. Charring was avoided by cooling the casserole so that the temperature of the mixture did not exceed 35°. After standing overnight the purple jelly was diluted to 1 liter with water, mixed with 50 g. of decolorizing carbon, boiled under a reflux condenser for three hours and filtered. The acid was neutralized to congo red with calcium carbonate, and the solution was filtered through activated carbon. The colorless filtrate, estimated by a copper reduction method to contain 95 g. of mannose, was transferred to a 2-liter distilling flask, cooled to 5°, and 80 g. of pulverized barium chloride dihydrate (1.2 equivalents) and 28.9 g. of sodium cyanide (1.1 equivalents) were added. The flask was stoppered carefully and shaken until all of the solid had dissolved. After standing overnight at 5°, the mixture of sirup and crystals which had formed was concentrated *in vacuo* to about two-thirds of its volume, or until bumping became troublesome. Crystallization was allowed to continue for about one week at 5°. The barium salt was separated from the sirup by filtration under a hood, washed with cold water, and identified by analysis as the barium D-manno-D-gala-heptonate trihydrate isolated by Kiliani.¹¹ It was purified by recrystallization from 12 parts of boiling water. An analysis, obtained on a sample which had been dried to constant weight at 30° *in vacuo*, agreed with Fischer's analysis of the anhydrous salt.¹² Air-dried samples also became anhydrous. The rotation, not hitherto recorded, was -9.5° in water (supersaturated solution; *c.* 2.0). The yield was 118 g.

Anal. Calcd. for $C_{14}H_{26}O_{16}Ba$: Ba, 23.33. Found: Ba, 23.30.

The lactone was prepared from the barium salt by the method of Fischer and Passmore; purified by recrystallization from ethyl alcohol it rotated -74.2° in water (*c.* 2.0) and melted at 149–151°. Reduction of the lactone with sodium amalgam produced a 38–44% yield of D-manno-D-gala-heptose. The sugar was thrice recrystallized by solution in one part of water and dilution with three parts of glacial acetic acid; the ash-free material had an equilibrium rotation of $+68.8 \pm 0.5^\circ$ in water (*c.* 2.0).

α -D-Manno-D-gala-heptose Monohydrate.—A solution of 20 g. of the heptose in 200 cc. of water was allowed to concentrate in a glass crystallizing dish at room temperature. After two weeks, the concentrate crystallized spontaneously to a dense mass of very small, rhombic plates. The sirup was thinned with 100 cc. of 50% methyl alcohol; the crystalline material, separated by filtration, was washed with 50% methyl alcohol, absolute methyl alcohol and ether, and dried to constant weight at 20° in a desiccator over calcium chloride. The yield was 13.1 g. of monohydrate melting at 115–120°. This process was repeated until the monohydrate had a constant initial rotation of $+113.9^\circ$ and a final rotation of $+63.5^\circ$ in water. The course of its mutarotation is shown in Table III. Dried to constant weight at 40° *in vacuo* the hydrate was transformed to a powder, m. p. 145°, mutarotating in water (*c.* 4) from $+124.0^\circ$ to $+69.0^\circ$; its mutarotation data are recorded in Table IV.

Anal. Calcd. for $C_7H_{14}O_7 \cdot H_2O$: H_2O , 7.89. Found: H_2O , 7.81. Calcd. for $C_7H_{14}O_7$: C, 40.00; H, 6.72. Found, on dried sample: C, 40.13; H, 6.77.

TABLE III
MUTAROTATION OF α -D-MANNO-D-GALA-HEPTOSE MONOHYDRATE IN WATER (*c.* 4; *l.* 2) AT 20°

Time, min.	Rotation of anhydrous sugar	$k_1 + k_2$
0	[+123.8]	
3	122.0	
4	121.8	0.0043
5	121.2	.0044
7	120.3	.0043
10	118.6	.0044
16	116.0	.0044
20	113.9	.0042
25	112.8	.0044
26	111.7	.0042
31	109.7	.0044
39	106.9	.0044
42	106.2	.0042
44	105.4	.0043
52	102.8	.0041
62	99.5	.0040
74	96.1	.0041
121	87.2	.0041
211	77.5	.0040
∞	69.0	
	Average	0.0042

TABLE IV
MUTAROTATION OF α -D-MANNO-D-GALA-HEPTOSE IN WATER (*c.* 4; *l.* 2) AT 20°

Time, min.	Rotation	$k_1 + k_2$
0	[+124.0]	
3.2	122.3	
4.1	121.8	0.0043
5.2	121.2	.0044
5.9	120.9	.0042
7	120.3	.0043
10	118.6	.0044
14	116.6	.0045
20	113.9	.0042
26	111.7	.0044
34	108.0	.0039
39	106.9	.0043
44	105.4	.0040
52	102.8	.0041
74	96.1	.0041
121	87.2	.0041
211	77.5	.0040
∞	69.0	
	Average	0.0042

(11) Kiliani, *Ber.*, **63**, 369 (1930). The separation of the barium salt from the reaction mixture as described above was carried out in 1930, and has been referred to in an article by Hudson, Hartley and Purves. *This Journal*, **56**, 1248 (1934).

(12) Fischer and Hirschberger, *Ber.*, **22**, 370 (1889).

α -D-Manno-D-gala-heptose Calcium Chloride Trihydrate.—A solution, prepared by warming 21 g. of the heptose, 30 g. of calcium chloride dihydrate, 40 cc. of water and 50 cc. of absolute alcohol, was kept at 0° for three days and then concentrated *in vacuo* (bath at 60°) until crystallization began. The mixture, weighing about 70 g., was shaken with 30 cc. of absolute alcohol and filtered. The crystals were washed with alcohol and ether and dried to constant weight in the air. The yield was 14.4 g. of thin, six-sided prisms which melted at 158° without browning. The equilibrium rotation, +38.6° in water, corresponded to a sugar content of 56.0%, in agreement with the formula determined by the analyses below. The course of its mutarotation, as recorded in Table V, appeared to be unimolecular after a short induction period. The initial rotation +68.4° is equivalent to +122.2° for the anhydrous heptose portion of the complex.

Anal. Calcd. for $C_7H_{14}O_7 \cdot CaCl_2 \cdot 3H_2O$: Ca, 10.69; Cl, 18.91. Found: Ca, 10.82; Cl, 18.82.

TABLE V

MUTAROTATION OF α -D-MANNO-D-GALA-HEPTOSE $\cdot CaCl_2 \cdot 3H_2O$ IN WATER (*c*, 4; *l*, 2) AT 20°

Time, min.	Rotation of anhydrous sugar	$k_1 + k_2$
0	[+122.2]	
2	122.2	
3	122.2	0.0000
5	121.0	.0033
7	119.8	.0040
10	117.8	.0044
15	115.9	.0042
20	113.2	.0044
30	109.0	.0044
60	97.0	.0046
90	90.4	.0044
141	82.3	.0042
∞	68.9	

Average 0.0042

α -D-Manno-D-gala-heptose Calcium Chloride Tetrahydrate.—A solution, prepared by warming 21 g. of the heptose and 22 g. of calcium chloride dihydrate in 30 cc. of

TABLE VI

MUTAROTATION OF α -D-MANNO-D-GALA-HEPTOSE $\cdot CaCl_2 \cdot 4H_2O$ IN WATER (*c*, 4; *l*, 2) AT 20°

Time, min.	Rotation of anhydrous sugar	$k_1 + k_2$
0	[+140.8]	
1.5	136.9	
2	135.6	0.016
3	133.1	.016
5	129.9	.014
8	127.8	.0095
12	125.4	.0079
17	122.1	.0068
21	120.1	.0061
30	115.1	.0056
45	109.5	.0052
68	103.5	.0044
90	94.1	.0044
135	87.6	.0044
∞	68.7	

water, was diluted with 90 cc. of absolute alcohol and kept at 0°. After two weeks a crop of thin four-sided plates was removed by filtration, washed with aqueous alcohol, absolute alcohol and ether and dried to constant weight over calcium chloride in a desiccator. The yield was 9 g. of α -D-manno-D-gala-heptose calcium chloride tetrahydrate melting at 141° without browning. It had an equilibrium rotation of +36.7° in water. The mutarotation, as shown in Table VI, was not unimolecular but was characterized by decreasing coefficients. The extrapolated initial rotation was +75.3°, or +140.8° expressed as a measurement of the anhydrous sugar.

Anal. Calcd. for $C_7H_{14}O_7 \cdot CaCl_2 \cdot 4H_2O$: Ca, 10.19; Cl, 18.03. Found: Ca, 10.34; Cl, 18.00.

β -D-Manno-D-gala-heptose Monohydrate.—An attempted recrystallization of the α -D-manno-D-gala-heptose calcium chloride tetrahydrate from aqueous alcohol resulted in the isolation of a hydrate of the β sugar. A solution prepared by warming 10 g. of the complex in 25 cc. of water was diluted with 125 cc. of absolute alcohol and kept at 0°. Overnight this solution deposited a uniform crop of single, long, six-sided prisms. These were removed by filtration, washed with aqueous alcohol and dried to constant weight in a desiccator over calcium chloride. The yield was 3.4 g. of β -D-manno-D-gala-heptose monohydrate melting at 104°. It rotated +63.4° in water at equilibrium; the mutarotation, as recorded in Table VII, was not unimolecular. The extrapolated initial rotation was +48.7°, or +52.9° calculated as the anhydrous sugar.

Anal. Calcd. for $C_7H_{14}O_7 \cdot H_2O$: C, 36.84; H, 7.07. Found: C, 36.62; H, 7.15.

TABLE VII

MUTAROTATION OF β -D-MANNO-D-GALA-HEPTOSE MONOHYDRATE IN WATER (*c*, 4; *l*, 2) AT 20°

Time, min.	Rotation of anhydrous sugar	$k_1 + k_2$
0	[+52.9]	
2	53.3	
9	54.6	0.0060
23.5	57.0	.0060
51	59.0	.0040
78	60.9	.0038
120	64.0	.0042
165	65.7	.0042
∞	68.8	

Average 0.0047

β -D-Manno-D-gala-heptose.—An anhydrous β -form was obtained by crystallization of the simple sugar. A solution, prepared by dissolving 20 g. of heptose in 20 cc. of water, was concentrated on the steam-bath to about two-thirds its volume, cooled and stirred with 5 volumes of glacial acetic acid; it deposited a crop of short, square prisms. After one-half hour, these were removed by filtration, washed with 50% ethyl alcohol and dried. The material obtained in this manner was recrystallized by the same process until the initial extrapolated rotation had a constant value of +43.1°. Extraction of the crystalline substance with 80% ethyl alcohol at 20° did not change this rotation. β -D-Manno-D-gala-heptose melted at 145° and had a rotation in water of +69.1° at equilibrium. The mutarotation data are shown in Table VIII.

Anal. Calcd. for $C_7H_{14}O_7$: C, 40.00; H, 6.72. Found: C, 39.88; H, 6.68.

TABLE VIII

MUTAROTATION OF β -D-MANNO-D-GALA-HEPTEOSE IN WATER
(*c*, 4; *l*, 2) AT 20°

Time, min.	Rotation	$k_1 + k_2$
0	[+43.1]	
2.9	43.7	
4.8	43.9	0.0034
8.5	44.9	.0038
10.4	45.3	.0034
13.3	45.8	.0033
14.9	46.2	.0037
17.7	46.8	.0038
20.5	47.7	.0037
25	48.4	.0035
30	49.0	.0038
35	50.2	.0038
40	51.0	.0038
55	53.6	.0040
90	57.3	.0040
120	60.0	.0037
∞	69.1	

Average 0.0036

(α,β)-D-Manno-D-gala-heptose.—Crystallization of a 2% solution of the heptose in 85% alcohol over a period of weeks at 0° resulted in the formation of the double compound in aggregates of clear, slender prisms melting at 132°. A typical mutarotation is recorded in Table IX.

Anal. Calcd. for $C_7H_{14}O_7$: C, 40.00; H, 6.72. Found: C, 39.90; H, 6.70.

TABLE IX

MUTAROTATION OF (α,β)-D-MANNO-D-GALA-HEPTEOSE IN WATER (*c*, 4; *l*, 2) AT 20°

Time, min.	Rotation	$k_1 + k_2$
0	[+82.0]	
4	81.3	
9	80.1	0.0074
13	79.6	.0105
17	78.8	.0103
21	77.9	.0107
31	75.3	.0083
43	74.4	.0091
58	73.4	.0080
120	71.8	.0052
∞	69.1	

Average 0.0086

The Second α -D-Manno-D-gala-heptose—Crystallization of a 2% solution of the heptose in 85% alcohol at 50° produced three types of crystals simultaneously: the anhydrous β -form, the α,β -double compound, and a new, anhydrous α -modification melting at 150°. This second α -sugar appeared as broom-like clusters of needles which could be separated from the other forms mechanically, in small yields. The mutarotation as recorded in Table X, was not unimolecular. The second α -form was obtained frequently by heating the α -monohydrate at 110 to 115°, and crystallizing the anhydrous, yellowish powder from hot aqueous methyl alcohol. The product separated

usually as the broom-like clusters but the initial extrapolated rotation varied from +124 to +144°.

Anal. Calcd. for $C_7H_{14}O_7$: C, 40.00; H, 6.72. Found: C, 39.85; H, 6.74.

TABLE X

MUTAROTATION OF THE SECOND α -D-MANNO-D-GALA-HEPTEOSE IN WATER (*c*, 4; *l*, 2) AT 20°

Time, min.	Rotation	$k_1 + k_2$
0	[+144.0]	
1.5	140.8	
2.5	135.6	0.0130
3.4	134.0	.0127
5.0	130.8	.0114
8.2	128.1	.0092
12.1	127.1	.0074
15	125.6	.0068
20	123.0	.0063
30	120.0	.0048
45	114.9	.0040
70	107.6	.0041
90	98.4	.0043
115	94.3	.0039
∞	68.9	

Average 0.0073

α -Acetochloro-D-manno-D-gala-heptose.—A solution of 10 g. of crystalline β -hexaacetyl-D-manno-D-gala-heptose in 40 cc. of chloroform was boiled gently under a reflux condenser with 6 g. of phosphorus pentachloride and 2.5 g. of anhydrous aluminum chloride for one hour. The product was crystallized from chloroform by dilution with petroleum ether in a yield of 7 g., rotating +173° in chloroform. After several recrystallizations from ether and petroleum ether, α -acetochloro-D-manno-D-gala-heptose was obtained as shining prismatic needles melting at 119° and rotating +175° in chloroform (*c*, 2). On treatment with silver acetate in warm acetic acid the chloro derivative was reconverted to the β -hexaacetate in a 65% yield.

Anal. Calcd. for $C_{17}H_{28}O_{11}Cl$: Cl, 8.10. Found: Cl, 8.00.

α -Acetobromo-D-manno-D-gala-heptose.—Crystalline β -hexaacetyl-D-manno-D-gala-heptose was treated with a saturated solution of hydrobromic acid in glacial acetic acid by the customary procedure. The product, purified by several recrystallizations from ether, was obtained as prisms rotating +208.0° in chloroform (*c*, 2). The yield of α -acetobromo-D-manno-D-gala-heptose, melting at 112°, was 84% of the theoretical. Treated with silver acetate, the bromo compound also was reconverted to the β -hexaacetate.

Anal. Calcd. for $C_{17}H_{28}O_{11}Br$: Br, 16.54. Found: Br, 16.48.

Pentaacetyl- β -methyl-D-manno-D-gala heptoside.— α -Acetobromo-D-manno-D-gala-heptose was condensed with methyl alcohol in the presence of silver carbonate by the usual Koenigs and Knorr synthesis. The product crystallized easily from ether and was recrystallized from absolute ethyl alcohol, as rosets of prisms, to a constant rotation of +8.3° in chloroform (*c*, 2). The yield of pentaacetyl- β -methyl-D-manno-D-gala-heptoside, melting at 105°, was 90% of the theoretical.

Anal. Calcd. for $C_{18}H_{26}O_{12}$: C, 49.74; H, 6.03; OCH_3 , 7.14; acetyl, 11.52 cc. of 0.1 *N* NaOH per 100 mg. Found: C, 49.63; H, 6.07; OCH_3 , 7.18; acetyl, 11.50 cc.

β -Methyl-D-manno-D-gala-heptoside.—Crystalline pentaacetyl- β -methyl-D-manno-D-gala-heptoside was deacetylated catalytically with barium methylate. The product was purified by several crystallizations from methyl alcohol. The yield of β -methyl-D-manno-D-gala-heptoside was 91% of the theoretical; the rotation was -5.1° in water (*c*, 2) and the melting point was 168° . The new glycoside was soluble in methyl alcohol, less soluble in ethyl alcohol, and practically insoluble in ethyl acetate and ether. The hydrolysis, as recorded in Table XI, was unimolecular; the final rotation of $+64.3^\circ$, calculated as the glycoside, is equivalent to $+68.8^\circ$, expressed as the anhydrous sugar.

Anal. Calcd. for $C_8H_{16}O_7$: C, 42.84; H, 7.19; OCH_3 , 13.84. Found: C, 42.87; H, 7.27; OCH_3 , 13.90.

TABLE XI

HYDROLYSIS OF β -METHYL-D-MANNO-D-GALA-HEPTOSIDE IN 0.05 *N* HYDROCHLORIC ACID (*c*, 3) AT 98°

Time, min.	Rotation	$k_1 + k_2$
0	-5.0	
30	-1.1	0.00079
95	+6.6	.00085
145	13.0	.00084
200	18.7	.00084
265	24.8	.00084
335	30.3	.00084
395	34.9	.00084
470	40.1	.00085
540	44.4	.00083
∞	64.3	

Average 0.00084

Pentaacetyl- α -methyl-D-manno-D-gala-heptoside.—A mixture of 100 g. of the sugar and 1 liter of methyl alcohol containing 1% of hydrogen chloride was boiled under a reflux condenser for eighteen hours; at that time an equilibrium rotation of 72° had been reached. The product, isolated in the usual way, was crystallized from methyl alcohol in a yield of approximately 55 g. of mixed glycosides. Fractionation was attempted in several solvents; about 5% of the pure β isomer was isolated but, upon recrystallization, the fractions of higher rotation formed persistently as complex, granular mixtures, frequently rotating about $+130^\circ$ in water. The solvents were removed from the entire preparation, therefore, and the residue was acetylated at 0° with acetic anhydride and pyridine. The acetate, crystallized by pouring the mixture into ice and water, was removed by filtration. Recrystallized from 4 parts of *n*-propyl alcohol by dilution with 10 parts of water, the product separated as well-built, iridescent plates and prisms weighing 135 g. and rotating $+138^\circ$ in chloroform. The rotation of pentaacetyl- α -methyl-D-manno-D-gala-heptoside was increased by ten recrystallizations from aqueous *n*-propyl alcohol to a constant value of $+149.5^\circ$ in chloroform (*c*, 2); the melting point was 156° .

Anal. Calcd. for $C_{18}H_{26}O_{12}$: C, 49.74; H, 6.03; OCH_3 , 7.14; acetyl, 11.52 cc. of 0.1 *N* NaOH per 100 mg. Found: C, 49.70; H, 6.07; OCH_3 , 7.10; acetyl, 11.54 cc.

α -Methyl-D-manno-D-gala-heptoside.—Crystalline pentaacetyl- α -methyl-D-manno-D-gala-heptoside was deacetylated catalytically with barium methylate. The product, purified by several recrystallizations from methyl alcohol, crystallized sometimes as needles and sometimes as prisms, rotating $+178^\circ$ in water (*c*, 2) and melting at 141° . On reacylation the original acetylated glycoside was obtained. The new glycoside was very soluble in methyl alcohol, soluble in ethyl alcohol and practically insoluble in ethyl acetate, acetone and ether. The hydrolysis, as recorded in Table XII, was unimolecular; the final rotation of $+64.3^\circ$, calculated as the glycoside, is equivalent to $+68.8^\circ$, expressed as the anhydrous sugar.

Anal. Calcd. for $C_8H_{16}O_7$: C, 42.84; H, 7.19; OCH_3 , 13.84. Found: C, 42.80; H, 7.21; OCH_3 , 13.90.

TABLE XII

HYDROLYSIS OF α -METHYL-D-MANNO-D-GALA-HEPTOSIDE IN 0.05 *N* HYDROCHLORIC ACID (*c*, 2) AT 98°

Time, min.	Rotation	$k_1 + k_2$
0	+177.0	
60	165.6	0.00081
115	155.8	.00082
175	146.5	.00081
230	140.0	.00079
290	134.4	.00077
350	127.0	.00078
410	122.9	.00078
∞	64.3	

Average 0.00080

β -Methyl-D-manno-D-gala-heptofuranoside.—The crystalline furanoside was separated from the mixture of glycosides obtained by the condensation of the heptose with acid methyl alcohol under the mild conditions favorable to furanoside formation. A mixture of 100 g. of the pulverized heptose and 1 liter of absolute methyl alcohol containing one-half per cent. of hydrogen chloride was shaken at 25° for eighteen hours; at that time the sugar was completely dissolved and the colorless, non-reducing solution had a rotation of -10° . The product, isolated as a sirup by the customary procedure, was dissolved in 150 cc. of methyl alcohol, cooled to 5° , diluted with acetone to a point just below saturation, and allowed to crystallize for several days. The product, weighing 40 g. and rotating -88° in water, was recrystallized at 5° from 100 cc. of methyl alcohol by dilution with 300 cc. of acetone; the yield of β -methyl-D-manno-D-gala-heptofuranoside was 29.6% of the theoretical. The rotation of the pure furanoside was -111° in water (*c*, 2), and the melting point 115° . The

TABLE XIII

HYDROLYSIS OF β -METHYL-D-MANNO-D-GALA-HEPTOFURANOSIDE IN 0.05 *N* HYDROCHLORIC ACID (*c*, 3) AT 98°

Time, min.	Rotation	$k_1 + k_2$
0	-111.0	
4	-79.3	0.021
8	-51.0	.022
15	-17.6	.022
30	+27.4	.021
45	51.9	.022
∞	64.2	

Average 0.022

hydrolysis, as recorded in Table XIII, was unimolecular; the final rotation of $+64.2^\circ$, calculated as the glycoside, is equivalent to $+68.7^\circ$, expressed as the anhydrous sugar.

Anal. Calcd. for $C_8H_{16}O_7$: C, 42.84; H, 7.19; OCH_3 , 13.84. Found: C, 42.80; H, 7.26; OCH_3 , 13.90.

Pentaacetyl- β -methyl-D-manno-D-gala-heptofuranoside.—The crystalline furanoside was acetylated at 0° with pyridine and acetic anhydride and the product isolated as a sirup by the customary procedure. The new acetate was crystallized at 25° from ether by dilution with petroleum ether, and recrystallized from these solvents to a constant rotation of -43.5° in chloroform (*c*, 2). The pentaacetyl- β -methyl-D-manno-D-gala-heptofuranoside was obtained as prisms melting at 78° , and in a 72% yield.

Anal. Calcd. for $C_{15}H_{26}O_{12}$: C, 49.74; H, 6.03; OCH_3 , 7.14; acetyl, 11.52 cc. 0.1 *N* NaOH per 100 mg. Found: C, 49.70; H, 6.07; OCH_3 , 7.18; acetyl, 11.54 cc.

Conversion to aldehydo-D-Manno-D-gala-heptose Hexaacetate.—The open-chain compound was obtained by treating the acetylated glycofuranoside (see preceding paragraph) with a 4% solution of sulfuric acid in a 70-30 mixture of acetic anhydride and acetic acid. The rotation of this solution changed to a final value of -33.0° within fifteen minutes. The acetate was separated as small, square prisms by pouring the solution into ice and water, and was purified as described previously.¹³ The yield of aldehydo-

¹³ Montgomery and Hirdson, *This Journal*, **56**, 2403 (1934).

D-manno-D-gala-heptose hexaacetate, rotating -34.1° in chloroform (*c*, 2) and melting at 146° , was 94% of the theoretical.

Summary

1. D-Manno-D-gala-heptose has been prepared by applying a modification of the cyanohydrin synthesis to mannose. Evidence has been presented to indicate the existence of two distinct α -modifications of initial $[\alpha]^{20}_D +124^\circ$ and $+144^\circ$, respectively. Two β -modifications also are reported.

2. The acetochloro- and acetobromo- derivatives, the α - and β -methyl-D-manno-D-gala-heptopyranosides and their acetates, and the β -methyl-D-manno-D-gala-heptofuranoside and its acetate have been described.

3. A comparison of the molecular rotations of D-manno-D-gala-heptose and its derivatives with the molecular rotations of the configurationally related D-galactose and its derivatives shows agreement between some compounds and disagreement between others.

BETHESDA, MD.

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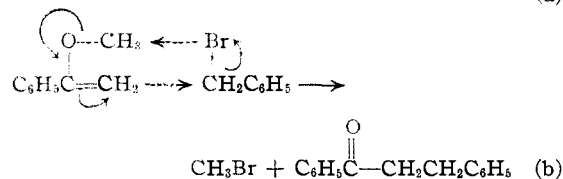
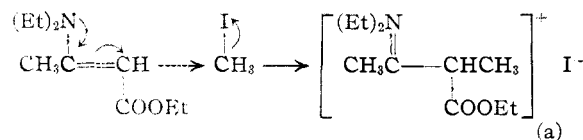
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Ketene Acetals. VII.¹ The Reaction of Ketene Diethylacetal with Various Halogen Compounds and Acids

BY S. M. McELVAIN AND D. KUNDIGER²

In previous papers³ of this series the unusual hetero-enoid structure of ketene diethylacetal has been discussed, and many of its reactions interpreted on the basis of the polarization that is characteristic of this type of structure. In the continuation of the study of the chemical properties of this compound, it seemed desirable to investigate the course of its reaction with a variety of organic halides. Two interesting cases of reaction between aliphatic hetero-enoid systems and alkyl halides have been reported in the literature: (a) the carbon alkylation of ethyl β -diethylamino-crotonate⁴ with methyl iodide, and (b) the condensation of α -methoxystyrene with such halides as benzyl bromide with the formation of an ω -al-

kylated acetophenone.⁵ These reactions may be illustrated as follows:



The work with ketene acetal which is now reported shows some interesting variations of the simple type of carbon alkylation that is illustrated above. In the case of butyl bromide, the least reactive of the halides that were used, the reaction did follow the above pattern with the formation of ethyl caproate and ethyl bromide

⁵ Mortenson and Spielman, *ibid.*, **62**, 1091 (1940).

(1) Paper VI of this series, Walters and McElvain, *This Journal*, **62**, 1482 (1940).

(2) Wisconsin Alumni Research Foundation Research Assistant, 1938-1941.

(3) McElvain, *et al.*, *This Journal*, **62**, 964, 1281 (1940).

(4) Robins, *J. Chem. Soc.*, **109**, 1038 (1916); Lauer and Jones, *This Journal*, **59**, 232 (1937).