TABLE II

OSMOTIC	AND	ACTIVITY	COEFFICIENTS	FOR	Barium	AND
STRONTIUM CHLORIDE SOLUTIONS						

Weight molality	Barium ¢(Osmotic	chloride γ(Activity	Strontius ¢(Osmotic	n chloride γ(Activity
(moles/1000 g. water)	coef- ficient)	coef- ficient)	coef- ficient)	coef- ficient)
0.05	0.860	(0.561)	0.892	0.572
.10	.844	.498	.871	.514
.20	.833	.440	.861	(.4 64)
.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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Crystalline Modifications of D-Manno-D-gala-heptose, and the Preparation of Some of Its Derivatives¹

BY EDNA M. MONTGOMERY AND C. S. HUDSON

D-Manno-D-gala-heptose, originally called $d-\alpha$ 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



(4) Hudson, This Journal, 60, 1537 (1938).

⁽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., 28, 327 (1915).

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-galaheptose 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	\mathbf{OF}	D-MANNO-D-GALA-		
HEPTOSE					

	$\mathbf{M}, \ \mathbf{p}, \ \ ^{\diamond}\mathbf{C},$	Initial rota- tion in water, calcd, as an- hydrous sugar	Muta- rotation velocity. d $k \times 10^{3}$
Second <i>a</i> -form, anhydrous	1.50	$\pm 144.0^{\circ}$	$13 \rightarrow 3.9$
α-Heptose CaCl ₂ ·4H ₂ O	141	140 8	$16 \rightarrow 4.4$
α -Monohydrate (Isbell ⁴)	107	180.3	- 6.1 → 4 -0
α-Monohydrate	115-120	123.8	4.2
α-Heptose, anhydrous	145	124.0	4 3
α-Heptose CaCl ₂ ·3H ₂ O	158	122.2	1.2
α,β -Heptose (Fischer ^b)	134	85.0	
α,β -Heptose (Isbell ^c)		\$5.0	
α, β -Heptose	132	82 0	$10.5 \rightarrow 5.2$
β-Monohydrate	104	52.9	$6 0 \rightarrow 4.2$
β-Monohydrate (Isbell ^a)	104	45.9	0.03.7
B-Heptose, anhydrous	145	43.1	3 6

^a Isbell, Ref. 6. ^b Fischer and Passmore, Ref. 2. ^a 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° 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° 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

(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 $\pm 144.0^{\circ}$ 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, $C_7H_{14}O_7$ · $CaCl_2\cdot 4H_2O$, which showed an initial rotation of $\pm 140.8^{\circ}$ for the heptose moiety, and decreasing coefficients of similar values for its mutarotation. The α -monohydrate reported by Isbell, with initial rotation $\pm 130.3^{\circ}$ 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 Dmanno-D-gala-heptose, we have prepared, by the usual reactions, the acetochloro- and acetobromoderivatives, 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 11. The values for the corresponding

⁽⁵⁾ Similar comparisons between D-gala-L-manno-heptose and Lmannose, D-gala-L-gluco-heptose and L-glucose, and D-gala-L-galaoctose 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 (1988), respectively.

^{(6) (}a) Isbell, J. Res. Natl. Bur. Standards, 18, 517 (1937); (b) Isbell, ibid., 20, 106 (1938).

⁽⁷⁾ Unless otherwise designated all rotations are specific rotations at 20° for sodium light; z represents the concentration in grams per

¹⁰⁰ cc. of solution, and l the length of the tube in decimeters

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

TABLE II

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

^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). ^e Skraup and Kremann, Monatsh., 22, 379 (1901). ^k Fischer and Armstrong, Ber., 35, 838 (1902). ⁱ Dale and Hudson, THIS JOURNAL, 52, 2534 (1930). ^j Because the methylgalacto-furanoside and its acetate are not crystalline, the specific and molecular rotations recorded here are for the ethylgalacto-furanoside 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 *aldehydo*-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 *a*-D-manno-D-gala-heptose rotating $+124^{\circ}$ and $+144^{\circ}$, respectively; two β forms also may occur. The form of rotation $+82^{\circ}$ 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 $+144^{\circ}$ 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-

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

⁽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).

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 1liter 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-galaheptonate trihydrate isolated by Killani.¹¹ It was purified by recrystallization from 12 parts of boiling water. Au 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 C₁₄H₂₆O₁₆Ba: 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 $149-151^{\circ}$. 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.

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MUTAROTATION OF α -D-MANNO-D-GALA-HEPTOSE MONO-HYDRATE IN WATER (c, 4; l, 2) AT 20°

Time min	Rotation of anhydro	ous	$k_1 + k_2$
0	[+123, 8]		
3	122.0		
4	121.8		0 0043
5	121.0		0.0010
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		
	0070	Average	0.0042

TABLE IV

MUTAROTATION OF α -D-MANNO-D-GALA-HEPTOSE IN WATER (c 4 · l 2) at 20°

	$(\iota, \pm, \iota, \omega)$ AI	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
50	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, **66**, 1248 (1934).

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

a-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 $+68.4^{\circ}$ is equivalent to $+122.2^{\circ}$ for the anhydrous heptose portion of the complex.

Anal. Calcd. for C₇H₁₄O₇ CaCl₂·3H₂O: Ca, 10.69; Cl, 18.91. Found: Ca, 10.82; Cl, 18.82.

TABLE V

Mutanotation of α -d-Manno-d-Gala-heptose CaCl₂: 3H₂O in Water (c, 4; l, 2) at 20°

Time, min.	Rotation of anhydrous suga	r	$k_1 + k_2$
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
8	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

Mutanotation of α -d-Manno-d-gala-heptose CaCl₂· 4H₂O 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
æ	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 $C_7H_{14}O_7$ CaCl₂·4H₂O: 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 $C_7H_{14}O_7 H_2O$: C, 36.84; H, 7.07. Found: C, 36.62; H, 7.15.

MUTAROTATION	OF β-D-MANNO-D-GALA	-HEPTOSE MONO-
HYDRA	TE 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
œ	68.8	
	Aver	age 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 twothirds 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 $+43.1^{\circ}$. 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 $+69.1^{\circ}$ 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.

usually as the broom-like clusters but the initial extra-polated rotation varied from +124 to $+144\,^\circ\!.$

Anal. Calcd. for C₇H₁₄O₇: C, 40.00; H, 6.72. Found: C, 39.85; H, 6.74.

	TA	ble X			
MUTAROTATION	OF THE	SECOND	α- D- Μ.	ANNO-D-GALA	
HEPTO	se in Wat	ER (c, 4;	l, 2) at 20°		
Time, min.	R	otation		$k_1 + k_2$	
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	
tő		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	
4 -		68.9			
		4	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 $C_{17}H_{23}O_{11}Cl$: 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 $\pm 208.0^{\circ}$ 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. Caled. for C₁₇H₂₃O₁₁Br: 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 $+8.3^{\circ}$ in chloroform (c, 2). The yield of pentaacetyl- β methyl-D-manno-D-gala-heptoside, melting at 105°, was 90% of the theoretical.

	TABLE VIII	
MUTAROTATION OF	F β -d-Manno-d-gala-1	HEPTOSE IN WATER
	(c, 4; l, 2) at 20°	
(Pinne main	Potation	he is he

ſime, 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
æ	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 C₇H₁:O₇: C, 40.00; H, 6.72. Found: C, 39.90; H, 6.70.

TABLE IX

MUTAROTATION	OF	(α, β) -d-Manno-d-Gala-Hepto	OSE IN
	WAT	100 (c 4 · 7 9) AT 90°	

Ŷ	VALUE $(0, T, t, \Delta)$ AL	<i>20</i>
l'ime, min.	Rotation	$k_1 - k_2$
0	[+82.0]	
+	81.3	
9	80.1	0.0074
13	79.6	.0105
17	78.8	.0103
21	77.0	.0107
31	75.3	.0083
43	74.4	.0091
58	73.4	. 0080
120	71.8	.0052
2	69.1	
	Av	erage 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 Anal. Calcd. for $C_{13}H_{26}O_{12}$: C, 49.74; H, 6.03; OCH₃, 7.14; acetyl, 11.52 cc. of 0.1 N NaOH per 100 mg. Found: C, 49.63; H, 6.07; OCH₃, 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; OCH₃, 13.84. Found: C, 42.87; H, 7.27; OCH₃, 13.90.

TABLE XI

Hydrolysis of β -Methyl-d-manno-d-gala-heptoside in 0.05 N Hydrochloric Acid (c. 3) at 98°

0.00 10 11	I DROCHLORIC I	(0, 0)	AI 50	
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	
œ	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-a-methyl-D-manno-D-galaheptoside 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. Caled. for $C_{18}H_{28}O_{12}$: C, 49.74; H, 6.03; OCH₃, 7.14; acetyl, 11.52 cc. 0.1 N NaOH per 100 mg. Found: C, 49.70; H, 6.07; OCH₃, 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 $\pm 178^{\circ}$ in water (c, 2) and melting at 141°. On reacetylation 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 $\pm 64.3^{\circ}$, calculated as the glycoside, is equivalent to $\pm 68.8^{\circ}$, expressed as the anhydrous sugar.

Anal. Calcd. for C₈H₁₆O₇: C, 42.84; H, 7.19; OCH₈, 13.84. Found: C, 42.80; H, 7.21; OCH₈, 13.90.

TABLE XII

Hydrolysis of α -Methyl-d-manno-d-gala-heptoside in 0.05 N Hydrochloric Acid (c, 2) at 98°

0.00 0.00		(-,/	
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
29 0	134.4		.00077
350	127.0		.00078
410	122.9		.00078
8	64.3		
		A	0 00000

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
80	64.2		
		Average	0.022

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

Anal. Calcd. for C₈H₁₆O₇: C, 42.84; H, 7.19; OCH₃, 13.84. Found: C, 42.80; H, 7.26; OCH₃, 13.90.

Pentaacetyl-\beta-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. Caled. for $C_{18}H_{28}O_{12}$: C. 49.74; H, 6.03; OCH₈, 7.14; acetyl, 11.52 cc. 0.1 N NaOH per 100 mg. Found: C, 49.70; H, 6.07; OCH₈, 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 icc and water, and was purified as described previously.¹⁶ The yield of aldehydo-

(13) Montgomery and Hudson, THIS JOURNAL, 56, 2463 (1934).

p-manno-p-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.

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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 -diethylaminocrotonate⁴ with methyl iodide, and (b) the condensation of α -methoxystyrene with such halides as benzyl bromide with the formation of an ω -alkylated acetophenone.⁵ These reactions may be illustrated as follows:

$$\begin{array}{c} (Et)_{2}N \\ CH_{3}C = CH & \longrightarrow CH_{3} \\ COOEt \end{array} \qquad \begin{bmatrix} (Et)_{2}N \\ CH_{3}C & -CHCH_{3} \\ COOEt \end{bmatrix}^{\perp} \\ \begin{array}{c} (a) \\ (a) \\ (a) \\ (a) \\ CH_{3}Br + C_{6}H_{5}C - CH_{2}CH_{2}C_{6}H_{5} \\ \end{array}$$

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 $\frac{60}{100}$ Mortenson and Spielman, *ibid.*, **52**, 1609 (1940)

⁽¹⁾ Paper VI of this series, Walters and McElvain, THIS JOURNAL. 62, 1482 (1940).

⁽²⁾ Wisconsin Alumini Research Foundation Research Assistant. 1938-1941.

⁽³⁾ McElvain, et al., THIS JOURNAL, 62, 964, 1281 (1940).

⁽⁴⁾ Robinson, J. Chem. Soc., 109, 1038 (1916); Lauer and Jones This JOURNAL, 59, 232 (1937).