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

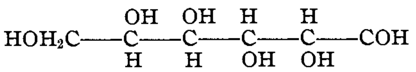
Crystalline *d*-Alpha-Galaheptose and Some of its Derivatives[1]

BY RAYMOND M. HANN, ALICE T. MERRILL AND C. S. HUDSON

In his pioneer studies of the two galaheptoses possible by addition of hydrocyanic acid to *d*-galactose, Fischer[2] isolated the *d*-[β-galaheptose] in crystalline condition, but was unsuccessful in his attempts to crystallize the isomeric *d*-[α-galaheptose]. He did, however, reduce the sirupy sugar with sodium amalgam and obtained the crystalline alcohol, *d*-[α-galaheptitol]. While Fischer recorded the rotation of this substance, it remained for Peirce[3] to point out that it is the antipode of *d*-[α-mannoheptitol] (perseitol), thus proving the configurations of the galaheptoses and the mannoheptoses.

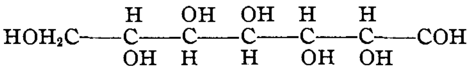
Recently the *d*-[α-galaheptose][4] has been obtained in crystalline condition as the monohydrate. The study of its derivatives has indicated that they crystallize with considerable difficulty, which was not unexpected because of the close similarity in configuration of the sugar to *l*-mannose. Incidental to the preparation of the lactone of *d*-[α-galaheptonic] acid, confirmation of the early work of Maquenne[5] and Kiliani[6] upon the isolation of crystalline *d*-[α-galaheptonic] acid has been obtained and a study of its rotational behavior has been made.

The data now at hand permit a good comparison of the properties of two aldoses which have very similar configurations, *l*-mannose and *d*-[α-galaheptose].



$$HOH_2C-\overset{OH}{\underset{H}{C}}-\overset{OH}{\underset{H}{C}}-\overset{H}{\underset{OH}{C}}-\overset{H}{\underset{OH}{C}}-COH$$

l-Mannose



$$HOH_2C-\overset{H}{\underset{OH}{C}}-\overset{OH}{\underset{H}{C}}-\overset{OH}{\underset{H}{C}}-\overset{H}{\underset{OH}{C}}-\overset{H}{\underset{OH}{C}}-COH$$

d-Alpha-galaheptose

Because of the paucity of data in the *l*-mannose series the comparisons will be made upon substances of the *d*-mannose series, which are opposite in sign of rotation. On the plausible hypothesis that the physical and chemical properties (though not the biological) of an aldose and most of its derivatives are conditioned in first measure by the space configurations of carbons one to five inclusive, it is to be expected that *l*-mannose and *d*-[α-galaheptose] will be especially similar sugars. This inference is fully borne out by the facts now at hand. Considering first those properties which are the same for the *d*- and *l*-forms of a given sugar, it is noted that mannose is characterized by a readily crystallizable phenylhydrazone of unusually low solubility; the same applies to the phenylhydrazone of the heptose in question, as indeed was noted by Fischer before the configurations of the galaheptoses were established. Mannose is also peculiar among aldoses in that the equilibrium between its α and β stable methyl glycosides in acidified methyl alcohol is usually far toward its α form; the same is now found to hold for its heptose analog, though because of conventions of nomenclature, this heptoside is to be named the β-form.[7] Other paralleling characteristics which have been observed in the two series are the sparing solubilities of the amides and phenylhydrazides as well as the ease of crystallization of the

TABLE I

SIMILARITY OF SPECIFIC ROTATIONS ($[\alpha]^{20}D$) OF SUBSTANCES IN THE MANNOSE AND ALPHA-GALAHEPTOSE SERIES

		d-Mannose series		*d*-Alpha-galaheptose series
Sugar, (initial)	(α)	+34	(β)	−26
(final)		+14.6		−15.3
Sodium salt of aldonic acid		− 8.8[8]		+ 9.6
γ-Lactone		+51.8[9]		−52.3[2]
Aldonic acid phenylhydrazide		− 8.1[10]		+ 8.5[10]
Aldonic acid amide		−17.3[11]		+14.3[11]
Methyl glycoside	(α)	+79.2[12]	(β)	−70.2
Methyl glycoside acetate		+49.1[13]		−20.4
Benzyl mercaptal		−32.9[14]		+30.3

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[1] Publication authorized by the Surgeon General, U. S. Public Health Service.

[2] Fischer, *Ann.*, **288**, 144 (1895).

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

[4] Hann, Merrill and Hudson, THIS JOURNAL, **56**, 1644 (1934).

[5] Maquenne, *Compt. rend.*, **106**, 286 (1888).

[6] Kiliani, *Ber.*, **21**, 915 (1888).

[7] The designation of *d*- and *l*- is made according to the configuration of the asymmetric carbon atom nearest the end of the sugar structure away from the carbonyl group (the Rosanoff nomenclature) and the designation α and β for isomeric substances of like structure in a given sugar series is in turn dependent, first upon this *d*- and *l*-classification, and second, upon the sign of rotation of carbon atom one.

[8] Levene and Meyer, *J. Biol. Chem.*, **26**, 355 (1916).

[9] Hedenburg, THIS JOURNAL, **37**, 345 (1915).

[10] Hudson, *ibid.*, **39**, 462 (1917).

[11] Hudson and Komatsu, *ibid.*, **41**, 1141 (1919).

[12] Fischer and Beensch, *Ber.*, **29**, 2927 (1896).

[13] Dale, THIS JOURNAL, **46**, 1048 (1924).

[14] Pacsu and v. Kary, *Ber.*, **62**, 2811 (1929).

γ-lactones in relatively pure condition, for the monobasic acids derived from the two aldoses.

In regard to optical properties, the data of Table I show a striking similarity in magnitude and full agreement in sign for substances of the two series. For reasons previously stated the values for mannose are taken from its d-series and hence for comparison the sign should be reversed.

The close similarity of properties in these particular sugar series is not limited to this pair but seems to be generally true, as can be readily verified by comparing known data,[15] and it appears to be of considerable practical value in furnishing a guide for preparative work and for studies of structure and configuration.

We express our appreciation to Dr. Reid Milner and Mrs. Mildred S. Sherman of the Fertilizer Investigations Laboratory, U. S. Department of Agriculture, for performing the micro analyses in connection with this work.

Experimental

Crude d-(α-Galaheptonic) Amide from d-Galactose.—To a solution of 500 g. of galactose in 750 cc. of water held at 0° in an ice–salt bath, 10 drops of concd. ammonia and 140 cc. of liquid hydrocyanic acid were added and the tightly stoppered flask allowed to stand in the ice box for two or three days, during which time the mixture set to a paste through crystallization of α-galaheptonic amide. It was thinned with 100 cc. of ice water, filtered on a large Büchner funnel and washed with three 50-cc. portions of ice water, dried for several hours at room temperature and finally in an oven at 60°. The yield varies according to the time necessary to obtain a satisfactory crystallization. In twenty-three experiments the lowest yield was 242 g. and the highest 355 g., an average yield of 47.5% being obtained. A considerable amount of α-galaheptonic lactone may be recovered from the filtrates by converting the soluble amides in solution to a mixture of α- and β-galaheptonic phenylhydrazides, separating by crystallization, and decomposing with copper sulfate as previously described.[16]

d-(α-Galaheptonic) Lactone from Crude d-(α-Galaheptonic) Amide.—A suspension of 500 g. of finely powdered amide in a solution of 300 g. of barium hydroxide octahydrate in 1000 cc. of water was boiled briskly under the hood for seven hours, water being added from time to time to replace that lost by evaporation. The barium was roughly precipitated with about 320 cc. of 6 N sulfuric acid and thereafter the solution balanced until free of barium and sulfate ions. The filtered solution was concentrated to a thick sirup and heated for six to eight hours on the steam-bath, 250 cc. of methyl alcohol was stirred in and upon standing overnight it crystallized to a solid mass; yield 380 g. (82.2%). The lactone can be conveniently recrystallized by dissolving 400 g. of crude lactone in 160 cc. of hot water, adding 1600 cc. of hot 95% alcohol and filtering through a preheated funnel. Overnight a yield of 285 g. of lactone (71.2%) showing a specific rotation[17] of −49.2° in water separates, and additional material may be recovered from the filtrate for further purification. One additional recrystallization from 3 parts of 90% alcohol yields the pure lactone, rotating −52.3° in water, in agreement with Fischer's[2] value.

d-(α-Galaheptonic Acid).—Under milder conditions of transformation the amide yields α-galaheptonic acid. A solution containing 138 g. of amide, 100 g. of barium hydroxide octahydrate and 500 cc. of water was boiled under reduced pressure at 60–70°, keeping the volume approximately constant by addition of water until ammonia could no longer be detected in the distillate. Sufficient 6 N sulfuric acid was added to the slightly warm solution to precipitate the barium exactly and upon filtering and cooling, a small amount of α-galaheptonic acid crystallized. The filtrate was concentrated *in vacuo* to 200 cc. and the main portion of the acid removed after cooling. The total yield of acid was 57.2 g. (41.3%). The mother liquor was heated in a shallow dish on the steam-bath for two days and yielded 33.5 g. of α-galaheptonic lactone.

α-Galaheptonic acid crystallizes from 100 parts of 95% alcohol in brilliant colorless leaflets melting at 143 to 147° (corr.) depending upon the rate of heating. A 5-g. sample heated under vacuum for one hour in a glycerol bath at 155–160° readily gave off water and the resulting melt, upon treatment with 10 cc. of methyl alcohol, deposited 2.8 g. of crystals. Examination of the recrystallized product showed it to be a mixture of needles and prisms, indicating a mixture of lactones. Confirmatory evidence was obtained on successive recrystallizations, the specific rotation decreasing in the order from −56.3, −54.2, −53.1 to −52.2° with disappearance of the needle form and separation of pure γ-d-[α-galaheptonic] lactone. Fresh solutions of the acid titrate immediately as an acid and upon standing they show the characteristic acid–lactone titration behavior. These solutions exhibit mutarotation and after the first twenty minutes closely follow a unimolecular course. Table II records the log of a typical rotation.

TABLE II

MUTAROTATION OF d-[α-GALAHEPTONIC] ACID IN WATER

Concentration 0.3431 g. in 25 cc.; tube length 2 dm.; $T = 20 \pm 0.5°$.

Time, min.	5	15	30	60	120	180
$[\alpha]^{20}_{D}$	+2.5	+2.3	+1.0	−0.6	−4.0	−6.9
Time, min.	240	360	720	72 hrs.	10 days	
$[\alpha]^{20}_{D}$	−8.8	−13.2	−19.5	−28.3	−28.3	

Anal. Acid titration: 0.1281 g. neutralized 5.65 cc. 0.1 N NaOH. Calcd., 5.67 cc. Calcd. for $C_7H_{14}O_8$: C, 37.2; H, 6.2. Found: C, 37.1; H, 6.3.

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[15] A good example is the ease with which the ketose, sedoheptose, now known to be d-altroheptulose, passes in acid solution to a non-reducing anhydro form by a balanced reaction, which was unique in the sugar group until the recent discovery that d-altrose, of closely similar configuration, behaves in like manner [Richtmyer and Hudson, THIS JOURNAL, **57**, 1716 (1935)].

[16] Hann and Hudson, *ibid.*, **56**, 957 (1934).

[17] Throughout the article the rotations are specific rotations at 20° for sodium light.

_d_-(α-Galaheptose).—Forty-five grams of α-galaheptonic lactone was reduced in cold acid solution in the usual manner with 2000 g. of 2.5% sodium amalgam. Following removal of the sodium sulfate, the solution was freed of the sodium salt of α-galaheptonic acid by concentrating to a sirup and treating repeatedly with methyl alcohol. In one case treatment of this sirup with phenylhydrazine yielded 31.4 g. of hydrazone and 7.1 g. of osazone, equivalent to 38.5 g. of galaheptose, whereas the theoretical yield would have been 45.4 g. of sugar. The salt-free sirup was placed in a calcium chloride desiccator and treated repeatedly with small amounts of methyl alcohol; it finally crystallized as a monohydrate after about four months. The yield averaged about 25 g. The sugar may be recrystallized in a yield of 80% by solution in one-half part of water and addition of 5 parts of 95% alcohol, separating in glistening prisms melting at 77–78° (corr.) to a colorless sirup. The course of its mutarotation (Table III) is not unimolecular. The final specific rotation of the sugar, considered as anhydrous ($C_7H_{14}O_7$), is −15.3° and the initial rotation is approximately −26°.

TABLE III

MUTAROTATION OF β-_d_-[α-GALAHEPTOSE] MONOHYDRATE IN WATER

Concentration 1.1560 g. in 10 cc. solution; tube length 1 dm.; $T = 20 \pm 0.5°$

Time after making solution, min.	$[\alpha]^{20}_D$	Time, min.	$k_1 + k_2$
2.4	−22.5	0	...
3.4	21.9	1	0.032
5.3	21.1	2.9	.027
6.3	21.0	3.9	.022
7.3	20.7	5.9	.018
15.4	18.9	13.0	.019
20.5	18.1	18.1	.018
25.4	17.4	23.0	.018
30.4	16.9	28.0	.017
35.4	16.5	33.0	.017
40.2	16.2	37.8	.016
55.1	15.3	52.7	.016
70.1	14.8	67.7	.016
93.1	14.4	90.7	.016
190.1	14.1 (equilibrium)	187.7	...
72 hrs. (final)	14.1	∞	...

Anal. Iodimetric Titration: 0.0519 g. consumed 4.56 cc. 0.1 *N* iodine equivalent to 0.0479 g. of heptose (92.3%): H_2O, 0.2632 g. lost 0.0214 g. (8.13%) on heating seven hours at 110° in Abderhalden drier. Calcd. for $C_7H_{14}O_7 \cdot H_2O$: C, 36.82; H, 7.07; sugar, 92.1; H_2O, 7.90. Found: C, 36.98; H, 7.13; sugar, 92.3; H_2O, 8.13.

Sodium _d_-[α-Galaheptonate].—This salt was obtained from the reduced solution following separation of the sodium sulfate by treatment of the sirup resulting upon vacuum concentration, with anhydrous methyl alcohol. It crystallized in clusters of glistening prisms showing a specific rotation of +9.7° in water. Recrystallized from one part of water by addition of one volume of methyl alcohol it rotated +9.5° (0.5265 g. in 10 cc. water in a 1-dm. tube rotated 0.50° to the right). Analysis showed it to be a monohydrate.

Anal. Calcd. for $C_7H_{13}O_8Na \cdot H_2O$: Na, 8.6; H_2O, 6.8. Found: Na, 8.6; H_2O, 6.7.

β-Methyl _d_-[α-Galaheptoside].—Ten grams of α-galaheptose monohydrate was refluxed for one hour with 100 cc. of methyl alcohol containing 1.5% of dry hydrochloric acid gas, when all reducing power disappeared. The solution was treated with 15 g. of dry silver carbonate and the halogen-free filtrate concentrated to a sirup and treated with about 20 cc. of ethyl alcohol, which induced crystallization readily. The substance was recrystallized from three parts of absolute alcohol; it separated in brilliant prisms rotating −70.1° in water. Upon recrystallization a rotation of −70.2° (0.2708 g. in 10 cc. of water in a 1-dm. tube rotated 1.90° to the left) was found. The compound melts at 132° (corr.); yield 6.4 g. (65%). The rate of hydrolysis in 0.05 *N* hydrochloric acid at 100° was 0.0004 (expressed in minutes and decimal logarithms), proving the glycoside to be of the stable type.

Anal. Calcd. for $C_8H_{16}O_7$: C, 42.83; H, 7.20. Found: C, 42.72; H, 7.19.

The substance is designated as the β-methyl glycoside because it is more negative in rotation than the β-form of the sugar, which belongs to the *d*-series. It has already been explained[7] how the accepted conventions of nomenclature led to this naming whereas the method of preparation and properties of the substance show it to be the analog of α-methyl *d*-mannoside. Likewise the crystalline form of *d*-α-galaheptose, for which the conventional naming is β, is the analog of the crystalline α-form of mannose.

Pentaacetyl β-Methyl _d_-[α-Galaheptoside].—Five and one-tenth grams of methyl-α-galaheptoside was dissolved in 30 cc. of pyridine and acetylated by adding an equal volume of acetic anhydride and allowing to stand overnight at room temperature. The solution was poured upon cracked ice and the gummy precipitate which formed was extracted with carbon tetrachloride and the dried extract concentrated to a sirup. It failed to crystallize by the usual procedure, but was finally obtained in crystalline condition by successive treatments with small amounts of absolute alcohol over a period of two months, yield 7.9 g. (80%). The compound may be recrystallized from two parts of 95% alcohol and separates in glistening plates. The specific rotation of −20.4° (0.2354 g. in 10 cc. of chloroform in a 1-dm. tube rotates 0.48° to the left) did not change appreciably upon recrystallization. The compound melts at 108° (corr.) to a colorless oil.

Anal. Calcd. for $C_{18}H_{26}O_{12}$: C, 49.74; H, 6.04. Found: C, 49.61; H, 6.11.

β-Ethyl _d_-[α-Galaheptoside].—This compound was prepared in an analogous manner to the methyl homolog and was obtained in a yield of 7.0 g. (67%). It was recrystallized from three parts of absolute alcohol as thin glistening plates, melting at 138° and showing a specific rotation of −65.4° (0.2310 g. in 10 cc. of water in a 1-dm. tube rotated 1.51° to the left), unchanged by recrystallization.

Anal. Calcd. for $C_9H_{18}O_7$: C, 45.35; H, 7.62. Found: C, 45.28; H, 7.70.

Pentaacetyl β-Ethyl _d_-[α-Galaheptoside].—This acetylated glycoside was obtained in a yield of 9.6 g. (85%) when 6.0 g. of the ethyl glycoside was acetylated with pyridine and acetic anhydride. It crystallized from five parts of 50% alcohol in long colorless needles melting at 92° (corr.) to a colorless oil. Its specific rotation was −24.9° (0.3570 g. in 10 cc. of chloroform in a 1-dm. tube rotated 0.89° to the left) after recrystallization to constancy.

Anal. Calcd. for $C_{19}H_{28}O_{12}$: C, 50.87; H, 6.30. Found: C, 50.81; H, 6.37.

d-[*α*-**Galaheptose**] **Benzyl Mercaptal.**—A solution of 5 g. of *α*-galaheptose monohydrate in 10 cc. of concd. hydrochloric acid was shaken with 10 cc. of benzyl mercaptan for ten minutes, when it set to a paste. After standing overnight at room temperature the solid was filtered, washed with 95% alcohol and dried, yield, quantitative. The mercaptal may be recrystallized readily from 75 parts of 95% alcohol, separating in small glistening plates, melting at 191° (corr.) and rotating +30.3° in pyridine (0.2212 g. in 10 cc. in a 1-dm. tube rotated 0.67° to the right).

Anal. Calcd. for $C_{21}H_{28}O_6S_2$: S, 14.56. Found: S, 14.50.

Hexaacetyl *d*-[*α*-**Galaheptose**] **Benzyl Mercaptal.**—A solution of 5 g. of mercaptal in 25 cc. of pyridine was treated with 25 cc. of acetic anhydride, allowed to stand overnight at room temperature and the acetate precipitated by pouring the solution over crushed ice. The compound crystallizes from 10 parts of 95% alcohol in clusters of elongated, very thin terminated plates, melting at 120° (corr.) and rotates −10.6° (0.2633 g. in 10 cc. in a 1-dm. tube rotated 0.28° to the left) in chloroform.

Anal. Calcd. for $C_{33}H_{40}O_{12}S_2$: S, 9.26. Found: S, 9.14.

Hexabenzoyl *d*-[*α*-**Galaheptose**] **Benzyl Mercaptal.**—A solution of 3 g. of mercaptal in 25 cc. of pyridine was treated dropwise with 11.5 g. of benzoyl chloride. The mixture became warm, developed a red color and soon became a mush of glistening crystals. The next day the mass was poured upon crushed ice, stirred and a red crystalline meal gradually formed. This was filtered off and recrystallized from 100 parts of 95% alcohol, the benzoate separating in clusters of colorless small prisms. The pure substance melts at 129° (corr.) and rotates −48.1° in chloroform (0.2950 g. in 10 cc. in a 1-dm. tube rotated 1.42° to the left).

Anal. Calcd. for $C_{63}H_{52}O_{12}S_2$: S, 6.02. Found: S, 6.03.

Summary

1. *d*-[*α*-Galaheptose] has been obtained in crystalline condition as the monohydrate of its beta form.
2. The rotational behavior of solutions of crystalline *d*-[*α*-galaheptonic] acid has been studied.
3. Methyl and ethyl glycosides of [*d*-*α*-galaheptose] and their acetates have been obtained in pure condition.
4. The benzyl mercaptal, its acetate and benzoate have been prepared and described.
5. Attention has been called to the parallelism of physical and chemical properties, as well as rotational behavior, of substances of configurationally related structure in the sugar group, as illustrated from substances of the mannose and *α*-galaheptose series.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Determination of Ionization by Ultraviolet Spectrophotometry: Its Validity and its Application to the Measurement of the Strength of Very Weak Bases[1]

BY LEO A. FLEXSER,[2] LOUIS P. HAMMETT AND ANDREW DINGWALL

It has been amply demonstrated that most organic oxygen compounds are bases of the same kind as ammonia or aniline, but of a much less pronounced basicity.[3] Quantitative knowledge of the strength of these very weak bases is practically non-existent,[4] yet is of crucial importance for the understanding and interpretation of the phenomena of acid catalysis. One of the most promising methods for obtaining these data[4] involves the measurement of the extent of ionization of the base (that is to say, the extent of conversion of the base B to the cation or conjugate acid BH^+) in mixtures of sulfuric acid and water. Such measurements of extent of ionization have previously been made by the method of visual colorimetry;[5] we have now made the rather obvious extension[4] to spectrophotometry in the ultraviolet for cases where there is no visible change in color.

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[1] This article is based upon the dissertation submitted by Leo A. Flexser to the Faculty of Pure Science of Columbia University in partial fulfilment of the requirements for the degree of Doctor of Philosophy, May, 1935. The material was presented at the New York meeting of the American Chemical Society, April, 1935. A preliminary Communication appeared in THIS JOURNAL, **56**, 2010 (1934).

[2] University Fellow in Chemistry, 1934–1935.

[3] (a) Hantzsch, *Z. physik. Chem.*, **61**, 257 (1908); (b) *ibid.*, **65**, 41 (1908); (c) Hammett and Deyrup, THIS JOURNAL, **55**, 1900 (1933).

[4] Hammett, *Chem. Rev.*, **13**, 61 (1933).

[5] (a) Hammett and Deyrup, THIS JOURNAL, **54**, 2721 (1932); (b) Hammett and Paul, *ibid.*, **56**, 827 (1934); (c) Hammett, *Chem. Rev.*, **16**, 67 (1935).