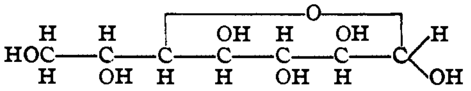
[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

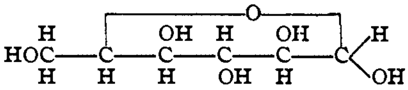
d-Beta-Galaheptose and Some of its Derivatives[1]

BY RAYMOND M. HANN AND C. S. HUDSON

In a recent publication[2] experimental details of the preparation and properties of *d*-alpha-galaheptose and of some of its derivatives were recorded. Attention was called to the close similarity of the configuration of this newly crystallized sugar to that of *l*-mannose, and the resulting similarity of the physical and chemical properties of these related sugars and of their compounds. In the present communication the properties of the epimeric *d*-beta-galaheptose, configurationally related to *l*-glucose, and of some of its derivatives, will be described.



α-Form of *d*-β-galaheptose (−19°)



β-Form of *l*-glucose (−19°)

This heptose was obtained in crystalline condition by Fischer,[3] but only cursory study of its behavior has been recorded. The sugar has an initial rotation[3a] of about −19° and mutarotates to an equilibrium value of −54°, comparable in magnitude with the recorded value for *d*-glucose, +19° (β-form) to +52°, and opposite in sign because the heptose is configurationally related to *l*-glucose, though it belongs in the *d*-series by Fischer's nomenclature. We name the heptose form of rotation −19° the alpha modification because its rotation is more toward the positive than the equilibrium rotation of the sugar (−54°), in accordance with generally accepted conventions; thus α-*d*-β-galaheptose and β-*l*-glucose are configurationally similar. This correspondence in rotation extends to several pairs of glucose and β-galaheptose derivatives and is sufficient for supplying an indication, though not a proof, of the structures and configurations in the β-galaheptose series. Because of the paucity of data in the *l*-glucose series the comparisons will refer to substances in the *d*-glucose series, which are opposite in sign of rotation.

TABLE I

COMPARISON OF SPECIFIC ROTATIONS [$[\alpha]^{20}$D] OF SUBSTANCES IN THE GLUCOSE AND β-GALAHEPTOSE SERIES

		d-Glucose series		*d*-β-Galaheptose series
Sugar (initial)	(β)	+ 19	(α)	−19
(final)		+ 52		−54
Aldonic acid phenylhydrazide		+ 12[4]		− 7.8
Aldonic acid amide		+ 31[5]		−20
Methyl glycoside	(β)	− 34.2[6]	(α)	+36
Ethyl mercaptal		− 29.8[7]		+37.8[8]
Benzyl mercaptal		− 98.4[9]		+73.8
Hexose pentaacetate or	(α)	+101.6	(β)	−55.8
Heptose hexaacetate	(β)	+ 3.8	(α)	+30.2
Methyl glycoside acetate	(β)	− 18.3	(α)	+51.8
Ethyl mercaptal acetate		+ 11.3[10]		+26.6[8]
Benzyl mercaptal acetate		+ 28.4[11]		+ 9.1

The parallelism noted in these rotations is evident also in the chemical behavior of the structurally related pairs of derivatives. Thus, *d*-glucose upon acetylation with sodium acetate and acetic anhydride yields largely the β-form of glucose pentaacetate which may be rearranged readily to the α-acetate by acid acetylating catalysts (zinc chloride or sulfuric acid). The heptose under the same conditions of acetylation yields a configurationally similar hexaacetate, which, because of conventions of nomenclature, is to be named the α-form, it being the more dextrorotatory member of a pair of isomers in the *d*-series. This acetate under the same experimental rearranging conditions yields the β-form, a result which may be anticipated due to the similarity in structure of the parent sugars. By application of the Koenigs and Knorr synthesis to β-*d*-glucose pentaacetate one obtains tetraacetyl-β-methyl glucoside while the same procedure with α-*d*-(β-galaheptose) hexaacetate yields pentaacetyl-α-methyl-*d*-β-galaheptoside. These results are

---

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

[2] Hann, Merrill and Hudson, THIS JOURNAL, **57**, 2100 (1935).

[3] Fischer, *Ann.*, **288**, 154 (1895).

[3a] Throughout the article the rotations are specific rotations at 20° for sodium light, unless otherwise stated.

[4] Hudson and Komatsu, THIS JOURNAL, **41**, 1141 (1919).

[5] Glattfeld and Macmillan, *ibid.*, **56**, 2482 (1934).

[6] Riiber, *Ber.*, **57**, 1797 (1924).

[7] Fischer, *ibid.*, **27**, 673 (1894).

[8] Hann and Hudson, THIS JOURNAL, **56**, 2080 (1934).

[9] Pacsu, *Ber.*, **57**, 849 (1924).

[10] Wolfrom, THIS JOURNAL, **51**, 2190 (1929).

[11] Unpublished results.

in complete agreement with those obtained in earlier studies in the mannose and α-galaheptose series and support the hypothesis that the physical and chemical properties of the heptose sugars may be in first measure predicted from the space configurations of carbons one to five inclusive, which show that aldohexose to which the heptose is similar.

The isorotation rules allow the calculation of the expected values of the rotations of some of these compounds; Table II summarizes these data.

TABLE II

OBSERVED AND CALCULATED SPECIFIC ROTATIONS $[\alpha]^{20}D$ IN THE *d*-β-GALAHEPTOSE SERIES

Substance	Obsd.	Calcd.
Sugar (α-form)	$-19°$	$-10°$
(β-form)	..	$-91°$
α-Methyl glycoside	$+36°$	...
α-Methyl glycoside acetate	$+52°$	...
β-Methyl glycoside	..	$-131°$
β-Methyl glycoside acetate	..	$-72°$
α-Acetate	$+30°$	$+35°$
β-Acetate	$-56°$	$-54°$

From well-known considerations of isorotation, the molecular rotation (30,830) of α-methylglucoside may be written as $A_{\mathrm{CH}_3} + B$, where A_{CH_3} is the contribution of the aldehydic carbon atom and B that of the basal chain, to the total rotation. The same considerations allow the expression $-A_{\mathrm{CH}_3} + B$ to signify the molecular rotation (-6630) of β-methylglucoside. By subtracting these equations one can evaluate the quantity A_{CH_3} as $+18{,}730$.[12] From α- and β-glucose, similarly, a value of A_{OH} of $+8460$ is obtained. Upon the assumption that A_{CH_3} will not differ widely in value in configurationally similar sugars, the molecular rotation of α-methyl-*d*-β-galaheptoside (8060) may be expressed as $18{,}730 + B' = 8060$, whence B' in the galaheptose series becomes $-10{,}670$ and the calculated molecular rotation of the α-form of *d*-β-galaheptose becomes $A_{\mathrm{OH}} + B' = -2210$, corresponding to a specific rotation of about $-10°$. The unknown β-form would be $-A_{\mathrm{OH}} + B'$, or $-19{,}130$ in molecular rotation and $-91°$ in specific rotation. The calculated molecular rotation of the unknown β-methyl-*d*-β-galaheptoside is $-A_{\mathrm{CH}_3} + B'$, $-29{,}400$, corresponding to $-131°$ in specific rotation.

By introducing the value of A'_{CH_3} (26,950) derived from the acetylated methyl glucosides[12] into the equation expressing the molecular rotation of pentaacetyl-α-methyl-*d*-galaheptoside, $A'_{\mathrm{CH}_3} + B_{\mathrm{Ac}} = +22{,}600$, one obtains the value of B_{Ac} in the β-galaheptose series as -4350 and this substituted in the expression $-A'_{\mathrm{CH}_3} + B_{\mathrm{Ac}}$ yields a molecular rotation of $-31{,}300$, indicating that the now unknown pentaacetyl-β-methyl-*d*-β-galaheptoside will have a specific rotation near $-72°$. Similar considerations using the value of A_{Ac} (20,700) of the glucose series and B_{Ac} (-4350) give calculated values of $+35$ and $-54°$ for the specific rotations of α- and β-*d*-β-galaheptose hexaacetate, respectively, in good agreement with the observed values of $+30$ and $-56°$.

In the preparation of β-galaheptonic amide use was made of the excellent method of Glattfeld and Macmillan;[5] sirupy β-galaheptonic lactone when dissolved in liquid ammonia readily yielded the desired crystalline amide. This substance rotated in the levo direction in accordance with the amide rule. The previously described phenylhydrazide also shows a negative rotation as would be expected from the phenylhydrazide rule. The mercaptals in pyridine agree in sign of rotation with those of the *l*-glucose series, but their acetates, measured in chloroform, do not; evidently no generalization regarding rotation may now be made of these open chain mercaptal derivatives.

Experimental

_d_-(β-Galaheptonic) Phenylhydrazide from _d_-Galactose.—Hydrocyanic acid was added to 500 g. of *d*-galactose as described previously.[2] The filtrate from the separation of the α-galaheptonic amide was transferred to a 3-liter Erlenmeyer flask and boiled with 400 g. of barium hydroxide octahydrate until ammonia was no longer evolved (twelve to fifteen hours), the volume being maintained at about 1500 cc. by occasional addition of water. The barium was precipitated by addition of 385 to 400 cc. of 6 *N* sulfuric acid, the barium sulfate was removed and the solution was balanced until free of sulfate and barium ions. It was adjusted to a volume of 1500 cc., 140 cc. of phenylhydrazine and 40 cc. of acetic acid were added and the solution was heated for five hours on the steam-bath. After cooling, the phenylhydrazide of α-galaheptonic acid was removed (fraction I), the filtrate was concentrated to 750 cc. and an equal volume of 95% alcohol was added. The next day the separated solid was filtered off (fraction II), the filtrate concentrated to 500 cc., an equal volume of alcohol added and after standing overnight the third fraction was removed. The filtrate was concentrated to 200 cc. and 200 cc. of 95% alcohol was added to obtain the final fraction. From seven preparations the average yields and specific rotations of the fractions were as follows:

---

[12] Dale and Hudson, THIS JOURNAL, 52, 2535 (1930).

fraction I, 133 g., +8.00°; fraction II, 96 g., −7.21°; fraction III, 12.5 g., +7.35°; fraction IV, 30.2 g., −5.80°.

Pure β-galaheptonic phenylhydrazide of specific rotation −7.8° and melting at 189–190° (corr.) was obtained by combining fractions II and IV, dissolving in 15 parts of water and allowing the solution to stand for twenty-four hours at 20° when the major portion of the α-phenylhydrazide separates. The β-isomer was recovered by concentrating the solution to one-half its volume and adding an equal volume of 95% alcohol. Fischer reports a melting point of 185° (uncorr.) and a specific rotation of −6.32°. Kiliani[13] reports 185° (uncorr.).

***d*-(β-Galaheptonic) Amide from *d*-(β-Galaheptonic) Phenylhydrazide.**—A solution of 100 g. of pure phenylhydrazide and 80 g. of copper sulfate pentahydrate in 1000 cc. of water was refluxed for five hours and filtered from the separated solid. The solution, freed of copper by hydrogen sulfide, was treated with a warm solution of 500 g. of barium hydroxide octahydrate in 500 cc. of water, the barium sulfate was filtered off and the filtrate was balanced until free of barium and sulfate ions. The yield of β-galaheptonic acid, as shown by titration, was 65.8 g. (92%). A portion of the galaheptonic acid sirup, which had been lactonized in part by heating for twenty-four hours on the steam-bath, upon standing for several weeks dried to a hard vitreous non-crystalline solid. A solution of 5.9 g. of this material in 150 cc. of liquid ammonia was allowed to evaporate to a sirup spontaneously at room temperature, then transferred to a vacuum desiccator over sulfuric acid and the residual ammonia removed, crystallization occurring during the process. The dark brown solid was dissolved in 20 cc. of water, 40 cc. of 95% alcohol added and the solution decolorized by carboraffin. Upon seeding, the amide crystallized in a yield of 3 g. It was recrystallized to constant properties by solution in one part of warm water and addition of one part of 95% alcohol, separating in colorless needles, melting at 170–171° (corr.) and having a specific rotation of −20° in water. (0.1940 g. in 25 cc. in a 4-dm. tube rotated 0.62° to the left.)

Anal. Calcd. for $C_7H_{15}O_7N$: N, 6.2. Found: N, 6.2.

***α-d*-(β-Galaheptose).**—The acid solution from 100 g. of pure *d*-(β-galaheptonic) phenylhydrazide was concentrated *in vacuo* to a thin sirup, transferred to a 3-liter beaker and heated on the steam-bath for eighteen hours. The heavy sirup was dissolved in 200 cc. of cold water and reduced in the usual manner with 2000 g. of 2.5% sodium amalgam. Following removal of the sodium sulfate by alcohol, the reduced solution was concentrated to a thin sirup which became a crystalline magma after several days. The crystals were separated by thinning the magma with a small amount of 50% alcohol, filtering and drying. The average yield of 13 experiments was 23.2 g. (38% based on the acid concentration). The sugar was recrystallized conveniently by solution in 2 parts of warm water and addition of 10 parts of warm 95% alcohol, separating in prisms, melting at 196–197° (corr.) with decomposition, and showing an equilibrium specific rotation in water of −54°. Fischer reports the corrected melting point as 195–199° and the rotation at equilibrium as −54.4°. The course of its mutarotation is recorded in Table III. It is designated the alpha form of *d*-(β-galaheptose) because the course of mutarotation indicates it to be the less levorotatory form of a sugar of the *d*-series. The mutarotation follows the unimolecular formula and the extrapolated initial rotation is about −19°.

TABLE III

MUTAROTATION OF *α-d*-[β-GALAHEPTOSE] IN WATER

Concentration 1.0027 g. in 25 cc. solution: tube length 2 dm.; $T = 20 \pm 0.5°$.

Time after making solution, min.	$[\alpha]^{20}_D$	Time min.	$k_1 + k_2$
5	−20.72	0	...
15	22.01	10	0.0017
30	24.60	25	.0022
75	30.86	70	.0023
90	32.80	85	.0023
105	34.96	100	.0024
120	36.25	115	.0024
135	37.55	130	.0024
150	38.84	145	.0024
165	40.14	160	.0024
180	41.43	175	.0024
195	42.73	190	.0025
210	43.80	205	.0025
225	44.45	220	.0025
240	45.32	235	.0025
270	46.61	265	.0025
330	48.98	325	.0025
345	49.20	340	.0025
375	49.85	370	.0025
12 hrs.	53.95 (equilibrium)		...
48 hrs. (final)	53.95	...	...
		Average	.0024

***α-d*-(β-Galaheptose) Hexaacetate.**—A suspension of 20.4 g. of oven-dried β-galaheptose and 5 g. of fused sodium acetate in 80 cc. of redistilled acetic anhydride was heated gently to incipient reaction, when the heat of reaction was sufficient to bring about a rise in temperature to the boiling point of the anhydride. Following subsidence of the reaction the solution was refluxed for fifteen minutes, cooled and poured into crushed ice, the crystalline acetate separating as the excess anhydride decomposed; yield 36 g. (80%). *α-d*-(β-Galaheptose) hexaacetate crystallizes from 10 parts of methyl alcohol in groups of colorless needles, 5 to 6 mm. long, giving the appearance of a silky mat upon filtration. The substance melts at 151–152° (corr.) to a clear colorless oil and when recrystallized to constant specific rotation gives a value of +30.2° (0.5002 g. in 25 cc. of chloroform in a 2-dm. tube rotated 1.21° to the right).

Anal. Acetyl: 0.2179 g. consumed 28.4 cc. of 0.1 *N* NaOH. Calcd. for six acetyl groups, 28.3 cc. Calcd. for $C_{19}H_{26}O_{13}$: C, 49.33; H, 5.67. Found: C, 49.34; H, 5.68.

***β-d*-(β-Galaheptose) Hexaacetate.**—A solution of 5.0 g. of *α-d*-β-galaheptose hexaacetate in 25 cc. of a rearranging solution, prepared by adding 2.3 cc. of concd. sulfuric acid dropwise to an ice-cold mixture of 68 cc. of acetic anhydride and 29 cc. of glacial acetic acid, showed a progressive change in specific rotation from +18.7 to −68.9° in forty-eight hours at 20°. The solution was poured upon cracked ice and the gum which separated was crystallized by repeated trituration with cold water; yield 3.3 g.

---

(13) Kiliani, *Ber.*, **55**, 99 (1922).

(66%). β-*d*-(β-Galaheptose) hexaacetate crystallizes from 5 parts of 50% ethyl alcohol in small needles melting at 100–101° (corr.) and when recrystallized to constant specific rotation showed a value of −55.8° (0.5150 g. in 25 cc. of chloroform in a 2-dm. tube rotated 2.3° to the left).

Anal. Calcd. for $C_{19}H_{26}O_{13}$: C, 49.33; H, 5.67. Found: C, 49.25; H, 5.68.

α - Methyl - *d* - (β - Galaheptoside) Pentaacetate.—A solution of 10 g. of α-*d*-(β-galaheptose) hexaacetate in 50 cc. of acetic acid saturated with gaseous hydrobromic acid was allowed to stand for one hour, concentrated *in vacuo* (bath 40°) to remove the major part of the acid and twice treated with 100 cc. of toluene and concentrated to a sirup, to remove the residual acid. The dry sirup was dissolved in 100 cc. of methyl alcohol and 10 g. of silver carbonate was added. Following completion of the reaction, which proceeded with local generation of heat, the hot solution was filtered to remove silver halide, the glycoside acetate crystallizing from the filtrate as it cooled; yield 6.9 g. (73%). α-Methyl-β-galaheptoside pentaacetate crystallizes from 5 parts of 50% acetic acid in colorless elongated plates, melting at 122–123° (corr.) and exhibits a specific rotation of +51.8° in chloroform (0.5717 g. in 25 cc. in a 2-dm. tube rotated 2.37° to the right), these properties remaining unchanged upon recrystallization.

Anal. Calcd. for $C_{18}H_{26}O_{12}$: C, 49.74; H, 6.04; OCH_3, 7.1. Found: C, 49.56; H, 6.02; OCH_3, 7.1.

α - Methyl - *d* - (β - Galaheptoside).—A solution of 4.8 g. of pentaacetyl-α-methyl-*d*-β-galaheptoside in 25 cc. of methyl alcohol was saturated with gaseous ammonia, allowed to stand overnight and concentrated *in vacuo* to dryness, crystallization occurring during the process. The dry solid was taken up in methyl alcohol, the solution filtered through carboraffin, and upon cooling the filtrate yielded the glycoside in a yield of 2.0 g. (80%). α-Methyl-*d*-β-galaheptoside crystallizes from methyl alcohol in small clear prisms, melting at 182–183° (corr.) without decomposition. Its specific rotation in water when pure is +36.0° (0.4096 g. in 25 cc. in a 2-dm. tube rotates 1.18° to the right).

Anal. Calcd. for $C_8H_{16}O_7$: C, 42.83; H, 7.20; OCH_3, 13.8. Found: C, 42.95; H, 7.28; OCH_3, 13.8.

***d*-(β-Galaheptose) Benzyl Mercaptal.**—A solution of 5 g. of powdered *d*-β-galaheptose in 10 cc. of concentrated hydrochloric acid was shaken with 10 cc. of benzyl mercaptan, crystallization occurring at the end of one and one-half hours. After a further half hour, 50 cc. of ice water and 25 cc. of 95% alcohol were added and the mercaptal filtered off; yield 3.3 g. (31%). The mercaptal crystallizes from 10 parts of 95% alcohol in a cottony mass of minute needles, which melt at 146–147° (corr.) and give a specific rotation of +73.8° in pyridine (0.2303 g. in 10 cc. in a 1-dm. tube rotated 1.70° to the right).

Anal. Calcd. for $C_{21}H_{28}O_6S_2$: S, 14.56. Found: S, 14.51.

Hexaacetyl-*d*-(β-galaheptose) Benzyl Mercaptal.—To a solution of 2.6 g. of *d*-β-galaheptose benzyl mercaptal in 20 cc. of pyridine, 20 cc. of acetic anhydride was added and the reaction mixture allowed to stand overnight. Upon pouring the solution into crushed ice and stirring, crystallization readily took place; yield 4.1 g. (quantitative). The mercaptal acetate was purified by recrystallization from 5 parts of 95% alcohol, separating in well formed prisms. The substance, recrystallized to constant physical properties, melts at 82–83° (corr.) and gives a specific rotation of +9.2° (0.3047 g. in 10 cc. of chloroform in a 1-dm. tube rotated 0.28° to the right).

Anal. Calcd. for $C_{33}H_{40}O_{12}S_2$: S, 9.26. Found: S, 9.10.

Summary

A number of crystalline derivatives of *d*-(β-galaheptose) have been prepared and described. Attention has been called to the parallelism in rotational behavior of certain derivatives of *d*-β-galaheptose with those of the configurationally related *l*-glucose. This similarity extends also to the chemical behavior of these sugars and would indicate that such properties are conditioned by the spacial arrangement of carbons one to five in the sugar molecule.

WASHINGTON, D. C. RECEIVED JANUARY 7, 1937