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

The Action of Diazomethane upon Acyclic Sugar Derivatives. IV.[1] Ketose Synthesis

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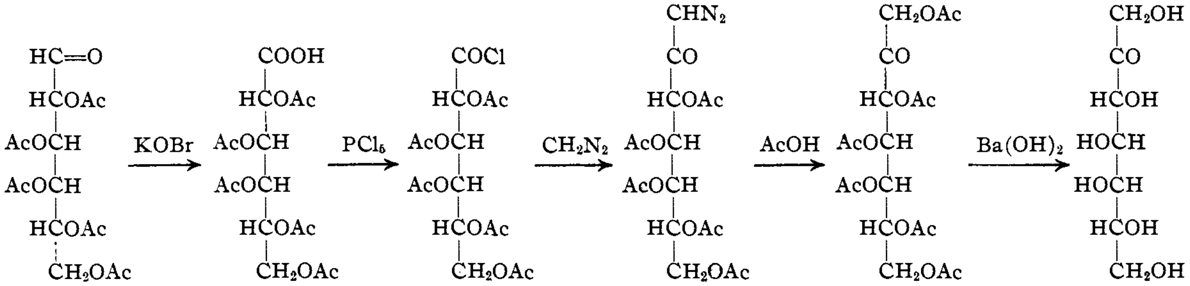
In extension of our previous work on ketose synthesis, we herein describe the synthesis in crystalline form of a new ketoheptose, D-galaheptulose (VI). This is the enantiomorph of perseulose, a sugar first prepared by Bertrand[4] by the action of *Bacterium xylinum* (syn. *Acetobacter xylinum*) on the naturally occurring heptitol perseitol, isolated from the avocado by Avequin.[5] The structure of perseulose was established as L-galaheptulose by Hudson and co-workers.[6] The similarity in structure and in mutarotatory and other characteristics exhibited between L-galaheptulose and D-fructose, as noted by Bertrand,[4c] Hudson[6] and Isbell,[7] would appear to justify the application of the name L-gala-D-fructo-heptose, in accordance with the higher sugar nomenclature of Hudson.[8] D-Galaheptulose may then be designated D-perseulose or D-gala-L-fructo-heptose. In the present work we have described also *d,l*-perseulose.[9] D-Galaheptulose crystallized as a hemihydrate. Hann and Hudson[6] found that L-galaheptulose likewise crystallized as a hemihydrate. *d,l*-Galaheptulose, however, was obtained in the anhydrous crystalline form.

D-Galactonic acid pentaacetate[10] (II) was prepared in this Laboratory by the oxidation of *aldehydo*-D-galactose pentaacetate (I) and was converted to crystalline D-galactonyl chloride pentaacetate (III). On reaction with diazomethane this acid chloride yielded the diazomethylketone (IV), designated 1-diazo-1-desoxy-*keto*-D-galaheptulose pentaacetate. With acetic acid, IV produced *keto*-D-galaheptulose hexaacetate (V), the enantiomorph of *keto*-L-perseulose hexaacetate, previously obtained by Khouvine and Arragon[11] on the direct acetylation of L-perseulose with acetic anhydride and pyridine.



I II III IV V VI

In our Laboratory *keto*-D-galaheptulose hexaacetate was isolated in two dimorphic forms (m. p. 102–103° and 116–117°) of like rotation in solution. The comparative X-ray powder diagrams[12] of these substances (Fig. 1) and the tabulated (Table I) interplanar spacings and relative intensity of the lines in the two diffraction patterns, clearly demonstrate the homogeneity and identity of each of these modifications. The melting point of 105° recorded by Khouvine and Arragon[11] would indicate that these workers encountered only the lower melting and less stable form.

Ketoses are very sensitive to alkali and the saponification of a *keto*-acetate presented a difficult problem until the procedure of Hudson and Brauns[13] for the conversion of D-fructose tetraacetate to D-fructose was employed. By this procedure *keto*-D-galaheptulose hexaacetate was converted smoothly into the crystalline D-gala-

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[1] Previous publication in this series: M. L. Wolfrom, S. W. Waisbrot and Robert L. Brown, THIS JOURNAL, **64**, 2329 (1942).

[2] Du Pont Fellow, 1941–1942.

[3] Allied Chemical and Dye Corporation Fellow, 1942–1943.

[4] (a) G. Bertrand, *Compt. rend.*, **147**, 201 (1908); (b) **149**, 225 (1909); (c) *Bull. soc. chim.*, [4] **5**, 629 (1909); (d) Evelyn B. Tilden, R. M. Hann and C. S. Hudson, THIS JOURNAL, **61**, 338 (1939); (e) Evelyn B. Tilden, *J. Bact.*, **37**, 629 (1939).

[5] J. B. Avequin, *Journal de chimie medicale, de pharmacie et de toxicologie*, [1] **7**, 467 (1831).

[6] R. M. Hann and C. S. Hudson, THIS JOURNAL, **61**, 336 (1939); N. K. Richtmyer, R. M. Hann and C. S. Hudson, *ibid.*, 340 (1939).

[7] H. S. Isbell, *J. Research Natl. Bur. Standards*, **18**, 513 (1937).

[8] C. S. Hudson, THIS JOURNAL, **60**, 1537 (1938).

[9] We are indebted to Dr. C. S. Hudson of the Division of Chemistry of the National Institute of Health, United States Public Health Service, Bethesda, Maryland, for a sample of L-perseulose.

[10] C. D. Hurd and J. C. Sowden, *ibid.*, **60**, 235 (1938).

[11] Yvonne Khouvine and G. Arragon, *Compt. rend.*, **206**, 917 (1938).

[12] For the X-ray photographs and measurements we are indebted to Dr. F. R. Senti of the Eastern Regional Research Laboratory, United States Department of Agriculture, Philadelphia, Pennsylvania.

[13] C. S. Hudson and D. H. Brauns, THIS JOURNAL, **38**, 1216 (1916).

heptulose (VI), agreeing well in properties with those recorded by Hudson and co-workers[6] for the enantiomorph. The mutarotation of this sugar is shown in Table II. From the downward nature of the mutarotation, the sugar may be classified as an α-form. On the other hand, mild pyridine acetylation of the enantiomorph yielded the *keto*-acetate[11] and thus an open chain or *keto*-structure for the crystalline sugar is not excluded. It is of interest to note that only those crystalline ketoses that possess the fructose configuration exhibit any significant mutarotation.

1-Diazo-1-desoxy-D-galaheptulose was obtained in crystalline form by the low-temperature saponification of its pentaacetate (IV). This unacetylated diazomethyl ketone is a very interesting substance and, to our knowledge, represents the first diazomethyl ketone of a polyhydroxy compound. Strangely, the diazomethyl ketone exhibited no inherent mutarotation in aqueous solution. Its aqueous solution evolved nitrogen very slowly at room temperature and more rapidly at elevated temperatures. This nitrogen evolution was catalyzed by cupric and silver ions and by acids. The compound was a powerful reducing agent, even reducing aqueous silver nitrate, and it also decolorized halogens.

D-Galactonyl chloride pentaacetate was converted to ethyl D-galactonate pentaacetate, apparently identical or dimorphic with the crystalline compound obtained by Kohn[14] in 1895 by the acetylation with acetic anhydride and zinc chloride of a calcium chloride addition compound of ethyl D-galactonate. When treated with phenylhydrazine, D-galactonyl chloride pentaacetate yielded D-galactonic acid phenylhydrazide pentaacetate and this on further acetylation produced the hexaacetyl derivative, designated D-galactonic acid acetylphenylhydrazide pentaacetate. An analogous pair of compounds was obtained in the D-gluconic acid structure, the pentaacetate being isolated in anhydrous and monohydrated forms. D-Gluconic acid acetylphenylhydrazide pentaacetate was identical with a compound prepared by Major and Cook[15] on acetylation of gluconic acid phenylhydrazide with acetic anhydride and zinc chloride and designated by these workers as D-gluconic acid phenylhydrazide pentaacetate. Our D-galactonic acid acetylphenylhydrazide pentaacetate was likewise found to be identical with a compound prepared by Robbins and Upson[16] by the similar acetylation of D-galactonic acid phenylhydrazide and designated by these workers as the pentaacetyl derivative. An analogous structure is probable for a whole series of acetylated aldonic acid phenylhydrazides prepared by Robbins and Upson.[16]

In a preceding publication[17] in this series, D-arabonyl chloride tetraacetate was employed as an intermediate but was not isolated. This substance exhibits a strong tendency to separate from solution as a gel but has now been characterized as a pure, crystalline compound.

In the preceding publication,[1] D-glucose was converted into *keto*-D-glucoheptulose hexaacetate. The latter compound has now been transformed into D-glucoheptulose (D-gluco-D-sorbo-heptose), thus completing this series of reactions and establishing the synthesis of this ketose by this method.

All compounds described herein were obtained in crystalline form.

Extension of this work is in progress in this Laboratory.

Experimental[18]

D-Arabonyl Chloride Tetraacetate.[19]—To a suspension of 6.6 g. (1.1 mole) of phosphorus pentachloride in 70 cc. of anhydrous ether was added 10 g. (1 mole) of D-arabonic acid tetraacetate,[16] prepared from crystalline potassium (instead of sodium) D-arabonate according to the method of Robbins and Upson.[16,20] The mixture was shaken mechanically for two hours. The resulting solution was filtered and diluted to 2 liters with petroleum ether. D-Arabonyl chloride tetraacetate, which crystallized slowly and showed a strong tendency to gel, was quickly filtered and washed well with petroleum ether; yield, 9.0 g. (85%), m. p. 74–75°. Pure material was obtained on recrystallization from dry ether by the addition of petroleum ether; yield 7.4 g., m. p. 74–75°, spec. rot. +46° (22°, *c* 3.0, abs. $CHCl_3$, D line).

Anal. Calcd. for $C_5H_5O_5Cl(CH_3CO)_4$. Cl, 10.05; sapon. value (6 equivs.), 17.0 cc. 0.1 *N* NaOH per 100 mg. Found: Cl, 10.05; sapon. value, 16.9 cc.

Preparation of D-Galactonic Acid Pentaacetate (II) **from** *aldehydo*-**D-Galactose Pentaacetate** (I).—*aldehydo*-D-Galactose pentaacetate[21] was prepared according to the improved demercaptalation procedure of Wolfrom and Konigsberg,[22] except that the chloroform used was free of

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(14) E. Kohn, *Monatsh.*, **16**, 333 (1895).

(15) R. T. Major and E. W. Cook, THIS JOURNAL, **58**, 2474 (1936).

(16) G. B. Robbins and F. W. Upson, *ibid.*, **62**, 1074 (1940).

(17) M. L. Wolfrom, S. W. Waisbrot and R. L. Brown, *ibid.*, **64**, 170 (1942).

(18) Experimental work by Mr. Robert L. Brown unless otherwise noted.

(19) Experimental work by Mr. Evan F. Evans.

(20) J. M. Brakenbury and F. Upson, THIS JOURNAL, **55**, 2512 (1933).

(21) M. L. Wolfrom, *ibid.*, **52**, 2464 (1930).

(22) M. L. Wolfrom, M. Konigsberg and D. I. Weisblat, *ibid.*, **61**, 574 (1939).

ethanol. From 150 g. of D-galactose diethyl mercaptal pentaacetate there was obtained 112 g. of crude *aldehydo*-D-galactose pentaacetate. Oxidation of the crude product was accomplished by a modification of the procedure utilized by Major and Cook[15] in the oxidation of *aldehydo*-D-glucose pentaacetate to D-gluconic acid pentaacetate.

To 35 g. of crude *aldehydo*-D-galactose pentaacetate was added 600 cc. of hot (80°) water. Following complete solution of the *aldehydo*-sugar the solution was rapidly cooled to 25° and 36 g. (4 moles) of potassium bicarbonate was added. After solution of the bicarbonate 17.2 g. (1.2 moles) of bromine was added slowly with mechanical stirring (foaming) and the resulting solution was stirred slowly for ninety minutes. The excess bromine was removed by dropwise addition of a solution of sodium thiosulfate and the reaction mixture was extracted twice with 40-cc. portions of chloroform to remove any unreacted *aldehydo*-acetate. The solution was acidified by the addition of 182 cc. of 2 N sulfuric acid (4 equivs.) and was extracted with a total of 350 cc. of chloroform in six portions. Any bromine appearing at this point was removed by washing the solution with aqueous sodium thiosulfate. The solvent was removed from the combined, dried extracts by distillation under reduced pressure to yield a crystalline mass of crude D-galactonic acid pentaacetate. The acid was dissolved in 200 cc. of dry toluene and 50 cc. of the solvent distilled off at atmospheric pressure in order to remove residual water. Upon cooling the solution to 0° the anhydrous acid separated slowly as white, beautifully crystalline material. Filtered and dried under reduced pressure at 50°, the yield of once-recrystallized acid was 18 g. (44% based upon D-galactose diethyl mercaptal pentaacetate); m. p. 127–130°, spec. rot. +16.5° (abs. $CHCl_3$, D line), mixed melting point with an authentic sample (m. p. 129–130°) 128–130°. For D-galactonic acid pentaacetate, first synthesized by Hurd and Sowden,[10] Wolfrom and Weisblat[22] record the constants: m. p. 131–132°, spec. rot. +16° (abs. $CHCl_3$, D line).

D-Galactonyl Chloride Pentaacetate (III).—This substance was synthesized by a modification of the procedure utilized by Major and Cook[23] in the preparation of D-gluconyl chloride pentaacetate. To a solution of 20 g. of anhydrous D-galactonic acid pentaacetate in 100 cc. of anhydrous ether was added 11.3 g. (1.1 moles) of phosphorus pentachloride. The mixture was shaken mechanically for about two hours at room temperature (complete solution of the phosphorus pentachloride occurred after thirty minutes). To the resulting solution was added 350 cc. of petroleum ether (30–60°) whereupon crystallization of the acid chloride occurred. The mixture was kept at 0° for several hours to ensure complete crystallization. The supernatant liquors were decanted from the crystals as carefully and completely as possible and the residual crystals were washed by decantation with petroleum ether. The acid chloride was redissolved in a minimum of warm ether, 350 cc. of petroleum ether was added to the solution and the mixture was cooled to 0°. The crystals were filtered from the greater portion of the liquid by means of gentle suction and were then washed on the filter with petroleum ether and quickly placed in a desiccator where the residual wash liquid was removed under reduced pressure; yield (once recrystallized) 17.2 g., m. p. 80–81°, spec. rot. +3° (21°, c 4, abs. $CHCl_3$, D line). These constants were unaltered by further recrystallization. A further quantity of 1.5–2.0 g. was recovered from the recrystallization and reaction liquors to give an over-all yield of 90–92%.

The compound crystallized from ether–petroleum ether as thin, six-sided plates which were soluble in ether, acetone, chloroform and benzene and were insoluble in petroleum ether. It decomposed slowly in air with the evolution of hydrogen chloride and with the formation of D-galactonic acid pentaacetate but remained undecomposed under reduced pressure over phosphorus pentoxide in the presence of solid potassium hydroxide.

Anal. Calcd. for $C_6H_6O_6Cl(CH_3CO)_5$: Cl, 8.35; saponification value (7 equivs.), 16.48 cc. 0.1 N NaOH per 100 mg. Found: Cl, 8.45; saponification value, 16.49 cc.

On reaction of D-galactonyl chloride pentaacetate with an excess of dry ammonia in dry ether solution, D-galactonamide pentaacetate separated in good yield and high purity; m. p. 165–166° (mixed m. p. unchanged), spec. rot. +27° (20°, c 3, abs. $CHCl_3$, D line). For this substance, Hurd and Sowden[10] reported the constants: m. p. 166–167°, spec. rot. +27° ($CHCl_3$, D line).

Ethyl D-Galactonate Pentaacetate.—D-Galactonyl chloride pentaacetate (1.5 g.) was dissolved in absolute ethanol (50 cc.) and refluxed for ten minutes. The ethanol was removed by distillation under reduced pressure and the sirupy residue was redissolved in ethanol (10 cc.) and cooled, whereupon crystallization ensued; yield 0.95 g., m. p. 100–106°. Four crystallizations from ethanol yielded pure ethyl D-galactonate pentaacetate; m. p. 110–111°, spec. rot. +9.5° (27°, c 4.8, abs. $CHCl_3$, D line). In the early stages of the purification the substance softened at 102° and melted at 109°. Kohn[14] prepared ethyl D-galactonate pentaacetate by both acetyl chloride and acetic anhydride (zinc chloride) acetylation of the calcium chloride addition compound of ethyl D-galactonate, $(C_6H_{11}O_7 \cdot C_2H_5)_2 \cdot CaCl_2$, and reported a melting point of 101–102° for the compound crystallized from ethanol. Kohn did not report a specific rotation for the ester. Our compound is probably a polymorphic modification of that reported by Kohn; however, the lower-melting substance could not be isolated in the pure state from our reaction liquors due possibly to the greater stability of the higher-melting modification.

Anal. Calcd. for $C_6H_6O_6(OC_2H_5)(CH_3CO)_5$: C, 49.77; H, 6.03; saponification value (6 equivs.) 13.81 cc. 0.1 N NaOH per 100 mg. Found: C, 49.68; H, 6.13; saponification value, 13.65 cc.

D-Galactonic Acid Phenylhydrazide Pentaacetate.—To a solution of D-galactonyl chloride pentaacetate (5 g.) in ether (80 cc.) was added 2.54 g. (2.32 cc., 2 moles) of phenylhydrazine. The precipitated phenylhydrazine hydrochloride was separated by filtration through a precoat of Super-Cel. Successive small portions of petroleum ether (30–60°) were added to the filtrate at intervals and the slow crystallization was allowed to come to completion at 0°; yield 3.5 g., m. p. 134.5–136°, spec. rot. +33.5° (U.S.P. $CHCl_3$, D line). A further quantity of 0.5 g. of product was obtained from the mother liquors. Pure material was obtained by crystallization from warm ether or

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(23) R. T. Major and E. W. Cook, THIS JOURNAL, **58**, 2477 (1936).

from 20:1 ether–methanol by the addition of successive small portions of petroleum ether; m. p. 136.5–137°, spec. rot. +36° (21°, *c* 1.85, U.S.P. $CHCl_3$, D line).

Robbins and Upson[16] reported the constants of "pentaacetyl-*d*-galactonic phenylhydrazide" as: m. p. 220°, spec. rot. +23.6° (25°, $CHCl_3$, D line). Obviously the structure of the "pentaacetyl" derivative of Robbins and Upson was not that of D-galactonic acid phenylhydrazide pentaacetate since, first, the analyses and the method of preparation establish our compound as having that structure and, second, the constants of the two compounds under consideration do not coincide.

Anal. Calcd. for $C_{12}H_{13}O_6N_2(CH_3CO)_5$: C, 53.22; H, 5.68; N, 5.64; CH_3CO, 10.07 cc. 0.1 *N* NaOH per 100 mg. Found: C, 53.15; H, 5.84; N, 5.69; CH_3CO (Freudenberg[24] method), 10.00 cc.

D-Galactonic Acid Acetylphenylhydrazide Pentaacetate.—That the "pentaacetyl-*d*-galactonic phenylhydrazide" of Robbins and Upson[16] might have been a hexaacetyl derivative was considered probable since (1) the analysis for carbon and hydrogen alone, as recorded by Robbins and Upson, would be insufficient to characterize the compound as a pentaacetyl derivative and (2) the structure of the true pentaacetate has been established by synthesis from D-galactonyl chloride pentaacetate. In view of these conclusions D-galactonic acid phenylhydrazide pentaacetate was subjected to the acetylating conditions of Major and Cook[15] which were utilized by Robbins and Upson in preparing a number of acetyl derivatives of aldonic acid phenylhydrazides. To a solution of 2 g. of freshly fused zinc chloride in acetic anhydride (25 cc.) was added 5 g. of the phenylhydrazide pentaacetate. The solution was maintained at 0° for one-half hour and at room temperature for fifteen hours thereafter. The solution was poured into ice and water and was stirred mechanically for one-half hour whereupon a white crystalline powder separated and was removed by filtration; yield 4.8 g., m. p. 214–217°. Pure material was obtained on crystallization from ethanol by the addition of ether and petroleum ether; m. p. 218°, spec. rot. +23° (29°, *c* 2, U.S.P. $CHCl_3$, D line). Acetyl analysis by the Freudenberg[24] procedure proved unequivocally that the compound contained six acetyl groups. Robbins and Upson have reported as constants for their 'pentaacetyl" compound: m. p. 220°, spec. rot. +26.6° ($CHCl_3$, D line). Thus it has been demonstrated that the acetylating conditions utilized by Major and Cook and by Robbins and Upson in the acetylation of aldonic acid phenylhydrazides not only fully esterifies the hydroxyl groups but also replaces one N-hydrogen with an acetyl group to yield N-acetyl aldonic acid phenylhydrazide acetates.

Anal. Calcd. for $C_{12}H_{12}O_6N_2(CH_3CO)_6$: C, 53.53; H, 5.62; N, 5.20; CH_3CO, 11.14 cc. 0.1 *N* NaOH per 100 mg. Calcd. for $C_{12}H_{13}O_6N_2(CH_3CO)_5$: C, 53.22; H, 5.68; N, 5.64; CH_3CO, 10.07 cc. 0.1 *N* NaOH per 100 mg. Found: C, 53.63; H, 5.67; N, 5.23; CH_3CO (Freudenberg[24] method), 11.10 cc.

The same substance was obtained[19] in good yield on acetylation of D-galactonic acid phenylhydrazide[25] at room temperature with acetic anhydride and pyridine under conditions that have yielded O-acetates of hydrazones and osazones.[26]

D-Gluconic Acid Phenylhydrazide Pentaacetate.—A solution of D-gluconyl chloride pentaacetate[23] (5.00 g.) in dry ether (150 cc.) was treated with phenylhydrazine as described previously for the synthesis of D-galactonic acid phenylhydrazide pentaacetate and the product was isolated in the same manner; yield 5.24 g., m. p. 125–127°. Pure material was obtained on crystallization from ether-petroleum ether and ethanol-petroleum ether; m. p. 127.5–128.5°, spec. rot. +17.5° (21°, *c* 1.16, 6 dm., abs. EtOH, D line), +37.0° (22°, *c* 3.9, U.S.P. $CHCl_3$, D line). The substance crystallized in hard, white rosets.

Major and Cook[15] have reported as constants for "pentaacetylgluconicphenylhydrazide," prepared by the zinc chloride-acetic anhydride acetylation of D-gluconic acid phenylhydrazide: m. p. 152–154°, spec. rot. +28° (EtOH, D line). The method of synthesis and the analyses prove that our compound is the normal pentaacetate of D-gluconic acid phenylhydrazide, evidently different from that of Major and Cook.

Anal. Calcd. for $C_{12}H_{13}O_6N_2(CH_3CO)_5$: C, 53.22; H, 5.68; N, 5.64; CH_3CO, 10.07 cc. 0.1 *N* NaOH per 100 mg. Found: C, 52.96; H, 5.76; N, 5.70; CH_3CO (Freudenberg[24] method), 10.08 cc.

D-Gluconic Acid Phenylhydrazide Pentaacetate Monohydrate.—When 1.2 g. of D-gluconic acid phenylhydrazide pentaacetate was dissolved in 70 cc. of hot water, treated with decolorizing carbon and cooled to 0° there crystallized 0.5 g. of beautifully white D-gluconic acid phenylhydrazide pentaacetate monohydrate; m. p. 86–88°. An air-dried sample of the hydrate was heated under reduced pressure over phosphorus pentoxide at the temperature of boiling toluene for four hours. The compound fused to a clear melt which slowly crystallized at that temperature to yield anhydrous D-gluconic acid phenylhydrazide pentaacetate, m. p. 128–128.5°. The loss in weight due to water indicated 3.52% water in the hydrate; calcd. for $C_{12}H_{13}O_6N_2(CH_3CO)_5{\cdot}H_2O$: H_2O, 3.50.

D-Gluconic Acid Acetylphenylhydrazide Pentaacetate.—D-Gluconic acid phenylhydrazide pentaacetate (4.5 g.) was acetylated as described by Major and Cook[15] for the acetylation of D-gluconic acid phenylhydrazide and the product was isolated and crystallized in the same manner; yield 4.1 g., m. p. 148–152°. Pure material was obtained on further crystallization from ethanol by the addition of ether; m. p. 152–153°, spec. rot. +25° (22°, *c* 1.03, 6 dm., abs. EtOH, D line), spec. rot. +33° (22°, *c* 3.5, U.S.P. $CHCl_3$, D line). Major and Cook reported as constants for "pentaacetylgluconicphenylhydrazide": m. p. 152–154°, spec. rot. +28° (20°, *c* 2, EtOH, D line).

The directions of Major and Cook were followed and their compound was prepared by the direct acetylation of gluconic acid phenylhydrazide with zinc chloride–acetic anhydride. The compound thus prepared was found to be identical in melting point and specific rotation with that prepared by the further acetylation of D-gluconic acid phenylhydrazide pentaacetate. A mixed melting point exhibited no depression. The analyses and the method of

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(24) K. Freudenberg and M. Harder, *Ann.*, **433**, 230 (1923).

(25) E. Fischer and F. Passmore, *Ber.*, **22**, 2728 (1889).

(26) M. L. Wolfrom and C. C. Christman, THIS JOURNAL, **53**, 3413 (1931); M. L. Wolfrom and L. W. Georges, *ibid.*, **58**, 490 (1936).

preparation indicated that the compound was D-gluconic acid acetylphenylhydrazide pentaacetate.

Anal. Calcd. for $C_{12}H_{12}O_6N_2(CH_3CO)_6$: C, 53.53; H, 5.62; N, 5.20; CH_3CO, 11.14 cc. 0.1 *N* NaOH per 100 mg. Calcd. for $C_{12}H_{13}O_6N_2(CH_3CO)_5$: C, 53.22; H, 5.68; N, 5.64; CH_3CO, 10.07 cc. 0.1 *N* NaOH per 100 mg. Found: C, 53.17; H, 5.70; N, 5.15; CH_3CO (Freudenberg[24] method), 11.12 cc.

The same substance was obtained[19] on acetylation of D-gluconic acid phenylhydrazide[25] at room temperature wtih acetic anhydride and pyridine.

1-Diazo-1-desoxy-*keto*-D-galaheptulose Pentaacetate (IV).—To a solution of D-galactonyl chloride pentaacetate (10 g.) in anhydrous ether (100 cc.), cooled to 0°, was added a cold, anhydrous solution of diazomethane (2.4 g., 2.5 moles) in 200 cc. of ether. There was an immediate evolution of nitrogen and subsequent precipitation of the product. The mixture was allowed to stand for two hours at room temperature to effect complete reaction and was then cooled to 0°, filtered and washed with cold ether; yield 8.7 g., m. p. 135–136°; spec. rot. +59° (abs. $CHCl_3$, D line). The product was recrystallized (decolorizing charcoal) twice by solution in five parts of acetone and the subsequent addition (at the boiling point of the mixture) of fifty parts of ether and twenty-five parts of petroleum ether (30–60°) to yield pure 1-diazo-1-desoxy-*keto*-D-galaheptulose pentaacetate as long, very light yellow,[27] fibrous needles; m. p. 136–137°, spec. rot. +64° (23°, *c* 2.4, abs. $CHCl_3$, D line). These constants were unaltered by further crystallizations from ether–benzene and chloroform–petroleum ether.

The compound was very soluble in acetone and chloroform, soluble in methanol, benzene and warm ethanol, moderately insoluble in ether and cold ethanol and was insoluble in water and petroleum ether. It reduced cold Fehling solution slowly. The substance decomposed just above its melting point with the evolution of nitrogen and the formation of an amber, friable, acetone-soluble plastic glass. The diazo compound could be refluxed in benzene solution for four hours and be recovered quantitatively, none of it having been decomposed. After three hours in boiling toluene only about one-half could be recovered unreacted. After only one and one-half hours in boiling xylene the substance was quantitatively decomposed as indicated by the volume of evolved nitrogen.

Anal. Calcd. for $C_7H_7O_6N_2(CH_3CO)_5$: C, 47.44; H, 5.15; N, 6.51; saponification value (5 equivs.), 11.62 cc. 0.1 *N* NaOH per 100 mg. Found: C, 47.48; H, 5.38; N, 6.41; saponification value, 11.53 cc.

1-Diazo-1-desoxy-D-galaheptulose.[19]—A suspension of 2.00 g. of 1-diazo-1-desoxy-*keto*-D-galaheptulose pentaacetate in 10 cc. of dried methanol was treated for several hours at 0–5° with a like volume of dried methanol, nearly saturated at room temperature with anhydrous ammonia. The resulting clear solution deposited dense, cream-colored crystals on standing overnight at icebox temperature; yield 0.73 g. (71%), m. p. 140° (dec.), spec. rot. +82° (23°, *c* 2.8, H_2O, D line). The substance could be recrystallized by the addition of ethanol to its cold water solution but was generally in the purest condition when first formed as above. The compound exhibited no inherent mutarotation in water. A solution of the substance in ice-water was made and maintained at 0°. Two minutes were required to effect solution and the first reading was taken two and one-half minutes later, the value for the specific rotation being +93° (*c* 2.8, D line). This value remained unchanged over an observation period of seven hours. The solution was then allowed to come to room temperature (23°), whereupon the specific rotation was found to be +82° (D line) and remained so over an observation period of two and one-half hours. That a slight decomposition had occurred, however, was evidenced by the formation of minute gas bubbles (nitrogen) in the polarimeter tube and in other experiments the dextrorotation was found to decrease markedly over a twenty-four hour period at room temperature. Formic acid (90%, 0.05 cc.) was then added to the solution and this initiated a brisk evolution of nitrogen. The specific rotation was observed four hours later, after the cessation of nitrogen evolution, and was found to be +11° (basis original weight of substance), unchanged over an observation period of three days. This rotation does not correspond to that of D-galaheptulose (+82°) and is not significantly changed on correcting for solution-volume temperature change (0 to 23°) or for the concentration change in the nitrogen evolution reaction (loss of nitrogen with or without the addition of water). Sirups that were not amenable to crystallization were obtained from such experiments as described.

1-Diazo-1-desoxy-D-galaheptulose was soluble in water, slightly soluble in boiling ethanol and was insoluble in other common organic solvents. The crystals decomposed slowly on storage. The following qualitative tests were performed on fresh solutions in distilled water. Nitrogen was evolved very slowly from an aqueous solution at room temperature and quite rapidly at elevated temperatures. Copper sulfate initiated a rapid nitrogen evolution and was reduced to cuprous oxide. Fehling solution and even aqueous silver nitrate were reduced at room temperature with nitrogen evolution. Hydriodic acid initiated a rapid nitrogen evolution and the iodine, initially liberated, was gradually decolorized. Bromine water was decolorized rapidly with a vigorous evolution of nitrogen.

Anal. Calcd. for $C_7H_{12}O_6N_2$: C, 38.18; H, 5.49; N, 12.72. Found: C, 38.49; H, 5.60; N, 12.52.

1-Diazo-1-desoxy-D-galaheptulose was heated in aqueous solution until the evolution of nitrogen had ceased. On removal of the solvent under reduced pressure a sirup was obtained that was not amenable to crystallization and which reduced Fehling solution at room temperature.

***keto*-D-Galaheptulose Hexaacetate (V).**—A solution of 1-diazo-1-desoxy-*keto*-D-galaheptulose pentaacetate (5.0 g.) in glacial acetic acid (75 g.) was refluxed to the cessation of nitrogen evolution (*ca.* fifteen minutes; delivery tube from condenser top placed in water as an indicator). The reaction mixture was poured into ice and water and the solution neutralized with sodium bicarbonate. The separated yellow crystalline mass was filtered, washed with water and dried; yield 4.15 g., m. p. 95–98°. The sub-

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(27) All of these diazomethyl ketones possess a slight yellow color, clearly seen when large individual crystals are grown. This property was not previously recorded in the description of 1-diazo-1-desoxy-*keto*-D-glucoheptulose pentaacetate by Wolfrom and Waisbrot (THIS JOURNAL, **63**, 203 (1941)) and of 1,8-bisdiazo-mucyldimethane tetraacetate (ref. 1).

stance was recrystallized by solution in 60 cc. of warm 30% ethanol (decolorizing charcoal) and the subsequent addition of 125 cc. of warm water followed by cooling. ***keto*-D-Galaheptulose hexaacetate** crystallized as white, very thin, rectangular plates; m. p. 100–102°, spec. rot. −1.6° (abs. $CHCl_3$, D line). Three further crystallizations from aqueous ethanol yielded pure material; m. p. 101.5–102.5°, spec. rot. −1.6° (27°, *c* 3, abs. $CHCl_3$, D line). Crystallization from 100 parts of 7:3 ether–petroleum ether did not alter these constants. In the course of a subsequent crystallization from aqueous ethanol the compound crystallized in rosets of long needles which had a melting point of 116–117° and a specific rotation (23°, *c* 3) of −1.6° (abs. $CHCl_3$, D line), −20° (C_6H_6, D line), −20.5° (C_6H_6, 5780 Å.). Following isolation of the high-melting polymorph all attempts to obtain the low-melting form were to no avail, there always resulting a mixture of the two modifications. The material melting at 102°, however, was quantitatively converted to the 117° form by solution in any of several suitable solvents followed by seeding with the high-melting modification. The distinctive nature of each of these crystallographic dimorphs, of the same optical rotatory power when dissolved, is clearly shown in the comparative X-ray powder diagrams of Fig. 1 and in the tabulation of the interplanar spacing and relative intensity of the X-ray diffraction lines as tabulated in Table I. For the enantiomorph, *keto*-perseulose hexaacetate, Khouvine and Arragon[11] recorded the constants: m. p. 105°, spec. rot. +20.8° (20°, *c* 4, C_6H_6, 5780 Å.).

TABLE I

X-RAY DIFFRACTION PATTERNS[a] (FIG. 1) OF THE DIMORPHIC FORMS OF *keto*-D-GALAHEPTULOSE PENTAACETATE

M. p. 102–103°		M. p. 116–117°	
Interplanar spacing, Å.	Relative intensity[b]	Interplanar spacing, Å.	Relative intensity[b]
8.9	W−	14.9	W−
8.3	S+	11.4	W−
7.6	M	8.7	S
6.5	W	7.7	M
5.8	W	7.0	S+
5.47	M+	6.2	M
5.16	M+	5.39	W
4.80	S	4.94	W
4.44	W	4.75	W
4.20	W	4.49	S−
4.11	W	4.32	M
3.95	W+	4.19	M
3.83	W+	3.89	S+
3.69	W	3.70	W
3.51	M−	3.52	M
3.41	W+	3.28	W+
3.24	M−	3.06	W
3.04	W+	2.87	W+
2.93	W−	2.77	W
2.84	W−		
2.68	W−		
2.56	W−		
2.49	W		
2.39	W		
2.32	W−		
2.16	W		
2.05	W−		
1.98	W−		

[a] *Cf.* ref. 12. The data were obtained with copper K_α radiation. The samples were in the form of pressed powder rods about 0.5 mm. in diameter. [b] S = strong, M = medium, W = weak.

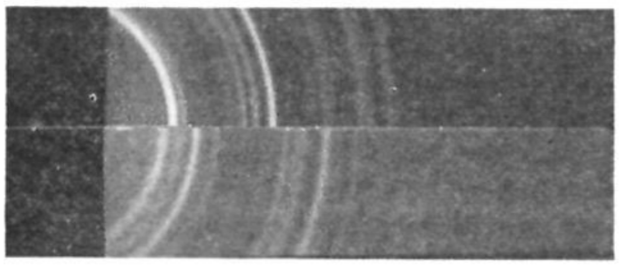

Fig. 1.—Comparative X-ray powder diagrams of the dimorphic forms (upper, m. p. 102–103°; lower, m. p. 116–117°) of *keto*-D-galaheptulose pentaacetate (*cf.* ref. 12 and Table I).

The compound (in either modification) was soluble in acetone, chloroform, warm ethanol and methanol, moderately soluble in cold ethanol and warm ether and was practically insoluble in petroleum ether and cold ether. It reduced hot Fehling solution vigorously.

Anal. Calcd. for $C_7H_8O_7(CH_3CO)_6$: C, 49.35; H, 5.67; CH_3CO, 12.97 cc. 0.1 *N* NaOH per 100 mg. Found: C, 49.34; H, 5.92; CH_3CO, 13.06 cc.

D-Galaheptulose (VI, D-Perseulose, D-Gala-L-fructoheptose) Hemihydrate.[19]—By employing barium hydroxide at low temperatures, as described by Hudson and Brauns[13] for fructose tetraacetate, *keto*-D-galaheptulose hexaacetate was deacetylated successfully to yield a new crystalline ketose, D-galaheptulose. An amount of 37.6 g. of barium hydroxide octahydrate was dissolved in 375 cc. of water and the solution filtered. The filtrate was cooled to 0–5° and 8.5 g. of *keto*-D-galaheptulose hexaacetate was added. With occasional shaking the crystals dissolved in about thirty minutes. The solution was kept one hour longer in the ice-bath, then saturated with carbon dioxide and the precipitated barium carbonate removed by filtration. A slight excess of 2 *N* sulfuric acid was added slowly and the barium sulfate removed by filtration through a bed of Super-Cel (Johns-Manville). Barium hydroxide was added carefully to neutralize the excess sulfuric acid and then the filtered solution was concentrated under reduced pressure at 40° to a thick sirup. The sirup was dried by the repeated addition of absolute alcohol and reconcentration to a sirup. The dried sirup, after standing for some time under ethanol, crystallized; yield 2.2 g. (two crops, 55%), m. p. 100–102°, spec. rot. +90.6° (extrapolated initial) → +75.3° (equil.) (25°, *c* 2.2, H_2O, D line). Pure material was obtained on recrystallization effected by solution in a minimum amount of warm water to which was then added 4–5 volumes of glacial acetic acid. The product was dried at 35° under reduced pressure over potassium hydroxide and phosphorus pentoxide; m. p. 102–103°, spec. rot. recorded in Table II. The compound had a sweet taste.

Anal. Calcd. for $2C_7H_{14}O_7 \cdot H_2O$: C, 38.35; H, 6.90. Found: C, 38.35; H, 6.82.

For the enantiomorphic perseulose or L-galaheptulose, Bertrand,[4] whose analysis corresponded to the anhydrous formula $C_7H_{14}O_7$, reported the constants: m. p. 110–115° (Maquenne block) and spec. rot. (D line) −90° (after solution) → −80 to −83° (equil., depending on temperature and concentration). According to Bertrand the specific rotation decreased with increasing temperature and increased slightly with the concentration. Hann and Hudson[6] obtained perseulose as the hemihydrate with the following constants: m. p. 102–103° (cor.), spec. rot. −96.4° (1.1 min. after making solution) → −82.3° (equil., 20°, H_2O, D line) and an average specific reaction rate constant ($k_1 + k_2$) of 0.059 at 20° (min. and dec. log.).

TABLE II

MUTAROTATION OF D-GALAHEPTULOSE HEMIHYDRATE

(16.5°, c 2.9, l 4, H_2O, D line)

Time after addition of solvent, min.	Spec. rot. (hemihydrate)	$k_1 + k_2$
0	+100.8°[a]	
3.7	98.2	0.017[b]
4.7	97.4	.018
5.4	97.1	.018
6.4	96.0	.020
7.2	95.4	.020
10.0	94.5	.018
12.5	93.8	.016
16.3	92.6	.015
21.3	91.1	.015
25.7	90.3	.014
32.4	88.9	.013
46.0	86.5	.013
61.5	84.3	.015
112	83.0	..
24 (hr.)	82.0	..
48 (hr.)	82.0	..
	Average	.016

[a] Extrapolated. [b] Min. and dec. log.

***d,l*-Galaheptulose (*d,l*-Perseulose, D(L)-Gala-L(D)-fructo-heptose).**[19]—Equal amounts (0.2324 g.) of D-galaheptulose and of L-galaheptulose or L-perseulose[9] were dissolved in 1.5 cc. of warm water and 10 cc. of warm glacial acetic acid was added. Crystalline material was obtained on standing at icebox temperature and recrystallization was effected in the same manner; m. p. 136–137°. *d,l*-Galaheptulose crystallized in large, clear crystals that contained no water of hydration.

Anal. Calcd. for $C_7H_{14}O_7$: C, 40.00; H, 6.71. Found: C, 39.92; H, 6.59.

D-Glucoheptulose (D-Gluco-D-sorbo-heptose) from *keto*-D-Glucoheptulose Hexaacetate.[19]—*keto*-D-Glucoheptulose hexaacetate[1] (5.4 g.) was saponified with barium hydroxide at low temperatures as described for the synthesis of D-galaheptulose. The final sirup crystallized spontaneously and for filtration was stirred with 5 cc. of 80% ethanol; yield 1.9 g. (77%), m. p. 167–170° (softening at 165°), spec. rot. +65° (23°, c 2.5, H_2O, D line). Pure material was obtained on one recrystallization from water by the addition of absolute ethanol; m. p. 171–173° (softening at 168°), spec. rot. +67° (18°, c 2.6, H_2O, D line, no mutarotation). For D-glucoheptulose, Austin[28] recorded the values: m. p. 171–174° (softening at 167°), spec. rot. +67.5° (20°, c 2.5, H_2O, D line).

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Summary

1. The preparation of D-galactonic acid pentaacetate from *aldehydo*-D-galactose pentaacetate is described.

2. D-Arabonyl chloride tetraacetate and D-galactonyl chloride pentaacetate have been synthesized.

3. The ethyl ester of D-galactonic acid pentaacetate has been characterized.

4. The phenylhydrazides of D-galactonic acid pentaacetate and of D-gluconic acid (and monohydrate) pentaacetate are described and it is shown that the substances previously reported in the literature under these names are the corresponding hexaacetyl derivatives (D-galactonic (and D-gluconic) acid acetylphenylhydrazide pentaacetate).

5. 1-Diazo-1-desoxy-D-galaheptulose and its *keto*-pentaacetate have been synthesized.

6. *keto*-D-Galaheptulose hexaacetate was synthesized from 1-diazo-1-desoxy-*keto*-D-galaheptulose pentaacetate and on careful saponification yielded D-galaheptulose, enantiomorphic with perseulose.

7. *d,l*-Galaheptulose (*d,l*-perseulose) has been described.

8. D-Glucoheptulose has been prepared from its *keto*-acetate.

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[28] W. C. Austin, THIS JOURNAL, **52**, 2106 (1930).