The Formation of 2,7-Anhydro-α-L-*galacto*-heptulofuranose and 2,7-Anhydro-β-L-*galacto*-heptulopyranose by the Action of Acid on L-*galacto*-Heptulose (Perseulose)[1]

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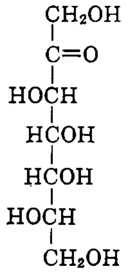
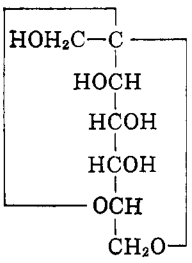
L-*galacto*-Heptulose has been transformed by hot dilute acid to give about a 5% yield of nonreducing anhydro sugars. Separation of the mixture on a Dowex 1 column (borate form) led to the isolation of about equal amounts of 2,7-anhydro-α-L-*galacto*-heptulofuranose and 2,7-anhydro-β-L-*galacto*-heptulopyranose, whose structures were established by the application of methods used earlier for similar compounds.

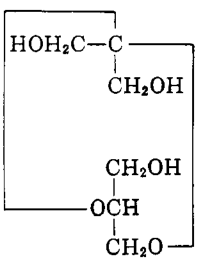
In the preceding paper on the transformation of reducing sugars to their nonreducing anhydrides in acid solution,[2] one of us showed that D-galactose is converted into 1,6-anhydro-α-D-galactofuranose and 1,6-anhydro-β-D-galactopyranose in yields of 0.95 and 0.71%, respectively. Since a heptulose with the *galacto* configuration was available, we now have studied the behavior of L-*galacto*-heptulose (perseulose, I)[3] and find that it, similarly, yields two crystalline anhydrides. Thus, L-*galacto*-heptulose, heated in 0.2 *N* sulfuric acid for three hours at 80°, gave about a 5% yield of nonreducing material. This was separated readily into two fractions on a column of Dowex 1 (borate form) by elution with sodium tetraborate.[2,4] The compound isolated from the fraction that formed a strong borate complex melted at 133–134° and showed $[\alpha]^{20}\mathrm{D}$ +25.5° in water. It was presumed to be the 2,7-anhydro-β-L-*galacto*-heptulopyranose II because it reacted with sodium metaperiodate with the consumption of two moles of reagent and the slow liberation of one mole of formic acid per mole of compound; this behavior resembled that of sedoheptulosan (2,7-anhydro-β-D-*altro*-heptulopyranose),[5] and the rotation of the expected dialdehyde was about equal in magnitude but opposite in sign to that observed in the periodate oxidation of sedoheptulosan. Final proof of the structure II was obtained by reducing the dialdehyde with sodium borohydride to the trihydric alcohol III, which has only one asymmetric carbon atom; the crystalline tri-*p*-toluenesulfonate of III was shown to be the enantiomorph of the corresponding compound derived similarly from sedoheptulosan. The trihydric alcohol (III) is readily recognized as 1,2-(1,3-dihydroxyisopropylidene)-D-glycerol [and as a 2,2,4-tris(hydroxymethyl)-1,3-dioxolane]; its enantiomorph, derived from sedoheptulosan, was, in fact, hydrolyzed to glycerol as part of its proof of structure.[5]



I

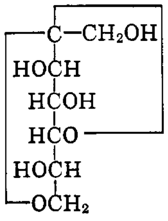


II

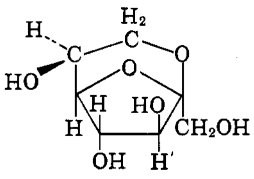


III

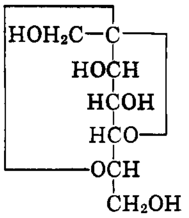
The fraction from the Dowex 1 column that did not form a borate complex yielded a nonreducing anhydroheptulose that melted at 134–135°, showed $[\alpha]^{20}\mathrm{D}$ −20.7° in water, and was not oxidized by periodate. By analogy with 1,6-anhydro-α-D-galactofuranose[6] and 2,7-anhydro-β-D-*altro*-heptulofuranose,[7] we should expect the new compound to be 2,7-anhydro-α-L-*galacto*-heptulofuranose (IV), with a locked pair of *trans* hydroxyl groups[8] at C-3 and C-4 (*cf.* the Haworth formula IVa). There are only two other formulas that might be written for a monomeric, nonreducing, periodate-resistant anhydroperseulose, namely, V and VI. These differ from IV in that each has a primary hydroxyl group at C-7. When the new anhydride was converted into its tetratosylate and the latter was heated with sodium iodide in 2,5-hexanedione for 75 hours at 100° there was no evidence of any exchange reaction and 63% of the tosylate was recovered. Since it is well known[9] that an ω-sulfonyloxy group of a sugar exchanges readily with sodium iodide to form an ω-deoxy-ω-iodo sugar under relatively mild condi-



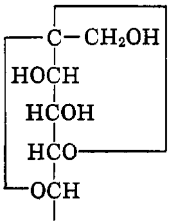
IV



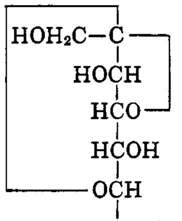
IVa



Va



Vb



VI

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[1] Presented in part before the Division of Carbohydrate Chemistry at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

[2] N. K. Richtmyer, *Arch. Biochem. Biophys.*, **78**, 376 (1958).

[3] E. B. Tilden, *J. Bacteriol.*, **37**, 629 (1939); R. M. Hann and C. S. Hudson, *J. Am. Chem. Soc.*, **61**, 336 (1939).

[4] J. X. Khym and L. P. Zill, *ibid.*, **74**, 2090 (1952).

[5] J. W. Pratt, N. K. Richtmyer, and C. S. Hudson, *ibid.*, **74**, 2200 (1952).

[6] For a review of the 1,6-anhydrohexofuranoses, see R. J. Dimler, *Advan. Carbohydrate Chem.*, **7**, 37 (1952).

[7] N. K. Richtmyer and J. W. Pratt, *J. Am. Chem. Soc.*, **78**, 4717 (1956).

[8] Other such sterically hindered vicinal glycols include: (a) the two *trans*-camphane-2,3-diols and cholestane-3β,6β,7α-triol [S. J. Angyal and R. J. Young, *ibid.*, **81**, 5467, 5251 (1959)]; (b) methyl 4,6-*O*-benzylidene-α-D-altropyranoside and its anomer [J. Honeyman and C. J. G. Shaw, *J. Chem. Soc.*, 2454 (1959)]; and (c) 2,6-anhydro-β-D-fructofuranose [H. R. Goldschmid and A. S. Perlin, *Can. J. Chem.*, **38**, 2178 (1960)].

[9] See R. S. Tipson, *Advan. Carbohydrate Chem.*, **8**, 181 (1953).

tions (whereas a sulfonyloxy group at C-1 of a ketose is resistant to exchange), we may conclude that neither formula V nor VI can represent our compound. This conclusion was substantiated by the fact that our compound yielded only a monotrityl derivative, just as had been found to occur with the two anhydrides of sedoheptulose,[7] neither of which has a primary hydroxyl group at C-7. Thus, the second anhydroperseulose must have the structure IV. Finally, the new anhydroperseulose was oxidized with lead tetraacetate in pyridine at 0°, a reagent that Goldschmid and Perlin[10] found would cleave even the sterically hindered vicinal diols; one molecular equivalent of reagent was consumed in about two hours, though overoxidation became evident on longer standing. This reaction is in agreement with what would be expected of a compound with the formula IV, and serves as additional evidence to exclude formula VI for the levorotatory anhydro-L-*galacto*-heptulose.

The mother liquor from the anhydride IV was chromatographed further on a cellulose column and a very small amount of a second nonreducing, orcinol-positive, periodate-resistant compound was obtained as a sirup that was not investigated further. It appears possible that perseulose upon acid treatment might yield, besides II and IV, other anhydrides such as V (which can be written either as the 2,5-anhydro-β-L-*galacto*-heptulopyranose Va or as the 2,6-anhydro-α-L-*galacto*-heptulofuranose Vb) or VI. A similar product was obtained from D-galactose and thought possibly to be 1,5-anhydro-α-D-galactofuranose.[2] Three examples of this rare type of nonreducing anhydro sugar, each with a five-membered and a six-membered ring, have been described previously: the 1,5-anhydro-β-D-ribofuranose of Vis and Fletcher,[11] the 2,6-anhydro-β-D-fructofuranose of Goldschmid and Perlin,[8c] and the sirupy 1,4-anhydro-2,3,6-tri-*O*-methyl-α-D-glucopyranose obtained by Pakhomov, Golova, and Nikolaeva[12] through the thermal decomposition of tri-*O*-methylcellulose *in vacuo*.[13]

A comparison of the mobilities on paper chromatograms of the known anhydroheptuloses is given in the Experimental section.

Experimental

The Reaction of L-*galacto*-Heptulose (Perseulose, I) with Dilute Acid and Isolation of the Nonreducing Material.—Preliminary experiments showed that when perseulose hemihydrate[3] in 0.2 *N* sulfuric acid was heated for 3 hr. at 80°; it lost about 9% of its reducing power as determined by the ferricyanide method.[14] At the same time, some further decomposition occurred, and about 1.5% of 5-(1,2-dihydroxyethyl)-2-furaldehyde (DHEF) was estimated to be present as calculated from its ultraviolet absorption spectrum.[7] For isolation of the products formed in this reaction, 120 g. of perseulose monohydrate was dissolved in 4 l. of 0.2 *N* sulfuric acid and the solution was heated quickly to 85° and then placed in an oven at 80° for 3 hr. The solution was cooled in running water, deacidified by passage through a column of Duolite A-4 ion-exchange resin, and concentrated *in vacuo* to a sirup from which most of the unchanged perseulose was crystallized by the addition of ethanol. A total of 392 g. of perseulose monohydrate was subjected to acid treatment in this way and 346 g. of it recovered. The rest of the perseulose in the mother liquor was destroyed by heating with an excess of aqueous barium hydroxide in an open, stainless steel container for several days. The solution was neutralized to phenolphthalein with a stream of carbon dioxide, filtered, and deionized with Amberlite IR-120 and Duolite A-4 ion-exchange resins. Concentration of the effluent *in vacuo* yielded 20 g. (*ca.* 5%) of a colorless sirup. Paper chromatograms, spotted with this sirup and developed in 1-butanol–pyridine–water (6:4:3) by the multiple ascent technique, revealed four spots that could be visualized with an orcinol–hydrochloric acid spray. The slowest, in trace amounts, was identified as perseulose, while the other three ran considerably faster and were nonreducing. Of these three, only the slowest was oxidizable by periodate sprays.

2,7-Anhydro-α-L-*galacto*-heptulofuranose (IV).—A 7-g. portion of the sirup described above was dissolved in 100 ml. of 0.005 *M* aqueous sodium tetraborate and the solution passed through a column (10 cm. × 3.5 cm.) of Dowex 1 strong-base ion-exchange resin in the borate form.[2,4] The resin was eluted with 0.005 *M* borate; five 200-ml. portions were sufficient to remove the two noncomplexing anhydroheptuloses as tested for with Brown's orcinol–ferric chloride reagent.[15] When the next liter of 0.005 *M* borate removed nothing further, a shift was made to 0.1 *M* aqueous sodium tetraborate and the complexing material removed by elution. The remainder of the original sirup was separated into noncomplexing and complexing fractions similarly.

The 0.005 *M* borate fractions were combined, freed from cations by passage through Amberlite IR-120, concentrated *in vacuo* to a mixture of anhydroheptuloses and boric acid, and the latter was removed by several distillations of methanol from the residue. The final sirup weighed 9 g. and was crystallized without difficulty. The 5.7 g. of 2,7-anhydro-α-L-*galacto*-heptulofuranose (IV) thus obtained was recrystallized thrice from methanol to form chunky prisms melting at 134–135° and showing $[\alpha]^{20}\mathrm{D}$ −20.7° in water (*c* 1.8). It was not oxidized by sodium metaperiodate in 30 hr. at 20°. Arthur S. Perlin has kindly measured its oxidation with an excess (3 moles/mole) of lead tetraacetate in pyridine at 0° and reports 0.25, 0.40, 0.77, 1.03, and 1.19 moles of oxidant/mole of compound consumed at the end of 10, 20, 60, 120, and 180 min., respectively. He obtained similar values of 0.36, 0.66, and 1.25 for 1,6-anhydro-α-D-galactofuranose and 0.70, 0.99, and 1.34 for 2,7-anhydro-β-D-*altro*-heptulofuranose at the end of 15, 30, and 180 min., respectively. Overoxidation was evident in all three cases.

Anal. Calcd. for $C_7H_{12}O_6$: C, 43.75; H, 6.30; mol. wt., 192.2. Found: C, 43.77; H, 6.39; mol. wt. (Mechrolab vapor pressure osmometer), 188.5.

The mother liquor from the 5.7 g. of IV was chromatographed on a cellulose column (36 cm. × 4 cm.) with acetone–water (95:5) as eluent. The principal and fastest-moving component was the same anhydroheptulose IV; it was followed by a slower-moving, nonreducing, periodate-negative heptulose derivative presumed to be the anhydride V; traces of perseulose appeared also in the latter fractions. The third anhydride was very small in amount, did not crystallize, and has not been investigated further.

2,7-Anhydro-1,3,4,6-tetra-*O*-*p*-tolylsulfonyl-α-L-*galacto*-heptulofuranose.—A solution of 0.5 g. of the anhydroheptulose IV and 6 g. of *p*-toluenesulfonyl chloride in 25 ml. of dry pyridine was kept at room temperature for 4 days and then poured onto cracked ice. A granular product (1.8 g.; 85%) was deposited, and became crystalline when a solution of it in 95% ethanol was allowed to evaporate slowly at 5°. It was recrystallized once from hot ethanol and twice from acetone–ethanol, forming fine needles with m.p. 115–118° and $[\alpha]^{20}\mathrm{D}$ −5.9° in chloroform (*c* 1).

Anal. Calcd. for $C_{35}H_{36}O_{14}S_4$: C, 51.97; H, 4.49; S, 15.85. Found: C, 52.20; H, 4.79; S, 16.16.

When the tetra-*O*-tosyl compound was heated with sodium iodide in 2-butanone for 6 hr. at 80°, no sodium tosylate separated and 93% of the starting material was recovered. Even after 75 hr. in 2,5-hexanedione at 100° no sodium tosylate was obtained and from the dark-colored reaction mixture 63% of the tetratosylate was recovered unchanged.

2,7-Anhydro-1-*O*-triphenylmethyl-α-L-*galacto*-heptulofuranose.—A solution of 0.5 g. of the anhydroheptulose IV and 2.6 g. (3.6 molecular equivalents) of chlorotriphenylmethane in 25 ml.

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[10] H. R. Goldschmid and A. S. Perlin, *Can. J. Chem.*, **38**, 2280 (1960)

[11] E. Vis and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **79**, 1182 (1957).

[12] A. M. Pakhomov, O. P. Golova, and I. I. Nikolaeva, *Izv. Akad. Nauk, SSSR, Otd. Khim. Nauk*, 521 (1957).

[13] Note added February 8, 1963: see also E. Husemann and J. Klar, *Makromol. Chem.*, **53**, 223 (1962), for three additional methods of preparing the anhydride of 2,3,6-tri-*O*-methyl-D-glucose.

[14] C. S. Hanes, *Biochem. J.*, **23**, 99 (1929); H. C. Hagedorn and B. N. Jensen, *Biochem. Z.*, **135**, 46 (1923).

[15] A. H. Brown, *Arch. Biochem.*, **11**, 269 (1946).

of dry pyridine was left at room temperature for 3 days and then poured onto cracked ice. After standing overnight at 5° the precipitated solid was filtered and washed with cold water; wt., 2.9 g., $[\alpha]^{20}D$ $-7.5°$ in chloroform. Trityl derivative was freed from the large amount of contaminating triphenylmethanol by crystallization from chloroform–pentane and ethanol–pentane; after two additional recrystallizations from the latter solvent pair and a final one from acetone–water, the prismatic needles of the trityl derivative of the anhydroheptulose IV melted at 190–192° and showed $[\alpha]^{20}D$ $-36.8°$ in chloroform (*c* 0.4). By a comparison of the two rotations the amount of trityl derivative in the 2.9 g. of crude product could be estimated as 0.6 g. (53%).

Anal. Calcd. for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03. Found: C, 72.10; H, 6.30.

2,7-Anhydro-β-L-*galacto*-heptulopyranose (II).—The 0.1 *M* sodium tetraborate eluate from the Dowex 1 column was decationized and freed from boric acid as described for the 0.005 *M* borate eluate. The solution, some of which was spilled accidentally, was concentrated *in vacuo* to a sirup that weighed 6 g. and showed $[\alpha]^{20}D$ $+18°$ in water. It failed to crystallize, even after being run through columns of Amberlite IR-120 and IRA-400 ion-exchange resins (the latter to remove any lactones and traces of perseulose); however, when the new sirup was chromatographed on a column of cellulose powder and eluted with 95% aqueous acetone, a number of the fractions crystallized spontaneously. Combination of the appropriate fractions yielded 2.8 g. of crystalline product from ethanol, and after several recrystallizations from water–acetone the fluffy needles of the 2,7-anhydro-β-L-*galacto*-heptulopyranose (II) melted at 133–134° and showed $[\alpha]^{20}D$ $+25.5°$ in water (*c* 2.4). A small sample of the material, when oxidized with an excess of sodium metaperiodate, consumed 1.94 and 1.95 moles of oxidant per mole of compound after 23 and 48 hr., respectively. The amount of formic acid liberated was 0.33 mole after 23 hr. and 1.2 moles after 19 days; the slow liberation of acid resembles the similar behavior of sedoheptulosan toward periodate.[5] The rotation also changed slowly, becoming constant only after 8 days; the rotation $[\alpha]^{20}D$ $+13.3°$, calculated as the expected dialdehyde, was of opposite sign and somewhat smaller in magnitude than the $-16.9°$ reported for the oxidation of sedoheptulosan.[5]

Anal. Calcd. for $C_7H_{12}O_6$: C, 43.75; H, 6.30; mol. wt., 192.2. Found: C, 43.75; H, 6.33; mol. wt. (Mechrolab vapor pressure osmometer), 184.4.

Periodate Oxidation of 2,7-Anhydro-β-D-*altro*-heptulopyranose (Sedoheptulosan). 1,2-(1,3-Dihydroxyisopropylidene)-L-glycerol Tri-*p*-toluenesulfonate.—To an ice-cold solution of 6.1 g. of sedoheptulosan hydrate in 100 ml. of water was added 180 ml. of 0.5 *M* aqueous sodium metaperiodate and, after 15 min. in the ice bath, the solution was left at room temperature for 10 days. Aqueous barium chloride was added to precipitate the iodate and excess of periodate ions, and the solution was filtered and deionized with Amberlite IR-120 and Duolite A-4 ion-exchange resins. The solution of dialdehyde was concentrated to 50 ml., decolorized with a small amount of carbon, added dropwise to a stirred solution of 3.6 g. of sodium borohydride in 50 ml. of water, and the mixture was stirred for an additional 2 hr. The next morning the excess borohydride was destroyed by the dropwise addition of 45 ml. of acetone; cations were removed by passage of the solution through Amberlite IR-120; and the liberated boric acid was removed by concentrating the solution *in vacuo* and distilling several portions of methanol from the residue. The final sirupy product weighed 2.4 g. (50% over all from sedoheptulosan).

A 0.7-g. portion of this sirup and 13 g. of *p*-toluenesulfonyl chloride were dissolved in 75 ml. of dry pyridine. After 2 days at room temperature the mixture was poured onto cracked ice and the resulting gum and aqueous layer were extracted with chloroform. The chloroform solution was washed in succession with ice-cold sulfuric acid, water, aqueous sodium bicarbonate, and water, dried with sodium sulfate, filtered with a small amount of carbon, and concentrated to 2.2 g. of sirup. A small sample of the sirup in a relatively large volume of 95% ethanol crystallized when kept in the refrigerator over a weekend. Crystallization of the main portion of sirup from chloroform–pentane proceeded slowly to yield 1.7 g. (64%). This product was recrystallized first from 60 ml. of hot 95% ethanol, and then twice from acetone–water. The prismatic needles of the tri-*O*-tosyl compound melted at 91–94° and showed only a small rotation, $[\alpha]^{20}D$ $+1.7°$ in chloroform (*c* 0.9).

Anal. Calcd. for $C_{27}H_{30}O_{11}S_3$: C, 51.74; H, 4.83; S, 15.35. Found: C, 52.02; H, 4.93; S, 15.05.

1,2-(1,3-Dihydroxyisopropylidene)-L-glycerol tri-*p*-nitrobenzoate was prepared by the action of *p*-nitrobenzoyl chloride on another portion of the sirup in dry pyridine in the usual manner. A great deal of difficulty was encountered in obtaining a pure product, but after two recrystallizations from acetone–pentane, two from acetone–water, and one from pyridine–water, the final product (small, grayish, prismatic needles) melted at 175–178° and gave a satisfactory analysis.

Anal. Calcd. for $C_{27}H_{21}N_3O_{14}$: C, 53.03; H, 3.46; N, 6.87. Found: C, 53.13; H, 3.19; N, 6.98.

Periodate Oxidation of 2,7-Anhydro-β-L-*galacto*-heptulopyranose (II). 1,2-(1,3-Dihydroxyisopropylidene)-D-glycerol Tri-*p*-toluenesulfonate.—One gram of the anhydroperseulose II was oxidized in the same manner as sedoheptulosan and the dialdehyde reduced with sodium borohydride to the dioxolane (III); the resulting sirup was tosylated to yield a crystalline product weighing 0.35 g. Recrystallization to constant m.p. from acetone–water gave prismatic needles melting at 92–95°, as compared to 91–94° for the tritosylate from sedoheptulosan. The amount of purified material was so small and the rotation of the compound so small in magnitude that no satisfactory comparison of rotations with the enantiomorph could be made. However, since the infrared spectrum of this tritosylate in chloroform solution was almost identical with that of the tritosylate obtained from sedoheptulosan as described earlier, and the melting point of a mixture of the two substances was depressed to 78–89°, the enantiomorphous nature of the two tosylates was considered to be confirmed thereby.

Anal. Calcd. for $C_{27}H_{30}O_{11}S_3$: C, 51.74; H, 4.83; S, 15.35. Found: C, 51.86; H, 4.58; S, 15.31.

Mobilities of 2,7-Anhydro Heptuloses on Paper Chromatograms.—With sedoheptulosan as a readily available standard, the mobilities of the known 2,7-anhydrides of the heptuloses in 1-butanol–pyridine–water (6:4:3) on Whatman no. 1 paper by the descending method are as follows: anhydro-*galacto*-heptulofuranose, 1.78; anhydro-*manno*-heptulopyranose, 1.53; anhydro-*gluco*-heptulopyranose, 1.50; anhydro-*galacto*-heptulopyranose, 1.46; anhydro-*altro*-heptulofuranose, 1.40; anhydro-*ido*-heptulopyranose, 1.39; anhydro-*gulo*-heptulopyranose, 1.29; and the standard, anhydro-*altro*-heptulopyranose, 1.00. The mobility of the third anhydro-*galacto*-heptulose (V?) is intermediate between the mobilities of the other two forms (II and IV), but a definite value is not available.

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