intervals of a minute or more, transferred to flasks containing a measured excess of perchloric acid in ethanol and back-titrated. The second order rate constant varied from 8.6 to 10.0 with no obvious trend.

Acknowledgments.—I am very grateful to Dr. Joseph C. Aub for his generous support, to Dr. Robert B. Woodward for many helpful discussions, and to Miss Yvette Delabarre of Brookhaven for carrying out most of the radioassays herein reported.

BOSTON 14, MASSACHUSETTS RECEIVED MARCH 19, 1951

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, FEDERAL SECURITY AGENCY]

The Preparation of Crystalline 6-Desoxy-L-glucose (L-Epirhamnose) from D-Gluco-D-*gulo*-heptose

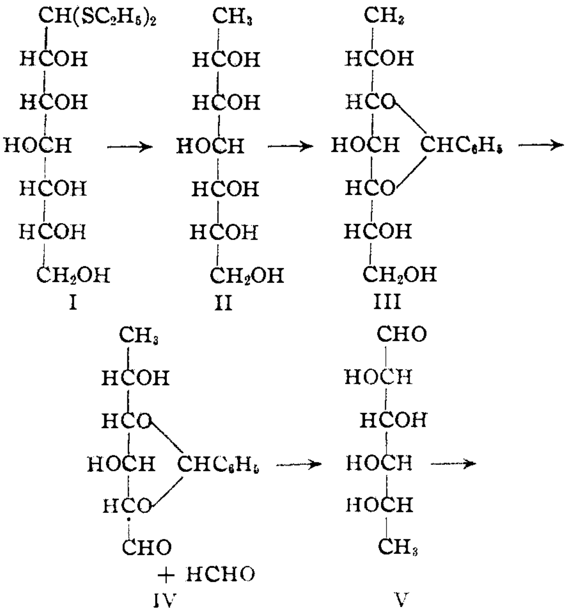
BY EMMANUEL ZISSIS, NELSON K. RICHTMYER AND C. S. HUDSON

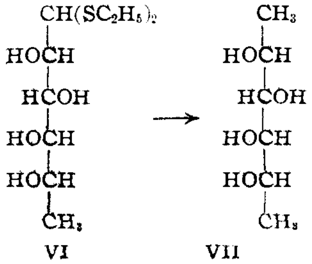
The steps here described for the preparation of 6-desoxy-L-glucose are the reductive desulfurization of D-gluco-D-*gulo*-heptose diethyl mercaptal to 1-desoxy-D-gluco-D-*gulo*-heptitol, a condensation with benzaldehyde and the oxidative cleavage with lead tetraacetate of the 3,5-benzylidene derivative of the desoxyheptitol, followed by subsequent removal of the benzylidene group by hydrolysis. The free sugar crystallized as an α form, mutarotating from $[\alpha]^{20}D$ −99.7 to −29.9° in water. Reductive desulfurization of 6-desoxy-L-glucose diethyl mercaptal yielded 1,6-didesoxy-L-glucitol (synonym, 1,6-didesoxy-D-gulitol), which was characterized through its crystalline acetyl and benzylidene derivatives.

6-Desoxy-D-glucose occurs in nature as a component of several glycosides, and it has been obtained synthetically through the reduction of a glucose derivative containing a bromine atom in place of the hydroxyl group on carbon 6. The sugar was crystallized as early as 1911 by Votoček.[1] The enantiomorphous 6-desoxy-L-glucose (isorhamnose; epirhamnose),[2] on the other hand, has been known until now only as a sirup with $[\alpha]D$ about −30°; its preparation was accomplished by Fischer and Herborn[3a] and by Votoček and Mikšič[3b] through the sodium amalgam reduction of L-epirhamnonic lactone which, in turn, was obtained by epimerization of L-rhamnonic lactone in aqueous pyridine.

For our new procedure the starting material was D-gluco-D-*gulo*-heptose, which was converted first to the known diethyl mercaptal (I), and then, by reductive desulfurization with Raney nickel, to 1-desoxy-D-gluco-D-*gulo*-heptitol (II). Upon reaction of the last-named substance with benzaldehyde and concentrated hydrochloric acid, a monobenzylidene derivative was obtained in 84% yield. The formation of a monobenzylidene derivative of II was to be expected, for Fischer[4] had found that the closely related gluco-*gulo*-heptitol produced only a monobenzylidene derivative, and that in nearly quantitative yield; later, Hann, Ness and Hudson[5] proved by periodate oxidation that the benzylidene group was attached at carbons 3 and 5 of the heptitol molecule. Similarly, our substance was shown to be the analogous 3,5-benzylidene derivative III, for upon oxidation with lead tetraacetate it consumed only one molar equivalent of oxidant and the resulting product (besides formaldehyde) was a sirupy, six-carbon aldehyde that must have been 2,4-benzylidene-6-desoxy-L-glucose (IV); its mild acid hydrolysis then yielded the desired 6-desoxy-L-glucose (V).

The 6-desoxy-L-glucose thus obtained crystallized without difficulty and like the antipodal 6-desoxy-D-glucose it was presumably an α form as judged by the course of its mutarotation in water. Final $[\alpha]^{20}D$ values of −29.9 and −30.1° (*c*, 2) were observed for samples of both needle and prism





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[1] E. Votoček, *Ber.*, **44**, 819 (1911).

[2] It may be of interest to note that thevetose, the 3-methyl ether of 6-desoxy-L-glucose, occurs in nature as a constituent of several cardiac glycosides from *Thevetia neriifolia* Jussieu, *Tanghinia venenifera* Poir. and *Cerbera Odollam* Gaertn. The synthesis of thevetose from L-glucose has been described by F. Blindenbacher and T. Reichstein [*Helv. Chim. Acta*, **31**, 1669 (1948)]; pertinent references to the earlier literature are given in their publication.

[3] (a) E. Fischer and H. Herborn, *Ber.*, **29**, 1961 (1896); (b) E. Votoček and J. Mikšič, *Bull. soc. chim. France*, [4] **43**, 220 (1928).

[4] E. Fischer, *Ann.*, **270**, 64 (1892); *Ber.*, **27**, 1524 (1894).

[5] R. M. Hann, A. T. Ness and C. S. Hudson, THIS JOURNAL, **68**, 1769 (1946).

forms. For the D-antipode, Votoček[1] reported $[\alpha]^{20}_{D}$ +31.5° (*c*, 10), Fischer and Zach[6] reported $[\alpha]^{20}_{D}$ +29.7° (*c*, 8.5), and Freudenberg and Raschig[7] reported $[\alpha]^{20}_{D}$ +30.8° (*c*, 9.1) and $[\alpha]^{18}_{D}$ +31.5° (*c*, 16). Data on the mutarotation are given in the Experimental part.

The reductive desulfurization of 6-desoxy-L-glucose diethyl mercaptal (VI)[1] with Raney nickel has led to the production of sirupy 1,6-didesoxy-L-glucitol (synonym, 1,6-didesoxy-D-gulitol) (VII), which has been characterized through its crystalline tetraacetyl and dibenzylidene derivatives.

Experimental

D-Gluco-D-*gulo*-heptose Diethyl Mercaptal (I).—A mixture of 25 g. of powdered D-gluco-D-*gulo*-heptose and 50 ml. of concentrated hydrochloric acid was shaken for about ten minutes to dissolve most of the sugar and then, as the solution began to assume a reddish color, 50 ml. of ethyl mercaptan was added and shaking was continued for 2.5 hours. The contents of the flask had solidified almost completely, and the product was allowed to stand overnight in the refrigerator. About 50 ml. of cold water was added, and the mercaptal filtered and washed with cold ethanol. The yield, after one recrystallization from ten parts of ethanol, was 23.5 g. (62%). Although this substance was first prepared many years ago by Fischer,[8] only its melting point (152–154°) was reported. Our product separated as needles and after four recrystallizations melted at 155–156° and showed $[\alpha]^{20}_{D}$ −7.7° in pyridine (*c*, 2) and −30.5° in water (*c*, 1).

Anal. Calcd. for $C_{11}H_{24}O_6S_2$: C, 41.75; H, 7.64; S, 20.26. Found: C, 41.74; H, 7.53; S, 20.56.

1-Desoxy-D-gluco-D-*gulo*-heptitol (= 7-Desoxy-L-gluco-L-*gulo*-heptitol) (II).[9]—Reductive desulfurization of the mercaptal (I) was accomplished by refluxing 20 g. of it with 135 g. of freshly prepared Raney nickel in 500 ml. of 70% ethanol for two hours. The ethanol solution was decanted, and the residue was washed thoroughly by digestion on the steam-bath with three 500-ml. portions of water. The combined solutions were deionized and then concentrated *in vacuo* to a thick sirup which crystallized spontaneously. Crystallization from absolute ethanol yielded 9.4 g. (76%) of the desired desoxyheptitol as clusters of needles. After three recrystallizations the product melted at 124–125° and showed $[\alpha]^{20}_{D}$ +6.8° in water (*c*, 1). In 5% aqueous ammonium molybdate (*c*, 0.40),[10] the $[\alpha]^{20}_{D}$ value was −29.3°; when 20 ml. of that solution was acidified with 5 ml. of *N* sulfuric acid, the $[\alpha]^{20}_{D}$ value was +47.3° (*c*, 0.32).

Anal. Calcd. for $C_7H_{16}O_6$: C, 42.85; H, 8.22. Found: C, 42.93; H, 8.19.

1-Desoxy-3,5-benzylidene-D-gluco-D-*gulo*-heptitol (= 3,5-Benzylidene-7-desoxy-L-gluco-L-*gulo*-heptitol) (III).—Condensation of 5 g. of the desoxyheptitol (II) with 5 ml. of benzaldehyde and 10 ml. of concentrated hydrochloric acid followed the procedure that was applied to gluco-*gulo*-heptitol by Hann, Ness and Hudson.[5] The crude product was recrystallized from 100 parts of water as long rods in a yield of 6.1 g. (84%). After three additional recrystallizations the benzylidene compound III melted at 183–185°, and showed $[\alpha]^{20}_{D}$ +13.3° in pyridine (*c*, 0.4); it was only slightly soluble in chloroform.

Anal. Calcd. for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.30; H, 7.18.

1-Desoxy-2,3,4,5,6,7-tribenzylidene-D-gluco-D-*gulo*-heptitol.—Accompanying the monobenzylidene compound (III) was a small amount of material that was insoluble in water. After two recrystallizations from ethanol as needles it melted at 193–197° and had the composition of a tribenzylidenedesoxyheptitol.

Anal. Calcd. for $C_{28}H_{28}O_6$: C, 73.02; H, 6.13. Found: C, 73.15; H, 6.28.

Oxidation of 1-Desoxy-3,5-benzylidene-D-gluco-D-*gulo*-heptitol (III) to 2,4-Benzylidene-6-desoxy-L-glucose (IV) and Preparation of Crystalline 6-Desoxy-α-L-glucose (V).—A preliminary oxidation of compound III with lead tetraacetate according to the procedure described by Hockett and McClenahan[11] indicated that the reaction was complete within 24 hours and that only one mole of oxidant was consumed. Accordingly, 24.5 g. of the benzylidenedesoxyheptitol was partially dissolved in 2500 ml. of glacial acetic acid, 45 g. of lead tetraacetate (1.2 molar equivalents) was added, and the mixture was shaken occasionally for three hours until solution was complete. After 20 hours, hydrogen sulfide was bubbled into the solution, the lead sulfide was removed by filtration, and the filtrate was concentrated *in vacuo* to about 300 ml. An equal volume of water was then added, and the solution was refluxed for three hours to effect hydrolysis of the benzylidene group. Removal of the acetic acid, benzaldehyde and water by concentration *in vacuo* left 14 g. of a thick sirup which crystallized readily when rubbed with acetone. The yield of crude 6-desoxy-L-glucose was 9.4 g. (66%).

Fischer and Zach[6] recrystallized their antipodal 6-desoxy-D-glucose from ethyl acetate and noted that the sugar apparently existed in two different forms. We found that 6-desoxy-L-glucose may separate either as prisms or as clusters of needles, with both forms often appearing at the same time. By dissolving the sugar in a small amount of warm methanol, adding a somewhat larger amount of ethyl acetate, and inoculating the solution with the needle form, we could obtain that type of crystal regularly. However, on standing for several days at room temperature the needles usually redissolved and were replaced by prisms. Both needle and prism forms were solvent free and had practically identical melting points, the two purified samples melting at 143–145° and 142–144°, respectively. A mixed melting point showed no depression.

Measurements of the mutarotation in water (*c*, 2) were made on twice-recrystallized samples of both prism and needle forms of 6-desoxy-L-glucose. Calculations of the velocity constants, $k_1 + k_2$, in minutes and decimal logarithms, showed the mutarotations to be unimolecular in type and of the same order of magnitude. Thus, the prisms had an extrapolated initial $[\alpha]^{20}_{D}$ −84.7°, the first observed reading being −79.0° at 3.2 minutes, and a final value of −30.1° (three hours), with $k_1 + k_2 = 0.0149$; the needles had an extrapolated initial $[\alpha]^{20}_{D}$ −99.7°, the first observed reading being −89.0° at 4.5 minutes, and a final value of −29.9° (three hours), with $k_1 + k_2 = 0.0161$. Fischer and Zach[6] reported for their synthetic 6-desoxy-D-glucose in water (*c*, 8.5) a final $[\alpha]^{20}_{D}$ +29.7° (three hours, constant), and intermediate values from which may be calculated that $k_1 + k_2 = 0.0111$ and that the initial $[\alpha]^{20}_{D}$ was +79.3°. Votoček[1] has reported $[\alpha]^{20}_{D}$ +31.5° for the equilibrium rotation of "isorhodeose" from purginic acid, and Freudenberg and Raschig[7] found $[\alpha]^{20}_{D}$ +30.8° for that of "quinovose" prepared from cinchona bark.

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: (needles) C, 44.04; H, 7.38; (prisms) C, 43.97; H, 7.39.

6-Desoxy-L-glucose Diethyl Mercaptal (VI).—One gram of crystalline 6-desoxy-L-glucose was shaken for 20 hours with 10 ml. of ethyl mercaptan and 2 g. of fused zinc chloride. Excess mercaptan was removed by decantation, and the viscous residue was stirred with ice-water to dissolve the inorganic material and to initiate crystallization of the mercaptal. The filtered product, plus a second crop obtained by concentration of the mother liquor, weighed 1.3 g. (79%). The mercaptal was recrystallized several times from chloroform by the addition of pentane, forming small needles melting at 97–98° and showing $[\alpha]^{20}_{D}$ +47.1° in water (*c*, 1). The melting point is in agreement with that reported by Fischer and Herborn[8a] who prepared the same compound from sirupy 6-desoxy-L-glucose; they used concentrated hydrochloric acid as the condensing agent, crystallized the product from ether, and gave no value for the specific rotation.

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(6) E. Fischer and K. Zach, *Ber.*, **45**, 3761 (1912).

(7) K. Freudenberg and K. Raschig, *ibid.*, **62**, 373 (1929).

(8) E. Fischer, *Ber.*, **27**, 673 (1894); the hexaacetyl derivative has been described by M. L. Wolfrom, M. Konigsberg and F. B. Moody, This Journal, **62**, 2343 (1940).

(9) Footnote added Aug. 31, 1951.—The hexaacetyl derivative of this compound has recently crystallized. It separated from aqueous ethanol as large prisms of m.p. 53–58° and $[\alpha]^{20}_{D}$ −7.8° in chloroform (*c*, 0.66). *Anal.* Calcd. for $C_{19}H_{28}O_{12}$: C, 50.89; H, 6.29; CH_3CO, 57.6. Found: C, 51.01; H, 6.29; CH_3CO, 58.7.

(10) See N. K. Richtmyer and C. S. Hudson, This Journal, **73**, 2249 (1951).

(11) R. C. Hockett and W. S. McClenahan, *ibid.*, **61**, 1667 (1939).

1,6-Didesoxy-L-glucitol (= 1,6-Didesoxy-D-gulitol) (VII).—Desulfurization of 10.7 g. of the mercaptal VI with 110 g. of Raney nickel in the usual manner yielded 5 g. of a sirup which failed to crystallize in the course of several days. In order to characterize the 1,6-didesoxy-L-glucitol, therefore, the sirup was dissolved in 10 ml. of concentrated hydrochloric acid, the mixture was cooled to 0°, and 5 ml. of benzaldehyde was added. Crystallization occurred immediately, and after one hour at 0° the mixture was diluted with ice water, filtered, washed and dried. The crude product weighed 7 g. Three recrystallizations from absolute ethanol furnished fine needles of a substance which was shown by analysis to be 1,6-didesoxy-2,3,4,5-dibenzylidene-L-glucitol. It melted at 171–173° when heated at the rate of 0.5° per minute and at 176–178° when heated 2° per minute. The $[\alpha]^{20}D$ value was +12.1° in chloroform (*c*, 4).

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.59; H, 6.80. Found: C, 73.51; H, 7.00.

The mother liquors from the recrystallization of the dibenzylidene compound yielded about 0.4 g. of a levorotatory substance ($[\alpha]^{20}D$ −3.2° in chloroform) which, after four recrystallizations from a mixture of chloroform and pentane as needles, melted at 170–172°. From its analysis it is presumed to be a 1,6-didesoxymonobenzylidene-L-glucitol.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.71; H, 7.68.

1,6-Didesoxy-2,3,4,5-tetraacetyl-L-glucitol.—Acetylation of 2.7 g. of sirupy 1,6-didesoxy-L-glucitol (VII) by heating with 0.7 g. of fused sodium acetate and 12 ml. of acetic anhydride for two hours on the steam-bath, followed by pouring the solution on cracked ice, produced an oil which crystallized when the mixture was left overnight in the refrigerator. The acetate weighed 3.6 g. It separated from chloroform upon the addition of ether and pentane as clusters of acicular prisms; after three such recrystallizations it melted at 80–82° and showed $[\alpha]^{20}D$ −25.5° in chloroform (*c*, 1).

Anal. Calcd. for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97; CH_3CO, 54.1. Found: C, 52.96; H, 6.99; CH_3CO, 54.3.

Acknowledgment.—The authors wish to thank Mr. John T. Sipes for preparing the D-gluco-D-*gulo*-heptose, and Mr. William C. Alford, Mrs. Margaret M. Ledyard, Miss Paula M. Parisius and Mrs. Evelyn G. Peake for carrying out the microchemical analyses.

BETHESDA, MARYLAND RECEIVED MARCH 9, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE PURDUE RESEARCH FOUNDATION, PURDUE UNIVERSITY]

The Reactions of Succinic Anhydride with Hydrazine Hydrate[1,2,3]

BY HENRY FEUER, G. BRYANT BACHMAN AND EMIL H. WHITE[4]

The reaction of succinic hydrazide with hydrazine hydrate has been studied under various conditions. Previous investigators have obtained only oily products. We have found that disuccinhydrazide diacid, succinhydrazide and polysuccinhydrazide may be obtained according to the relative amounts of the reagents used and the conditions employed. The reaction to form succindihydrazide has been shown to involve disuccinhydrazide diacid and the hydrazonium salt of succinhydrazide monoacid as intermediates. Cyclic succinhydrazide, a new compound, has been prepared by the reduction of cyclic maleic hydrazide. Its properties indicate that earlier investigators who report cyclic succinhydrazide had actually prepared polysuccinhydrazide. Perhydro-1,4,6,9-tetraketopyridazo-(1,2-a)-pyridazine, representing a new bicyclic system, has been prepared by the reaction of cyclic succinhydrazide with succinyl chloride or diethyl succinate.

In an attempt to prepare succindihydrazide (III) by treating succinic anhydride with hydrazine hydrate, it was discovered that several products are formed, depending upon the reaction conditions. The literature contains only one reference to the above reaction, the authors[5] stating that an oil was obtained as the only product. We have found that this reaction is an excellent method for the preparation of disuccinhydrazide diacid (I), succindihydrazide (III) and a polymeric material to which the name polysuccinhydrazide (IV) is assigned. Compound I is produced as an immediate precipitate by the addition of one-half mole of hydrazine hydrate to one mole of succinic anhydride in ethanol. Addition of more than this quantity of hydrazine hydrate leads to dissolution of I and separation of an oil phase. The latter is probably the oil to which Alexa[5] referred. Heating converts the oil into compound III which dissolves in the ethanolic phase. The data of Table I indicate that the oil first formed is composed of compounds I and II, and excess hydrazine hydrate. As heating proceeds, the oil becomes richer in II. The acids I and II exist, no doubt, in the oil phase in the form of their hydrazonium salts. Compound II can be isolated as the hydrazonium salt if the oil is evaporated *in vacuo* for several days. However, a part of the acid is dehydrated by this operation to succindihydrazide (III). It is preferable to determine the amount of II in the oil phase by isolating its monobenzal derivative.

TABLE I

COMPOSITION OF THE OIL PHASE[a]

Initial temp., °C.	Reaction time,	Reaction temp., °C.	Hydrazine hydrate, %	Disuccinhydrazide diacid (I), %	Succinhydrazide monoacid (II), %	Ratio of (I) to (II)
30	1 min.	30	29.3	60.7	14.0	4.34
70	10 min.	60	21.9	51.3	15.4	3.33
70	15 hr.	30	32.8	37.9	32.0	11.8
70	10 hr.	60	27.9	35.6	39.3	0.91

[a] In these runs, succindihydrazide was not detected in the oil phase.

Polysuccinhydrazide (IV) is obtained by the reaction of equimolar quantities of succinic anhydride and hydrazine hydrate, with or without a solvent. It is an extremely insoluble material, for which no suitable solvent has been found. Alkali decomposes it to hydrazine hydrate and a salt of succinic acid. Refluxing with hydrazine

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(1) Presented before the Division of Organic Chemistry at the Chicago Meeting of the American Chemical Society, September 7, 1950.

(2) Abstracted from a thesis by Emil H. White, submitted to the Faculty of the Graduate School of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, February, 1950.

(3) Financial support of this research was supplied by the United States Office of Naval Research.

(4) Department of Chemistry, University of Chicago, Chicago, Illinois.

(5) V. Alexa and G. Gheorghiu, *Bull. soc. chim.*, [4] 49, 1112 (1931).