Summary

The reductive desulfurization of D-mannose diethyl mercaptal by Raney nickel has yielded 1-desoxy-D-mannitol which was proved to be identical with 6-desoxy-D-mannitol (= D-rhamnitol). This furnishes a very simple and direct experimental proof of the equivalence of carbon atoms 1 and 6 in D-mannitol.

Reductive desulfurization of the mercaptals of higher-carbon sugars provides a new method of correlating these sugars, through their alcohols, with the higher-carbon ω-desoxy sugars which may be synthesized from L-fucose, L-rhamnose, etc. The configurations of such higher-carbon ω-desoxy sugars may thus be established in an absolute manner.

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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY AND CHEMOTHERAPY, EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

A Definitive Proof that "α-Fucohexose" Is 7-Desoxy-L-gala-D-*manno*-heptose

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

The addition of hydrogen cyanide to fucose (L-fucose; 6-desoxy-L-galactose) was effected first by Mayer and Tollens,[1] while the corresponding addition of cyanide to the enantiomorphous rhodeose (D-fucose) was described shortly afterward by Votoček[2] and especially by Krauz.[3] Some years later Votoček[4] studied both of these reactions and their products in considerable detail, preparing many derivatives of the "fucohexonic" and "rhodeohexonic" acids and also of "α-fuchohexose." By the application of the amide rule of rotation[5]—the methylamide of "α-fucohexonic" acid is levorotatory whereas that of the β acid is dextrorotatory—Votoček concluded that in the α series the hydroxyl on carbon 2 is on the left, and that "α-fucohexose" has the configuration shown in formula I. In the same manner, application of Levene's rule of rotation for the salts of aldonic acids[6]—the barium salt of the "α-fucohexonic" acid was levorotatory whereas that of the β acid was dextrorotatory—led Votoček to the same conclusion regarding the configuration at carbon 2 in "α-fucohexose" (I). Furthermore the benzylphenylhydrazone of that sugar was dextrorotatory in agreement with the generalization first noted by one of us[7] and later studied more extensively by Votoček, Valentin and Leminger.[8] Subsequently Votoček[9] reported the benzylphenylhydrazone of the epimeric "β-fucohexose" to be levorotatory, as expected.

Although the formulation I for "α-fucohexose" as determined by Votoček was consistent with three of the rules relating to rotatory power and structure in the sugar group, we sought a conclusive proof of the configuration of this sugar by application of the new method described in the preceding communication.[10] This method depends in part upon the principle first used by Emil Fischer and later designated *the proof by way of identical or antipodal active alcohols from two different aldoses.*[11] Votoček and Valentin[12] had purified "α-fucohexose" through its crystalline phenylhydrazone, but the liberated sugar still remained a sirup. However, upon reduction with sodium amalgam, it yielded a crystalline "α-fucohexitol" (now established as 7-desoxy-L-gala-D-*manno*-heptitol, IIa) melting at 179–180°, and with $[\alpha]_D + 0.3°$ in water; the epimeric "β-fucohexitol" melted at 150° and appeared to have no rotation.[9] Now, by the reductive desulfurization of D-manno-D-*gala*-heptose diethyl mercaptal (III)[13] with Raney nickel, we have prepared the 1-desoxy-D-manno-D-*gala*-heptitol (IIb). The identity of the desoxyheptitols IIa and IIb was established by a direct comparison of the two substances through their melting points and their rotations in several solvents, and by a similar comparison of their respective hexaacetates. Since the configuration of D-manno-D-*gala*-heptose is already known with certainty,[14] "α-fucohexose" is thus proved conclusively to be 7-desoxy-L-gala-D-*manno*-heptose (I). As a consequence the epimeric "β-fucohexose" and the two "rhodeohexoses" are also proved to have the configurations originally assigned to them by Votoček[7]: "β-fucohexose" is 7-desoxy-L-gala-D-*gluco*-heptose, "α-rhodeohexose" is 7-desoxy-D-gala-L-*manno*-heptose and "β-rhodeohexose" is 7-desoxy-D-gala-L-*gluco*-heptose.

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[1] W. Mayer and B. Tollens, *Ber.*, **40**, 2434 (1907); see also *ibid.*, **38**, 3022 footnote 1 (1905), and B. Tollens and F. Rorive, *ibid.*, **42**, 2009 (1909).

[2] E. Votoček, *ibid.*, **43**, 469 (1910).

[3] C. Krauz, *ibid.*, **43**, 482 (1910); *Z. Zuckerind. Böhmen*, **35**, 570 (1911).

[4] E. Votoček, *Collection Czechoslov. Chem. Communs.*, **6**, 528 (1934).

[5] C. S. Hudson, THIS JOURNAL, **40**, 813 (1918).

[6] P. A. Levene, *J. Biol. Chem.*, **23**, 145 (1915); P. A. Levene and G. M. Meyer, *ibid.*, **26**, 355 (1917).

[7] C. S. Hudson, THIS JOURNAL, **39**, 462 (1917).

[8] E. Votoček, F. Valentin and O. Leminger, *Collection Czechoslov. Chem. Communs.*, **3**, 250 (1931).

[9] E. Votoček, *ibid.*, **10**, 273 (1938).

[10] N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **72**, 3880 (1950).

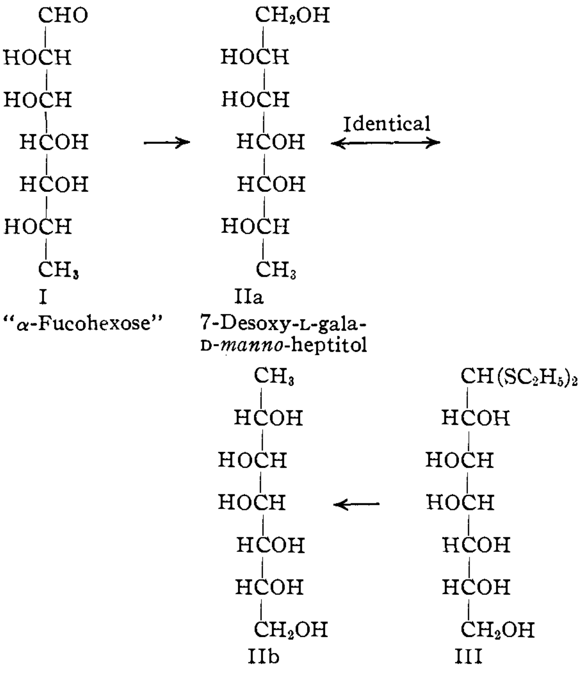
[11] E. Fischer and R. Stahel, *Ber.*, **24**, 528, 2144 (1891); R. M. Hann, A. T. Merrill and C. S. Hudson, THIS JOURNAL, **66**, 1912 (1944).

[12] E. Votoček and F. Valentin, *Collection Czechoslov. Chem. Communs.*, **10**, 77 (1938).

[13] E. Montgomery and C. S. Hudson, THIS JOURNAL, **56**, 2463 (1934).

[14] First through the correlations by G. Peirce, *J. Biol. Chem.*, **23**, 327 (1915).

This direct proof of configuration can now be applied to support the validity of the several empirical rules which Votoček used as a guide in his studies. We have tested also the benzimidazole rule[15] which states that whenever the hydroxyl group on the second (or alpha) carbon atom of an aldonic acid is on the right in the conventional projection formula, the rotation of the derived benzimidazole is positive and, conversely, when the hydroxyl group is on the left, the rotation of the benzimidazole is negative. As expected, the "α-fucohexonic" acid yielded a levorotatory benzimidazole and the "β-fucohexonic" acid yielded a dextrorotatory benzimidazole. The $[\alpha]^{20}_D$ values of −22.9° and +14.6° may be compared with the values −23.7° and +8.7° reported previously for the benzimidazoles derived from the related D-mannonic and D-gluconic acids, respectively. One advantage that benzimidazoles have over other derivatives, such as the rather insoluble amides[4] and phenylhydrazides[1] in the present instance, is that they are readily soluble in *N* hydrochloric acid, the accepted solvent in which their rotations are measured.



I "α-Fucohexose"

IIa 7-Desoxy-L-gala-D-*manno*-heptitol

IIb 1-Desoxy-D-manno-D-*gala*-heptitol

III D-Manno-D-*gala*-heptose diethyl mercaptal

Experimental Part

Addition of Hydrogen Cyanide to L-Fucose.—Instead of using liquid hydrogen cyanide as was done by earlier investigators, we tried a modification in which slightly more than one equivalent each of sodium cyanide and ammonium chloride was added to a cold solution of L-fucose in water. The reaction mixture was left overnight or longer at room temperature, boiled for several hours with excess barium hydroxide, neutralized with carbon dioxide, heated to boiling, filtered through activated carbon, and concentrated *in vacuo*. The crystalline barium salts were obtained without difficulty, the first crops being mainly the α form. After several recrystallizations from water the separated products obtained from 260 g. of L-fucose consisted of 102 g. of barium 7-desoxy-L-gala-D-*manno*-heptonate (the barium "α-fucohexonate") with $[\alpha]^{20}_D$ −6.3° in water (*c*, 5) and 39 g. of barium 7-desoxy-L-gala-D-*gluco*-heptonate (the barium "β-fucohexonate") with $[\alpha]^{20}_D$ +4.4° in water (*c*, 5), representing a total yield of 32% of pure products. The rotations are in good agreement with the $[\alpha]_D$ values of −6.6° and +4.3°, respectively, as reported by Votoček.[4]

Rotation of Barium 7-Desoxy-L-gala-D-*manno*-heptonate in Hydrochloric Acid.—In order to characterize further this low-rotating barium salt we have measured the mutarotation it undergoes when dissolved in an excess of *N* hydrochloric acid (Table I). The final rotation, calculated as lactone (*c*, 4), was $[\alpha]^{20}_D$ +52.5°. Votoček[4] reported for his crystalline "α-fucohexonic" lactone hydrate an equilibrium rotation in water (*c*, 4) of $[\alpha]_D$ +48.0°, which is equivalent to +52.5° for the anhydrous lactone. His corresponding value for the antipodal "α-rhodeohexonic" lactone hydrate was −47.4°, equivalent to −51.8° for the anhydrous lactone.

TABLE I

ROTATION OF BARIUM 7-DESOXY-L-GALA-D-*manno*-HEPTONATE IN *N* HCl (*c*, 5.9)

Time, min.	$[\alpha]^{20}_D$
3.3	+21.7
4.5	26.1
5.5	28.7
6.6	30.2
7.8	31.4
8.9	32.2
10.6	33.4
15.5	34.6
70	35.2
Constant	36.3

Final rotation, calculated as lactone, +52.5°

2-[L-*gala*-D-*manno-hepto*-1,2,3,4,5-Pentahydroxyhexyl]-benzimidazole.—A mixture of 5 g. of barium "α-fucohexonate" (0.009 mole), 2.2 g. of *o*-phenylenediamine (0.02 mole), 6.8 ml. of concentrated hydrochloric acid (0.04 mole), 8 ml. of water and 2 ml. of alcohol was heated for two and one-half hours in an oil-bath at 130°. The crystalline magma was dissolved in a small amount of hot water, filtered with the addition of activated carbon, and the filtrate made alkaline with aqueous ammonia. The benzimidazole crystallized readily and, after being washed thoroughly with water and dried, weighed 3.8 g. (75%). It was recrystallized thrice from 400 parts of boiling water, yielding clusters of small prisms of m. p. 243–245° (decomp.) and $[\alpha]^{20}_D$ −22.9° in *N* hydrochloric acid (*c*, 2).

Anal. Calcd. for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.93. Found: C, 55.17; H, 6.42; N, 9.97.

2-[L-*gala*-D-*gluco-hepto*-1,2,3,4,5-Pentahydroxyhexyl]-benzimidazole.—In the same manner 5 g. of the barium "β-fucohexonate" was converted to 3.6 g. (71%) of the corresponding benzimidazole. This substance is considerably more soluble in water than its epimer described above, and crystallized readily from 15 parts of that solvent in clusters of rod-like prisms. A thrice-recrystallized sample melted at 227–228° (decomp.) after preliminary sintering and discoloring at 212°. It showed $[\alpha]^{20}_D$ +14.6° in *N* hydrochloric acid (*c*, 2).

Anal. Calcd. for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.93. Found: C, 55.34; H, 6.33; N, 10.01.

Conversion of Barium 7-Desoxy-L-gala-D-*manno*-heptonate to "α-Fucohexitol."—To a solution of 66.5 g. of barium "α-fucohexonate" in 500 ml. of hot water was

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[15] N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **64**, 1612 (1942).

added an equivalent amount of *N* sulfuric acid and the precipitated barium sulfate removed by filtration. The solution of the liberated heptonic acid was concentrated *in vacuo* to a sirup which was heated for several hours on the steam-bath to ensure thorough lactonization. Although the lactone is known to be crystalline,[4] our product did not crystallize readily so the sirupy material weighing 40.4 g. (88%) was reduced in the usual manner with 2000 g. of 2.5% sodium amalgam. The neutralized aqueous solution was concentrated *in vacuo* to about 500 ml. and then poured into 1 liter of hot 95% ethanol to precipitate most of the sodium sulfate. The filtrate was concentrated *in vacuo* to remove the ethanol and the aqueous solution was deionized by passage through ion-exchange columns of Amberlite IR-120 and Duolite A-3. Concentration of this solution *in vacuo* yielded 19.5 g. (48%) of colorless, sirupy "α-fucohexose."

One-half of this sirup, dissolved in 100 cc. of water, was shaken with 9 g. of Raney nickel and hydrogen at 2500 lb. per sq. in. (about 167 atmospheres) for eight hours at 100°. The product was filtered, then deionized to remove traces of soluble nickel, and concentrated *in vacuo* to a crystalline mass. Recrystallized from 95% ethanol it weighed 4.1 g.; after three additional recrystallizations it was proved to be identical with the substance obtained by the reductive desulfurization of D-manno-D-*gala*-heptose diethyl mercaptal. The pertinent data are given in Table II; a mixed melting point showed no depression.

TABLE II

PROPERTIES OF 7-DESOXY-L-GALA-D-*manno*-HEPTITOL AND ITS HEXAACETATE

	From "α-fucohexose"	From L-manno-D-*gala*-heptose diethyl mercaptal
Melting point, °C.	181–182°[a]	181–182°
$[\alpha]^{20}\mathrm{D}$ in water (*c*, 6.7; *l*, 4)	+ 1.1°[b]	....
$[\alpha]^{20}\mathrm{D}$ in 5% ammonium molybdate (*c*, 0.47; *l*, 4)	+ 52.8°	+ 52.9°
$[\alpha]^{20}\mathrm{D}$ in acidified ammonium molybdate (*c*, 0.48; *l*, 4)[c]	+203°	+203°
Hexaacetate, melting point	136–137°	136–137°
Hexaacetate, $[\alpha]^{20}\mathrm{D}$ in chloroform (*c*, 4.3; *l*, 4)	+ 6.5°	+ 6.7°

[a] Votoček and Valentin (ref. 12) reported m. p. 179–180°. [b] Votoček and Valentin, using a 1-dm. tube, with *c*, 6.3, reported $[\alpha]\mathrm{D}$ + 0.3°; their $[\alpha]\mathrm{D}$ value in borax was only +1.7°. [c] About 0.12 g. of substance was dissolved in 20 ml. of 5% ammonium molybdate and the solution was diluted exactly to 25 ml. with *N* sulfuric acid.

Reductive Desulfurization of D-Manno-D-*gala*-heptose Diethyl Mercaptal to "α-Fucohexitol."—A mixture of 20 g. of the mercaptal[13] and 180 g. of freshly prepared Raney nickel in 500 ml. of 70% ethanol was refluxed gently for one hour. The ethanol solution was decanted and the Raney nickel extracted thoroughly by digesting it on the steam-bath three times with a total of 1600 ml. of water. The combined, filtered extracts were concentrated to a mass of needles. One recrystallization yielded 7.1 g. (57%) of nearly pure product which was recrystallized three additional times from 95% ethanol and shown to be identical with "α-fucohexitol" (data in Table II).

Hexaacetyl-7-desoxy-L-gala-D-*manno*-heptitol.—For further proof of identity of the two samples of "α-fucohexitol," each was acetylated by heating with acetic anhydride and fused sodium acetate. The product in each case was obtained in nearly theoretical amount, and was purified by several recrystallizations from chloroform by the addition of pentane. Data on melting points and rotations of the thin, irregularly hexagonal plates are recorded in Table II. A mixed melting point showed no depression.

Anal. Calcd. for $C_{19}H_{28}O_{12}$: C, 50.89; H, 6.29; CH_3CO, 57.6. Found: (compound from "α-fucohexose") C, 50.98; H, 6.37; CH_3CO, 57.7; (compound from mercaptal) C, 51.08; H, 6.45; CH_3CO, 57.5.

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Summary

D-Manno-D-*gala*-heptose diethyl mercaptal has been reductively desulfurized; the product is identical with "α-fucohexitol." Thus "α-fucohexose" is proved definitively to be 7-desoxy-L-gala-D-*manno*-heptose, which is the structure that Votoček had assigned previously by application of several empirical rules correlating rotatory power and structure. Conversely, the validity of these rules is given added support.

The benzimidazoles derived from the epimeric 7-desoxy-L-gala-D-*manno*-heptonic and 7-desoxy-L-gala-D-*gluco*-heptonic acids have been prepared and their signs of rotation found to be in accord with the proved configurations of these acids.

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