Preparation of 2-(2-Naphthoxy)-1-phenylethanol (III).—The procedure of Fritz[12] was used to prepare ω-(2-naphthoxy)-acetophenone from 2-naphthol and phenacyl bromide. The product melted at 102–104° compared with m. p. 104–106° reported by Fritz. The oxime derived from this ketone melted at 143–144° while Fritz reported m. p. 144–145°. **The 2,4-dinitrophenylhydrazone**, crystallized from ethyl acetate, melted at 228.5–229°.

Anal. Calcd. for $C_{24}H_{18}N_4O_5$: C, 65.15; H, 4.10. Found: C, 65.04; H, 4.16.

Reduction of the ketone with aluminum isopropoxide to the corresponding alcohol, 2-(2-naphthoxy)-1-phenylethanol (III), was accomplished readily (87.5%), m. p. 87–88°. The crystallizing solvent was heptane.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.70; H, 6.16.

The *p*-nitrobenzoate prepared from this alcohol melted at 104–105° after recrystallization from dilute ethanol and then from heptane.

Anal. Calcd. for $C_{25}H_{19}NO_5$: C, 72.63; H, 4.63. Found: C, 72.72; H, 4.75.

Summary

The alkali-catalyzed reaction of styrene oxide with 2-naphthol, in aqueous medium, was found to proceed in part in a manner not previously observed for olefin oxides and phenols under these conditions. In addition to the ether, 2-(2-naphthoxy)-2-phenylethanol (I) there was obtained up to 51% of a naphthol, 2-(2-hydroxy-1-naphthyl)-2-phenylethanol (II).

In dioxane as the solvent the alkali-catalyzed reaction gave a relatively greater amount of the ether (I) and its isomer, 2-(2-naphthoxy)-1-phenylethanol (III). The composition of the isomeric mixture of ethers was determined by the use of a phase diagram.

LOS ANGELES 7, CALIF. RECEIVED FEBRUARY 20, 1950

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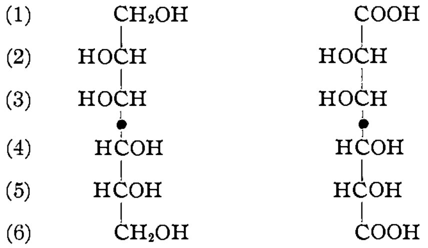
(12) Fritz, *Ber.*, **28**, 3028 (1895).

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

A Direct Proof of the Equivalence of Carbon Atoms 1 and 6 in D-Mannitol and a New Method of Correlating Certain Higher-Carbon Sugars and Alcohols

BY NELSON K. RICHTMYER AND C. S. HUDSON

It has long been recognized in the formulas for D-mannitol (I) and D-mannosaccharic acid (II), each with a center of symmetry between carbon atoms 3 and 4 for 180° rotations within the plane of the paper, that C_1 is equivalent to C_6, C_2 to C_5, and C_3 to C_4. Emil Fischer[1] was the first to draw this conclusion from stereochemical theory and he demonstrated experimentally that it was immaterial whether the C_1 or the C_6 end of the double lactone of D-mannosaccharic acid was reduced with sodium amalgam: one, and only one, hexonic lactone, which was the expected D-mannonic lactone, could be obtained.



$$\begin{array}{lcc} (1) & CH_2OH & COOH \\ & | & | \\ (2) & HOCH & HOCH \\ & | & | \\ (3) & HOCH & HOCH \\ & \bullet & \bullet \\ (4) & HCOH & HCOH \\ & | & | \\ (5) & HCOH & HCOH \\ & | & | \\ (6) & CH_2OH & COOH \end{array}$$

I II

Utilization of the principle of equivalent symmetry in D-mannitol has enabled one of us[2] to furnish conclusive proof of the structure of turanose. Catalytic hydrogenation of that ketone sugar yielded two alcohols, one of which, the 3-[α-D-glucopyranosyl]-D-mannitol, was found to be identical, by direct comparison of the crystalline nonaacetates, with the 4-[α-D-glucopyranosyl]-D-mannitol obtained by the catalytic hydrogenation of epimaltose. Conversely, if the earlier data[3] suffice to prove the structure of turanose, then the new evidence furnished an experimental proof of the equivalence of the C_3 and C_4 positions in D-mannitol, a result which proves also that C_1 is equivalent to C_6, and C_2 to C_5.

In the present paper we present a simple and more direct experimental proof of the equivalence of carbon atoms 1 and 6 in D-mannitol. This was obtained by desulfurizing D-mannose diethyl mercaptal (III) with Raney nickel and showing that the 1-desoxy-D-mannitol (IVa) thus prepared[4] is identical with the 6-desoxy-D-mannitol (synonym, D-rhamnitol) (IVb) prepared previously in this Laboratory by Haskins, Hann and Hudson.[5] In the earlier work D-mannose was transformed to D-rhamnose (V) through a series of reactions which converted the terminal CH_2OH group at C_6 to a CH_3 group; in the present instance it was the potential CHO group at C_1 that was changed to a CH_3 group. The identity of the two products IVa and IVb thus proves experimentally the

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(1) E. Fischer, *Ber.*, **24**, 1845 (1891).

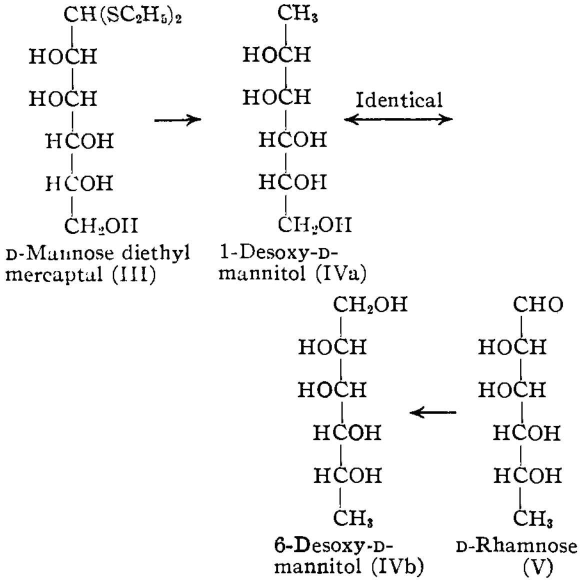
(2) C. S. Hudson, *J. Org. Chem.*, **9**, 117, 470 (1944).

(3) Especially H. S. Isbell and W. W. Pigman, *J. Research Natl. Bur. Standards*, **20**, 773 (1938); E. Pacsu, E. J. Wilson, Jr., and L. Graf, THIS JOURNAL, **61**, 2675 (1939).

(4) A similar desulfurization of D-mannose diethyl mercaptal pentaacetate by G. N. Bollenback and L. A. Underkofler [THIS JOURNAL, **72**, 741 (1950)], followed by deacetylation of the sirupy product, has independently been demonstrated to yield D-rhamnitol. The desulfurization of sugar mercaptals by Raney nickel was first accomplished by M. L. Wolfrom and J. V. Karabinos, THIS JOURNAL, **66**, 909 (1944).

(5) W. T. Haskins, R. M. Hann and C. S. Hudson, THIS JOURNAL, **68**, 628 (1946).

equivalence of the 1 and 6 positions in D-mannitol. Obviously, a corollary is that the C_2 and C_5, and the C_3 and C_4 positions are likewise equivalent, for only then could IVa and IVb be identical.


D-Mannose diethyl mercaptal (III)

1-Desoxy-D-mannitol (IVa)

Identical

6-Desoxy-D-mannitol (IVb)

D-Rhamnose (V)

In the hexitol series similar evidence could undoubtedly be obtained to prove experimentally the equivalent symmetry of D-iditol, and of the enantiomorphous L-mannitol and L-iditol. In the seven-carbon sugar alcohols no such center of symmetry is possible; D-gala-L-*gala*-octitol[6] appears to be the only known octitol possessing a configuration that implies equivalent symmetry, but this symmetry is present in the configurational formulas of several unknown octitols.

One of the classical methods of establishing conclusively the configuration of a higher-carbon sugar may be designated *the proof by way of identical or antipodal active alcohols from two different aldoses.*[7] Thus Peirce[8] correlated D-manno-D-*gala*-heptose (= D-α-mannoheptose) and D-gala-L-*manno*-heptose (= D-α-galaheptose) by his recognition that their previously known reduction products represented a pair of antipodal sugar alcohols. LaForge[9] correlated his D-gulo-L-*gala*-heptose (= D-α-guloheptose) with D-gala-L-*gluco*-heptose (= D-β-galaheptose) by identifying the corresponding guloheptitol with Peirce's D-gala-L-*gluco*-heptitol.[8] More recently Hann, Merrill and Hudson[10] correlated D-gala-L-*gulo*-octose and D-gluco-L-*gala*-octose by reducing them to the same octitol.

Now, by combining this type of correlation with the procedure for the reductive desulfurization of mercaptals, there becomes available a new method for determining the configuration of the higher-carbon ω-desoxy sugars and their derivatives. For example, as will be shown in the following paper,[11] the "α-fucohexitol" described by Votoček and Valentin[12] proves to be identical with the 1-desoxy-D-manno-D-*gala*-heptitol prepared by the reductive desulfurization of the diethyl mercaptal of D-manno-D-*gala*-heptose. Since the configuration of the latter heptose has previously been established in a definitive manner, it follows that "α-fucohexose" is 7-desoxy-L-gala-D-*manno*-heptose; these results confirm the formulation derived by Votoček and Valentin by application of the empirical rules relating to the optical rotations of the amides and barium salts of aldonic acids and the benzylphenylhydrazones of aldoses.

Experimental Part (with EMMANUEL ZISSIS)

D-Mannose Diethyl Mercaptal.—Although Fried and Walz[13] have recently found that the action of ethyl mercaptan and concentrated hydrochloric acid on methyl α-D-mannoside for eighteen hours at room temperature produces a small yield of ethyl 1-thio-β-D-mannoside, the principal product of this reaction when carried out according to the directions of Scattergood and Pacsu[14] was the desired D-mannose diethyl mercaptal. Our average yield of 44% of recrystallized product was somewhat lower than the 54% reported in the one experiment described by those authors.

D-Rhamnitol from D-Mannose Diethyl Mercaptal.—The reductive desulfurization of D-mannose diethyl mercaptal was effected by refluxing each 20-g. lot of that substance with about 180 g. of freshly prepared Raney nickel[15] in 500 ml. of 70% ethanol for one hour. The alcohol solution was decanted, and the Raney nickel extracted thoroughly by digesting it on the steam-bath with two 500-ml. and three 300-ml. portions of water. The filtered extracts were combined and concentrated *in vacuo* to a thin sirup which was dissolved in 30 ml. of hot absolute alcohol. The product, D-rhamnitol, crystallized slowly in small prisms in a yield of 64% (22.3 g. from 60 g. of mercaptal). After several recrystallizations from 95% alcohol, it was identified completely as D-rhamnitol through its melting point of 122–123°, and the fact that this value was not depressed when the substance was mixed with authentic D-rhamnitol[5] of the same melting point. The rotations of our D-rhamnitol and authentic D-rhamnitol, respectively, in water (c, 1) were $[\alpha]^{20}\text{D}$ −11.6° and −12.0°[5]; in 5% aqueous ammonium molybdate (c, 0.41) they were $[\alpha]^{20}\text{D}$ +23.9° and +24.3°; and in acidified ammonium molybdate (c, 0.41), prepared by dissolving about 0.1 g. of the substance in 20 ml. of 5% ammonium molybdate and diluting exactly to 25 ml. with N sulfuric acid, they were $[\alpha]^{20}\text{D}$ +150° and +153°. The closely related D-mannitol, which has practically no rotation in water, was found to have $[\alpha]^{20}\text{D}$ +16.7° in 5% ammonium molybdate (c, 0.40)[16] and +143° in acidified ammonium molybdate (c, 0.40).[17]

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[6] E. Fischer, *Ann.*, **288**, 139 (1895); W. D. Maclay, R. M. Hann and C. S. Hudson, THIS JOURNAL, **60**, 1035 (1938).

[7] E. Fischer and R. Stahel, *Ber.*, **24**, 528, 2144 (1891).

[8] G. Peirce, *J. Biol. Chem.*, **23**, 327 (1915).

[9] F. B. LaForge, *ibid.*, **41**, 251 (1920).

[10] R. M. Hann, A. T. Merrill and C. S. Hudson, THIS JOURNAL, **66**, 1912 (1944).

[11] E. Zissis, N. K. Richtmyer and C. S. Hudson, *ibid.*, **72**, 3882 (1950).

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

[13] J. Fried and D. E. Walz, THIS JOURNAL, **71**, 140 (1949).

[14] A. Scattergood and E. Pacsu, *ibid.*, **62**, 903 (1940).

[15] Exhaustive washing of the Raney nickel to remove the last traces of alkali is unnecessary because there are no alkali-sensitive groups in the unacetylated mercaptal.

[16] In close agreement with the value $[\alpha]^{20}\text{D}$ +16.9° reported by A. T. Merrill, W. T. Haskins, R. M. Hann and C. S. Hudson, THIS JOURNAL, **69**, 70 (1947).

[17] M. Frèrejacque [*Compt. rend.*, **200**, 1410 (1935); **208**, 1123 (1939)] found $[\alpha]_{546}$ +169° for D-mannitol in the presence of excess molybdic acid.

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.

BETHESDA, MARYLAND RECEIVED FEBRUARY 20, 1950

[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).