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

Sugar Interconversion under Reducing Conditions. II[1,2]

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In continuation of our studies on sugar interconversion under reducing conditions, there has been investigated a second commercial product made by the electrolytic reduction of D-glucose under conditions of relatively high alkalinity (*p*H 10–13) and below 30°. The product (denoted product B) is a much more complex mixture

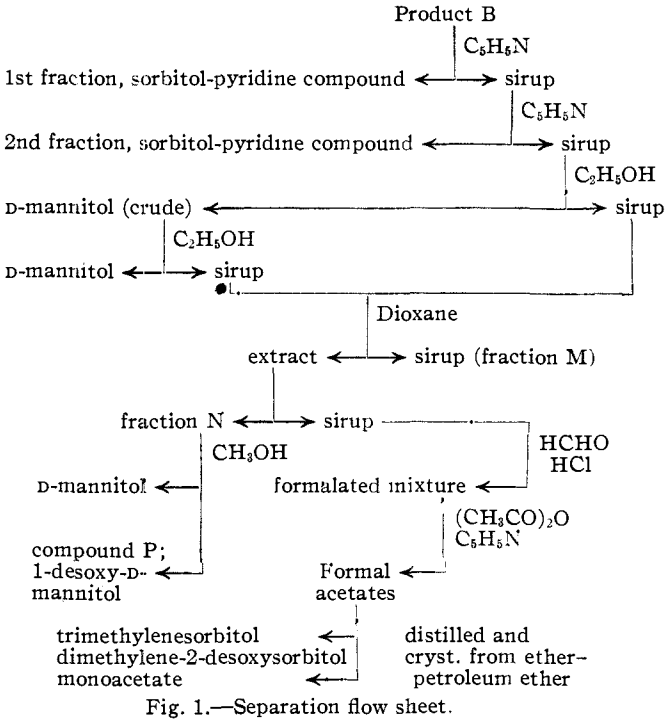


Fig. 1.—Separation flow sheet.

of polyhydric alcohols than that (product A) previously studied.[1] Goepp and Soltzberg[5] investigated a product similar to but not identical with product B by removing most of the sorbitol[6] present, methylating the remainder and subjecting the methyl ethers to vapor phase fractionation. The nature of the carbon skeletons present was then determined on the separated fractions by reduction with hydrogen iodide and identification of the secondary iodides formed. It was thus shown that most of the non-hexitol portion of the material was branched-chain in nature and consisted of products that apparently were the reduced analogs of the saccharinic acids.

It then became the immediate objective of this work to identify individual components of this complex mixture. The general procedures employed in isolating the components of the less complex product (product A) previously reported were applied to product B (*cf.* Fig. 1). The sorbitol was removed as the pyridine compound (two crops), D-mannitol was removed by crystallization from ethanol and the resulting sirup was extracted with dioxane to yield a crystalline product which, after removal of some contaminating D-mannitol, was a pure substance (designated compound P) that gave elementary analytical values in agreement with those required for a desoxyhexitol. The substance was then subjected to oxidation with sodium metaperiodate to yield the data shown in Table I. These data definitely delineated the substance as a 1-desoxyhexitol. The yield of acetaldehyde formed in this oxidation was determined by the procedure of Vorländer,[7] a method which has been shown,[8] subsequent to the performance of this work, to yield low results. Of the known 1-desoxyhexitols, the properties of 1-desoxy-D-mannitol (*syn.* D-rhamnitol), first described by Votoček and co-workers,[9] were found to be in agreement with those of compound P (Table II). Comparison was also made with an authentic sample of the enantiomorph. Compound P was thus identified as 1-desoxy-D-mannitol.

TABLE I

OXIDATION OF COMPOUND P WITH SODIUM METAPERIODATE

	Moles per mole of compound P	
	Found	Calcd. for a 1-desoxyhexitol
Oxidant consumed	3.9	4
Total acidity	3.0	3
Acidity as formic acid	3.0	3
Formaldehyde	1.0	1
Acetaldehyde	0.7	1

The sirupy mother liquor material from fraction N (*cf.* Fig. 1) was formalated, acetylated and

(1) Preceding communication in this series: M. L. Wolfrom, M. Konigsberg, F. B. Moody and R. M. Goepp, Jr., THIS JOURNAL, **68**, 122 (1946).

(2) Presented before the Division of Sugar Chemistry and Technology at the 107th Meeting of the American Chemical Society, Cleveland, Ohio, April 6, 1944.

(3) Atlas Powder Company Research Associate of The Ohio State University Research Foundation, 1939–1940 (M. K.), 1940–1941 (F. B. M.).

(4) Research Department, Atlas Powder Company, Wilmington, Delaware.

(5) R. M. Goepp, Jr., and S. Soltzberg, paper presented before the Division of Sugar Chemistry and Technology at the 99th Meeting of the American Chemical Society, Cincinnati, Ohio, April 11, 1940; *cf.* K. R. Brown, U. S. Patent 2,172,357 (1940).

(6) We denote as sorbitol the common form of this hexitol as obtained by the reduction of D-glucose. Carbon one of this sorbitol corresponds to its precursor in D-glucose.

(7) D. Vorländer, *Z. anal. Chem.*, **77**, 321 (1929).

(8) B. H. Nicolet and L. A. Shinn, *J. Biol. Chem.*, **139**, 687 (1941).

(9) E. Votoček, F. Valentin and F. Rác, *Collection Czechoslov. Chem. Commun.*, **2**, 402 (1930).

TABLE II

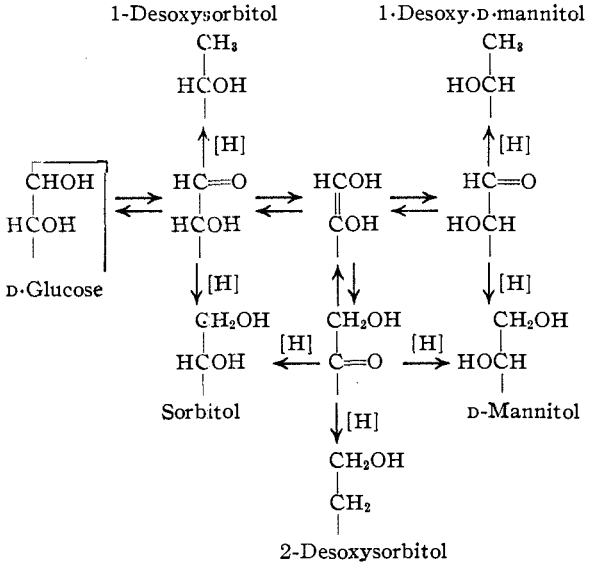
IDENTIFICATION OF COMPOUND P AS D-RHAMNITOL (1-DESOXY-D-MANNITOL)

	M. p., °C.	$[\alpha]^{20-25}D$ (c < 5)
D-Rhamnitol (isolated)	122–123	−12.8° (water)
D-Rhamnitol (Votoček *et al.*[a])	123	−12.4 (water)
Dibenzylidene-D-rhamnitol (isolated)[b]	207–209	+60 (chloroform)
Dibenzylidene-D-rhamnitol (Votoček, *et al.*[a])	207	+60.7 (chloroform)
Monotrityl-D-rhamnitol (isolated)[d]	131–133	−5.6 (chloroform)
Monotrityl-L-rhamnitol (this work)[d]	131–132	+5.4 (chloroform)
Monotrityl-L-rhamnitol (Valentin[c])	132–135	+4.0 (c 0.5, benzene)

[a] Ref. 9. [b] Prepared by the method of Votoček, *et al.* ref. 9. [c] F. Valentin, *Coll. Czechoslov. Chem. Commun.*, **3**, 499 (1931). [d] Prepared by the method of Valentin.[c]

subjected to fractional distillation under reduced pressure. From one of the fractions there was obtained crystalline material that consisted of a separable mixture of trimethylenesorbitol and a product which was identical with that obtained by the formalation and subsequent acetylation of an authentic specimen of 2-desoxysorbitol (synonym 2-desoxy-D-mannitol). 2-Desoxysorbitol was therefore identified as a component of product B.

The isolation of sorbitol, D-mannitol, 1-desoxy-D-mannitol and 2-desoxysorbitol is in accordance with the theory of sugar interconversion under reducing conditions elaborated in our previous communication[1] and illustrated in the accompanying formulas. From this theory it may be predicted that 1-desoxysorbitol should likewise be present in the mixture.



Experimental

Material Subjected to Analysis.—The material investigated was a product (denoted as product B) manufactured by the Atlas Powder Company of Wilmington, Delaware, by the electroreduction of D-glucose under conditions of relatively high alkalinities (*p*H 10–13) and below 30°, according to the general operating conditions described in United States Patent 1,990,582,[10] and from which D-mannitol had been removed by crystallization procedures. The product was a thick sirup of a dark straw color.

Anal. Moisture, 15.93; ash, 0.85; reducing sugar as D-glucose, 0.22.

Removal of Excess Sorbitol[6] and Isolation of D-Mannitol.—An amount of 1 kg. of product B was treated as described previously[1] to remove sorbitol as the sorbitol-pyridine (1:1) addition compound in two crops (*ca.* 300 g. and 100 g., not further investigated). From the mother liquor material (700 g.), D-mannitol was isolated by crystallization from ethanol solution as described previously.[1] The crude D-mannitol was purified by further crystallization from 95% ethanol; yield 22.4 g., m. p. 163–165° undepressed on admixture with an authentic specimen of D-mannitol (m. p. 166–167°), $[\alpha]^{25}D$ 0° (c 5, water), $[\alpha]^{25}D$ +28.6° (c 5, aqueous borax, borax c 10).

Isolation of 1-Desoxy-D-mannitol (Synonym D-Rhamnitol).—The mother liquors from the mannitol crystallizations were combined, concentrated under reduced pressure to a sirup (660 g.) and this repeatedly (9 times) extracted with dioxane as described previously.[1] A crystalline product (fraction N, *cf.* Fig. 1) separated from the dioxane solution on standing at icebox temperature; yield 28 g. This product was a mixture of D-mannitol (individual needles) and a substance crystallizing in rosets. Further recrystallization from hot methanol yielded D-mannitol in a fair state of purity; yield 0.25 g. (total yield of D-mannitol, 22.7 g., m. p. 157–160°. A portion of this material was acetylated with pyridine and acetic anhydride to yield D-mannitol hexaacetate; m. p. 124–125° unchanged on admixture with an authentic specimen of like melting point.

The mother liquor material (9.5 g., m. p. 119–120°) from the D-mannitol separation was further purified by recrystallization from 80% aqueous acetone; m. p. 122–123°, $[\alpha]^{25}D$ −12.8° (c 5, water). Elementary analysis indicated that the substance (compound P, Fig. 1) was a desoxyhexitol.

Anal. Calcd. for $C_6H_{14}O_5$: C, 43.37; H, 8.49. Found: C, 43.08; H, 8.38.

Oxidation of the substance (1 millimole) with sodium metaperiodate (5 millimoles) according to the general procedure of Hudson and co-workers[11] yielded the data recorded in Table I. To determine the formic acid, an aliquot portion of the oxidized solution was steam distilled until the acidity in the last portion of the distillate was negligible. The formic acid, after neutralization and concentration, was treated with mercuric chloride in dilute acetic acid–sodium acetate solution and the weight of mercurous chloride formed was determined.[12] The acetaldehyde and formaldehyde were determined by the dimedone (5,5-dimethyl-cyclohexanedione-1,3) reagent as described by Vorländer.[7]

The data of Table I show definitely that compound P was a 1-desoxyhexitol and the data of Table II identify it as D-rhamnitol (1-desoxy-D-mannitol).

Isolation of 2-Desoxysorbitol (Synonym 2-Desoxy-D-mannitol) as Dimethylene-2-desoxysorbitol Monoacetate.—The dioxane-soluble fraction after removal of fraction N weighed 320 g. A portion (150 g.) of this sirup was dissolved in 40% formalin (400 cc.) and the solution cooled

(10) H. J. Creighton, U. S. Patent 1,990,582 (1935).

(11) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 994 (1937); R. M. Hann, W. D. Maclay and C. S. Hudson, *ibid.*, **61**, 2432 (1939).

(12) Scott, "Standard Methods of Chemical Analysis," Vol. 2, 4th Ed., D. Van Nostrand Co., New York, N. Y., 1927, p. 1545.

to 0°. Hydrogen chloride was introduced into the stirred and cooled solution at such a rate that the temperature remained below 10°; hydrogen chloride absorbed, 400 g. After standing for twelve hours at 0° the solution was poured into a water suspension of excess sodium bicarbonate and this solution was concentrated to dryness under reduced pressure at 50°. After dehydration with ethanol, the material was extracted with hot absolute ethanol (1 liter total) in portions, followed by removal of most of the inorganic salts by filtration. The ethanol was removed by concentration under reduced pressure and the resultant sirup was acetylated for twelve hours at room temperature with pyridine (350 cc.) and acetic anhydride (700 cc., initial cooling). This solution was concentrated under reduced pressure at 55° and the resultant thin sirup (260 g.) was poured into ice and water (1.5 liters) containing excess sodium bicarbonate. After stirring for thirty minutes, the aqueous solution which contained some insoluble sirup was extracted with several portions of chloroform. The chloroform solution (1 liter) was washed with sodium bicarbonate solution and with water, dried with calcium chloride and concentrated under reduced pressure; yield 182 g. of a light yellow sirup.

The sirup was distilled at approximately 1-mm. pressure through a 15-cm. fractionating column, 11 mm. in diameter, equipped with a nichrome wire spiral of about 1 turn per centimeter. The fraction (41.8 g.) boiling between 120–130° at a bath temperature of 70–80° was dissolved in an equal volume of ether and allowed to stand for twelve hours at 15°. The first crop of crystalline material (0.45 g.) melted at 200–208°. It was recrystallized from methanol and identified as trimethylenesorbitol; yield 0.27 g., m. p. 210–214°, $[\alpha]^{20}D$ −32° (*c* 2.5, chloroform). Ness, Hann and Hudson[13] cite as constants for 1,3:2,4:5,6-trimethylenesorbitol: m. p. 212–216°, $[\alpha]^{20}D$ −31° (*c* 1.2, chloroform).

A second crop of crystals was obtained when the ethereal mother liquor was treated with petroleum ether to incipient opalescence and allowed to stand for several weeks at 0°; yield 3.4 g. Pure material was obtained on further crystallization from ether–petroleum ether; yield 2.5 g., m. p. 107.5–108°, $[\alpha]^{26}D$ −61° (*c* 2.5, chloroform).

Anal. Calcd. for a diformal desoxyhexitol monoacetate ($C_8H_{13}O_5 \cdot COCH_3$): C, 51.72; H, 6.95; CH_3CO, 4.3 cc. 0.1 *N* sodium hydroxide per 100 mg. Found: C, 51.86; H, 6.92; CH_3CO, 4.3 cc.

This substance was identified as dimethylene-2-desoxysorbitol monoacetate by comparison with a synthetic product of known structure. An amount of 0.5 g. of dimethylene-2-desoxysorbitol, the synthesis of which is described below, was acetylated with pyridine and acetic anhydride and the product recrystallized from ethanol; m. p. 107–108° unchanged on admixture with the isolated product, $[\alpha]^{22}D$ −61° (*c* 4.5, chloroform).

Dimethylene-2-desoxysorbitol (Synonym Dimethylene-2-desoxy-D-mannitol).—2-Desoxysorbitol (10 g.) was treated at 0° with 40% formalin (50 cc.) and hydrogen chloride (44 g.) as described above. Neutralization and ethanol extraction of the dried mixture of sirup and sodium chloride yielded crystalline material (4 g.) after ethanol removal. Pure dimethylene-2-desoxysorbitol was obtained on further crystallization from acetone–petroleum ether; m. p. 148–149°, $[\alpha]^{28}D$ −17.5° (*c* 5, chloroform).

Anal. Calcd. for $C_8H_{14}O_5$: C, 50.57; H, 7.43. Found: C, 50.64; H, 7.69.

Summary

1. D-Mannitol and 1-desoxy-D-mannitol (D-rhamnitol) have been isolated in crystalline condition from a commercial product manufactured by the electroreduction of D-glucose at *p*H 10–13 and below 30°.

2. Identification of 1-desoxy-D-mannitol was made by periodate oxidation and by the preparation of its crystalline dibenzylidene and monotrityl derivatives.

3. 2-Desoxysorbitol (synonym 2-desoxy-D-mannitol) was isolated from the same source as crystalline dimethylene-2-desoxysorbitol monoacetate, identification being effected by comparison with a synthetic product of known structure.

4. The above results are in harmony with an enolic mechanism of sugar interconversion under reducing conditions.

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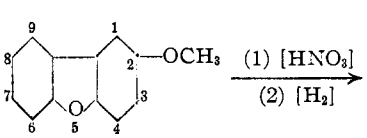
(13) A. T. Ness, R. M. Hann and C. S. Hudson, THIS JOURNAL, **66**, 665 (1944); *cf.* M. Schulz and B. Tollens, *Ann.*, **289**, 20 (1896).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

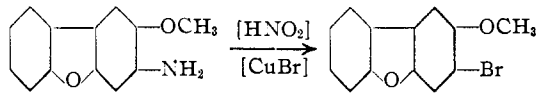
Dibenzofuran. XXIV. Some Dialkylaminoalkylamino Derivatives[1]

BY HENRY GILMAN AND S. AVAKIAN

The availability of some aminodibenzofurans suggested an examination of the corresponding dialkylaminoalkylamino derivatives for antimalarial action. One of the mono-substituted aminodibenzofurans used in this study was prepared by way of the nitration of 2-methoxydibenzofuran. The following reactions were used to establish the position of the nitro or amino group.



(1) Paper XXIII: Gilman and Avakian, THIS JOURNAL, **67**, 349 (1945).



A second amino derivative used in this study, 1-amino-3,4-dimethoxydibenzofuran, is most conveniently prepared by reduction of 1-nitro-3,4-dimethoxydibenzofuran which was obtained in a 96% yield by nitrating an acetic acid solution of 3,4-dimethoxydibenzofuran with fuming nitric acid. The structure of the nitro compound was established by reduction to an amine which was shown to be identical with an authentic specimen of 1-amino-3,4-dimethoxydibenzofuran prepared from the known 1-bromo-3,4-dimethoxydibenzofuran.