

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Bimolecular Dianhydrides of L-Sorbose¹BY M. L. WOLFROM AND H. W. HILTON²

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Concentrated hydrochloric acid was allowed to react with L-sorbose at -5° and, after removal of excess L-sorbose by carbon column chromatography, two crystalline di-L-sorbose dianhydrides, designated diheterosorbosans I and II, were isolated through their crystalline hexaacetates. Periodate assay established the former definitively as di-L-sorbopyranose 2,1':2',1-dianhydride (VII) and the latter as probably L-sorbofuranose-L-sorbopyranose 2,1':2',1-dianhydride (V). The nature and yields of these two products are similar to those for the two main substances obtained in the analogous reaction with D-fructose. Intermediates are proposed to explain the formation of these dimeric anhydrides.

D-Fructose is known to form bimolecular dianhydrides containing the central dioxane ring when acted upon by aqueous acids. Six such substances have been characterized.³⁻⁶ The first member of this series was obtained by the action of concentrated hydrochloric acid upon D-fructose at 0° ³ and such reaction conditions have now been extended to the isomeric ketohexose L-sorbose. After removal of excess L-sorbose by carbon column separation according to the excellent general technique of Whistler and Durso,⁷ the crude sorbosan mixture was isolated and partially separated into two fractions by crystallization from methanol. Acetylation of each of these fractions then yielded two isomeric and crystalline hexaacetates which gave on deacetylation the parent substances in crystalline condition.

These two diketose dianhydrides, herein designated diheterosorbosans I and II by analogy with the terms diheterolevulosans I and II, were subjected to periodate assay. Diheterosorbosan I consumed (per mole of reductant) 4 moles of oxidant with the concomitant production of 2 moles of formic acid and no formaldehyde whereas diheterosorbosan II consumed 3 moles of oxidant and produced 1 mole of formic acid and no formaldehyde. These results are strictly analogous to those obtained with the diheterolevulosans I and II which are formed from D-fructose under like conditions in the same total yield of 40-45% and in the same ratio of II:I = 2:1.^{5a,6} If the central dioxane ring be assumed, as was done with the D-fructose derivative, then the periodate oxidation is definitive for the structure di-L-sorbopyranose 2,1':2',1-dianhydride (VII) for diheterosorbosan I. The structure V, L-sorbofuranose-L-sorbopyranose 2,1':2',1-dianhydride, is favored over VI, but not proved, for diheterosorbosan II by analogy with that established for diheterolevulosan II on the basis of both periodate^{5a} and methylation^{5b} data. Other dianhydrides are probably formed in small amount, as was the case with D-fructose.^{5b,6}

It is remarkable that diheterosorbosan II exhibited no detectable optical rotation throughout the visible portion of the spectrum and in two solvents

although it was obtained by simple saponification of an optically active and non-reducing hexaacetate of $[\alpha]_D -19^{\circ}$ (chloroform). It is possible that the two optically active carbon atoms in the dioxane ring of this compound are anomeric and opposite in sign. If the diheterosorbosans I and II have structures analogous to the diheterolevulosans I and II, then they would differ, respectively, only in the configuration of the two C-5 centers in each and should show an essentially constant C-5,C-5' epimeric difference. The following calculations show that this is the case.

$$\begin{array}{r} [M]_D \text{ of diheterolevulosan I} = (-45.8^{\circ})(324) = -14,800 \\ [M]_D \text{ of diheterosorbosan I} = (-11.5^{\circ})(324) = -3,700 \\ \Delta_{C-5} = \underline{-11,100} \\ [M]_D \text{ of diheterolevulosan II} = (-39^{\circ})(324) = -12,600 \\ [M]_D \text{ of diheterosorbosan II} = (0^{\circ})(324) = 0 \\ \Delta_{C-5} = \underline{-12,600} \end{array}$$

It is thus apparent that the configuration of C-5 has little effect upon this type of reactivity of the ketohexose molecule. It is probable that the products are formed according to the scheme shown in Fig. 1 which fits into the generalized scheme of Lowry^{8,9} in that a proton or hydronium ion is added at one point of a molecule and ejected at another with intermediate bond adjustment. The proton from the hydrochloric acid solution is added at C-2 where the hemiacetal hydroxyl acts as a base to form the transient carbonium ions I and II. These then react with the L-sorbofuranose or L-sorbopyranose neutral molecules to form the intermediates III and IV with the elimination of a proton from the hydroxyl groups at the C-1 positions. This process is then repeated to form VII (diheterosorbosan I) or V (probably diheterosorbosan II) or the alternative VI formed by reaction at C-3 instead of C-1. It is not excluded that the proton additions and ejections could occur essentially simultaneously.

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Experimental

The Action of Cold Concentrated Hydrochloric Acid upon L-Sorbose and Recovery of the Reaction Products.—L-Sorbose (75 g.) was dissolved in 300 g. of concentrated hydrochloric acid (sp. gr. 1.19 at 15.56°) at -5° and the solution was maintained at that temperature for 72 hr. The dark red solution was poured on 500 g. of crushed ice and the resultant red solution was passed over a 65×7 cm. (diam.)

(1) A preliminary report of this work appears in *Abstracts Papers Am. Chem. Soc.*, **122**, 3R (1952).

(2) Visking Corporation Fellow, 1951-1952.

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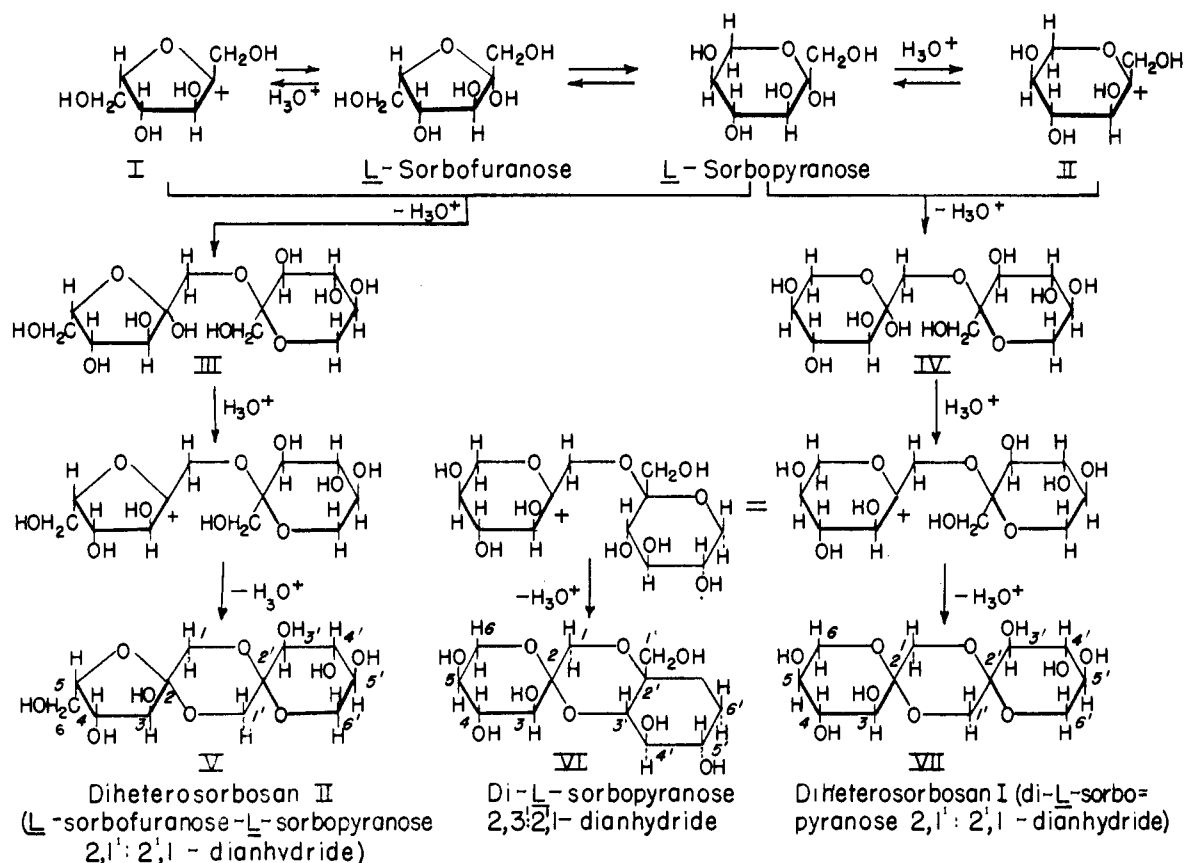


Fig. 1.—Postulated course of dehydration of L-sorbose by cold concentrated hydrochloric acid. Anomeric configurations unknown.

column of Duolite A-4¹⁰ anion acceptor prewashed with water near 0°. Solvent removal at 50° under reduced pressure yielded a tan colored sirup; yield 77 g. of a partially dried product.

A solution of 25 g. of the above sirup in 250 ml. of water was placed at the top of a 23 × 7.5 cm. (diam.) column of Darco G-60¹¹-Celite¹² (5:1 by wt.) and the column was washed with 3000 ml. of water. The effluent contained L-sorbose recoverable on solvent removal under reduced pressure; yield 40 g. from three such chromatograms. The column was then washed with 4000 ml. of ethanol-water (30:70 by vol.). A partially crystalline residue was obtained from the effluent on solvent removal under reduced pressure; yield 32 g. (43%) of crude diketose dianhydride from three such chromatograms. This product was recrystallized by solution in 40 ml. of warm absolute methanol followed by crystallization at 40° for 24 hr. and then at 5° for 48 hr. The crystals were removed by decantation and thrice washed with 20 ml. of absolute ethanol, each wash remaining in contact with the crystals for 8 hr. at 40° and then for 16 hr. at 5°; yield 10.1 g. (Fraction A), m.p. 225–230° (dec.), $[\alpha]^{25}_D -12.1^\circ$ (*c* 5, water). The residue obtained on solvent removal from the combined decantate and washings was crystallized from 40 ml. of methanol-ethanol (1:1 by vol.); yield 1.28 g. (Fraction B), m.p. 243–246° (dec.), $[\alpha]^{25}_D -12^\circ$ (*c* 1, water). The final mother liquor material was a sirup reducing toward Benedict solution; yield 20.2 g., $[\alpha]^{25}_D -24^\circ$ (*c* 20, methanol).

Di-L-sorbopyranose 2,1':2',1'-Dianhydride Hexaacetate (Diheterosorbosan I Hexaacetate).—An amount of 1.0 g. of Fraction A above was acetylated in pyridine (10 ml.) and acetic anhydride (10 ml.) for 16 hr. at 0–5°. The crystalline acetate that formed on pouring the reaction mixture

onto 50 g. of crushed ice was removed by filtration, washed with 200 ml. of water and recrystallized from ether; yield 1.50 g. (85%), needles, m.p. 168–169°, $[\alpha]^{25}_D +3.7^\circ$ and $[\alpha]^{25}_{160} +5.0^\circ$ (*c* 3.3, chloroform); main X-ray powder diffraction lines¹³: 8.51 (5), 5.40 (2), 4.76 (1), 4.39 (4), 4.03 (3). The compound was soluble in benzene, chloroform and warm ethanol; less soluble in warm ether.

Anal. Calcd. for C₂₄H₃₂O₁₆: C, 49.99; H, 5.60; mol. wt., 576.5. Found: C, 49.48; H, 5.69; mol. wt. (Rast), 565.

Di-L-sorbopyranose 2,1':2',1'-Dianhydride (VII, Diheterosorbosan I).—An amount of 1.175 g. of di-L-sorbopyranose 2,1':2',1'-dianhydride hexaacetate was dissolved in 50 ml. of absolute methanol and heated at 70° for 5 min. after the addition of 4 ml. of 0.1 *N* NaOMe. Water (50 ml.) was added to the turbid solution and the resultant clear solution was decationized by passage through a 60 × 1 cm. (diam.) column of Amberlite-IR-100.¹⁴ The sirup obtained on solvent removal from the effluent (treated with decolorizing carbon) was crystallized from 40 ml. of absolute ethanol; yield 490 mg., m.p. 249–250° (dec.), $[\alpha]^{25}_D -11.5^\circ$ (*c* 2.6, water), prisms, Molisch (+), Benedict (–) but (+) after treatment with concd. HCl at 100° for 2–3 minutes; main X-ray powder diffraction lines¹³: 5.86 (3), 5.46 (2), 4.96 (1), 3.68 (5), 2.73 (4). The substance was soluble in water and was insoluble in methanol and ethanol.

Anal. Calcd. for C₁₂H₂₀O₁₀: C, 44.44; H, 6.22. Found: C, 44.43; H, 6.20.

Periodate assay (moles per mole of reductant; 0.05 *M* NaIO₄ in 0.004 *M* reductant, 25 ± 2°, 4 days required for complete reaction): oxidant consumed, 4.0; formic acid (acidity toward brom cresol purple), 1.8; formaldehyde, 0.0.

Diheterosorbosan II Hexaacetate.—An amount of 1.0 g. of Fraction B above was acetylated as described above for

(10) A product of the Chemical Process Co., Redwood City, California.

(11) Decolorizing carbon, a product of the Darco Department, Atlas Powder Co., New York, N. Y.

(12) No. 535, a siliceous filter aid, a product of Johns-Manville Co., New York, N. Y.

(13) Interplanar spacing in Å.; CuK α radiation of $\lambda = 1.5418$ Å.; 1, strongest line.

(14) A product of the Resinous Products and Chemical Co., Philadelphia, Pa.

diheterosorbosan I hexaacetate and the crystalline product, isolated in the same manner, was recrystallized from ethanol; yield 940 mg., m.p. 177–179°, $[\alpha]_{25}^D -19^\circ$ (*c* 2.1, chloroform), needles; main X-ray powder diffraction lines¹³: 7.85 (3), 5.17 (2), 4.37 (1), 3.94 (4), 3.16 (5). The substance was soluble in benzene, chloroform and in warm ethanol and ether.

Anal. Calcd. for C₂₄H₃₂O₁₆: C, 49.99; H, 5.60; mol. wt., 576.5. Found: C, 50.27; H, 5.73; mol. wt. (Rast), 582.

The combined aqueous decantate and washings from the acetylation was neutralized to pH 6–7 with sodium bicarbonate and extracted with six 10-ml. portions of chloroform. The combined chloroform extracts were washed with water, *N* HCl, saturated aqueous NaHCO₃ and again with water. The sirup obtained on solvent removal from the dried chloroform solution was added to the sirupy mother liquor material from the crystallization of the above acetate; total yield 800 mg. This material was dissolved in 100 ml. of benzene and added to the top of a 30 × 7.7 cm. (diam.) column of Magnesol¹³-Celite¹² (5:1 by wt.) and the chromatogram was developed with 2800 ml. of benzene-ethanol (100:1 by vol.). The permanganate indicator (1% KMnO₄ in 2.5 *N* NaOH)

(15) A hydrated magnesium acid silicate produced by the Westvac Chlorine Products Corp., South Charleston, West Virginia.

streak located a main zone on the extruded column 100–150 mm. from the column top which was desorbed with 1500 ml. of acetone; yield 400 mg. (total 1.34 g. or 76%) of the above acetate, m.p. 171–173.5° raised to 179° by one recrystallization from benzene-ether (1:10), mixed m.p. 177–179°. The X-ray diffraction patterns were identical.

Diheterosorbosan II (V or VI).—An amount of 500 mg. of diheterosorbosan II hexaacetate was deacetylated as described above for diheterosorbosan I hexaacetate and the product, isolated in the same manner, was crystallized from ethanol; yield 180 mg., m.p. 188–189°, $[\alpha]_{25}^D 0.00^\circ$ (*c* 1 in water and in methanol; throughout the visible portion of the spectrum), prisms, Benedict (–) but (+) after hydrolysis with concd. HCl at 100°; main X-ray powder diffraction lines¹³: 6.39 (4), 5.13 (3), 4.78 (2), 4.49 (1), 3.22 (5). The substance was soluble in water and methanol and was insoluble in ethanol.

Anal. Calcd. for C₁₂H₂₀O₁₀: C, 44.44; H, 6.22. Found: C, 44.43; H, 6.25.

Periodate assay (moles per mole of reductant; 0.05 *M* NaIO₄ in 0.004 *M* reductant, 26 ± 3°, 7 days required for complete reaction): oxidant consumed, 3.1; formic acid (acidity toward brom cresol purple), 1.0; formaldehyde, 0.0.

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[CONTRIBUTION FROM THE DIVISION OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

Threitan and Erythritan and their Reaction with Periodate¹

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Dehydration of L-threitol and erythritol with 50% sulfuric acid has provided the corresponding 1,4-anhydrides, L-threitan (III) and erythritan (IV), respectively. Both III and IV react with one molecular proportion of sodium periodate and periodic acid; IV, with a *cis*-glycol structure, undergoes cleavage at a greater rate than III which has a *trans*-glycol structure.

Periodic acid and its sodium and potassium salts have been extensively used in determination of the structure of carbohydrates.² The results of a large number of experiments have shown that this oxidizing agent cleaves the bond between two carbon atoms carrying hydroxyl groups. It matters little whether the glycol grouping is of the *cis* or the *trans* type although the former is attacked at a greater rate. From these observations the failure of a polyhydroxy compound to react with periodate has been taken to indicate the absence of a 1,2-diol grouping. More recently, however, the danger inherent in using such negative evidence in structural studies has been demonstrated by the fact that both β-1,6-anhydro-D-glucofuranose (I) and α-1,6-anhydro-D-galactofuranose (II), which possess a glycol group, have been found to be completely resistant to periodate oxidation.^{3–5} This resistance was attributed to the stereochemical effects caused by the presence of two interlocking rings. Inspection of molecular models of I and II shows that this type of structure with two interlocking rings, which is known to induce unexpected properties in carbohydrate com-

pounds,^{6–8} results in the molecules of I and II being essentially rigid and the hydroxyl groups assuming a fixed *trans* configuration. The fixed *trans* positions of the OH groups at C₂ and C₃ thus prevent the formation of an intermediate chelate complex with the periodate ion which appears to be necessary before cleavage can take place.⁹

The importance of this observation, in connection with the use of periodate oxidation in structural studies of the polysaccharides, is that certain sugar residues might not undergo cleavage by periodate, if the stereochemical arrangement of the polysaccharide molecule forces them to assume a rigid conformation in which the adjacent hydroxyl groups take up a fixed *trans* position with respect to each other. Such a contingency might possibly affect the behavior of the interior but not the terminal units, and hence is unlikely to interfere with the very convenient periodate method of end-group analysis.^{10–12}

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