JOURNAL OF THE
AMERICAN CHEMICAL SOCIETY

VOLUME 68 JUNE 18, 1946 NUMBER 6

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FORDHAM UNIVERSITY, AND FROM THE RESEARCH DEPARTMENT, ATLAS POWDER CO.]

Hexitol Anhydrides. Synthesis and Structure of Arlitan, the 1,4-Monoanhydride of Sorbitol[1]

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Two crystalline monoanhydrides of sorbitol have hitherto been described: the naturally occurring polygalitol[4] or aceritol,[5] which is the 1,5-sorbitan,[6] and the 3,6-sorbitan of Fischer and Zach.[7] The sirupy 2,5-hexitan of Brigl and Grüner,[8] characterized as its dibenzoate, is in all probability a sorbitan, according to Hockett, Goepp and Zief.[9]

Mueller and Hoffman,[10] disclose a non-crystalline monoanhydridization product of sorbitol, obtained by removing water by aid of heat and acidic or basic catalysts. This material was characterized only by the boiling point of 220° (0.5 mm.).

In 1936 one of us (S.S.) carried out the anhydridizing of sorbitol with sulfuric acid catalyst by heating under vacuum at 130–140°, until substantially one mole of water had been taken off. The reaction product, after removal of catalyst as the barium salt, treating with decolorizing carbon, in aqueous solution, and concentrating, threw down a crop of crystals. After recrystallizing from isopropyl alcohol, the compound melted at 115°, rotated $-21.5°$ (water) and on analysis proved to be a hexitan. From pure sorbitol, a yield of 36% of the theoretical may be obtained. The trivial name arlitan is proposed.[11]

The stability of arlitan to water, dilute acids or alkalies precludes the presence of an epoxy ring. Excluding 4-membered and 7-membered rings as unlikely where 5 and 6-membered rings could be formed narrows the probabilities to three: the 1,4-, the 2,5- and the 2,6-, if no Walden inversion has occurred.

Identification as the 1,4-derivative (I) was obtained by methylating to the sirupy tetramethyl ether, and comparing this derivative with the tetramethyl-1,4-sorbitan (II) made from Irvine's[12] 2,3,5,6-tetramethylsorbitol (IV), by anhydridizing with sulfuric acid. The two preparations agreed in rotation, specific gravity and refractive index. The tetramethylsorbitol was obtained by reducing the corresponding tetramethyl-D-glucose (III) over Raney nickel.[13]

By way of confirmation, the tetramethylarlitan was oxidized with nitric acid to a dimethyltartaric acid, V, identified, by way of the dimethyl ester, as the diamide of dimethyl-L-threaric acid (dimethoxysuccinic acid).[14]

These chemical proofs of arlitan structure are consistent with the lead tetraacetate oxidation

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(1) Part of the material in this paper was presented before the Division of Sugar Chemistry and Technology at Detroit, September, 1940.

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(4) Chodat, *Arch. sci. phys. nat.* [3] **20**, 599 (1888); P. Picard, *Bull. soc. chim. biol.*, **9**, 692 (1927).

(5) A. G. Perkin and Y. Uyeda, *J. Chem. Soc.*, **121**, 66 (1922).

(6) N. K. Richtmyer, C. J. Carr and C. S. Hudson, THIS JOURNAL, **65**, 1477 (1943); W. Freudenberg and E. F. Rogers, *ibid.*, **59**, 1602 (1937).

(7) E. Fischer and Zach, *Ber.*, **45**, 2068 (1912).

(8) P. Brigl and Grüner, *ibid.*, **66B**, 1945 (1934); **67B**, 1582 (1935).

(9) R. C. Hockett, M. Zief and R. M. Goepp, Jr., THIS JOURNAL, **68**, 935 (1946).

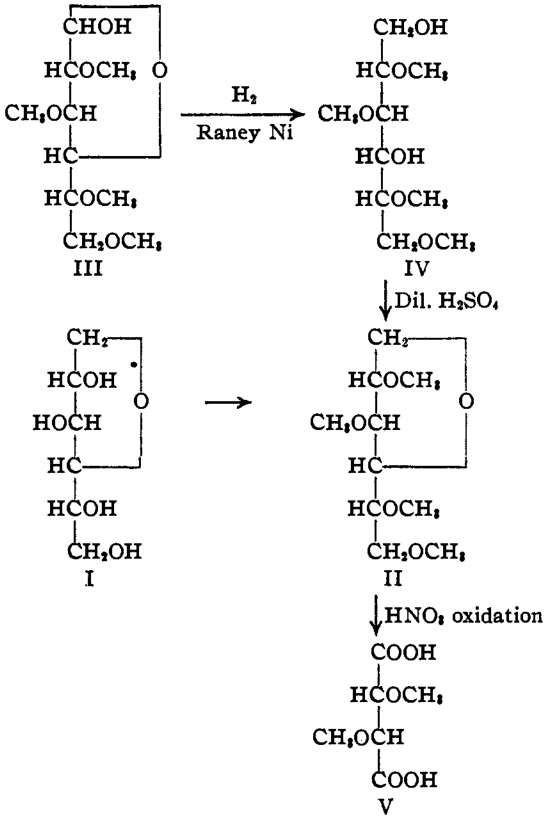
(10) U. S. Patent 1,757,468; German Patent 488,602 (1927).

(11) From the initials of the Atlas Research Laboratory, the laboratory of origin.

(12) J. C. Irvine, *J. Chem. Soc.*, **107**, 524 (1915).

(13) The authors are obliged to Dr. R. C. Hockett for carrying out the hydrogenation.

(14) R. C. Hockett [THIS JOURNAL, **57**, 2262 (1935)] has already proposed "threitol" for the optically active erythritol, and G. Pierce [*J. Biol. Chem.*, **23**, 327 (1915)] has generalized the "aric" ending for the higher polyhydroxy dibasic acids. The authors propose the extension of Hockett's suggestion to the tartaric acids, to bring their systematic nomenclature in line with that of other carbohydrates.



studies reported in the following paper[15] and with the behavior of the arlitan–boric acid complex published earlier by Krantz and co-workers.[16] The arlitan–boric acid complex shows a specific conductivity of 122 × 10^{-6}, compared to 939 × 10^{-6} for 1,4-mannitan (α-mannitan). Similarly, the potentiating effect on titration of boric acid is significantly less for arlitan than for 1,4-mannitan.[17] It would be expected that the locked *trans*-2,3-glycol pair in 1,4-sorbitan would have less potentiating effect than the corresponding *cis*-glycol pair of 1,4-mannitan.[18]

Smith, Finkelstein and Smith[19] have studied arlitan, together with certain hexitols, in renal function, and have found the clearance to be the same as that for inulin or creatinine. The same paper reports a method for analyzing arlitan, in the blood, and the absence of any toxic effect in man on intravenous administration of up to 70 g. within two hours. Kunkel, Carr and Krantz[20] found that arlitan resembled polygalitol, styracitol and several five- and six-carbon polyhydric alcohols in the slow rate of hemolysis of dog blood corpuscles.

The testing of arlitan tetranitrate as a vasodilator is reported by Krantz and co-workers.[21]

When condensed with benzaldehyde in the absence of acid, arlitan yields two monobenzal derivatives, melting at 136–140°, and 121–122°. Both compounds could be hydrolyzed to benzaldehyde and arlitan, melting at 115–116°.

The mother liquors from arlitan synthesis, when treated with *m*-nitrobenzaldehyde according to Bleyer, Diemair and Lix[22] yield as sole crystalline product a di-*m*-nitrobenzylidene derivative of a hexitan, m. p. 194°. The same derivative was also isolated from the mixture of hexitol anhydrides recovered from the saponification of a sorbitol alkyd resin by Goepp and Brown.[23] This compound is not identical with the corresponding *m*-nitrobenzylidene derivatives of any of the known hexitol monoanhydrides.

Experimental

Arlitan (1,4-Sorbitan.—One hundred grams of crystalline sorbitol, 1.1 g. of concentrated sulfuric acid, and 10–15 cc. of water were warmed under vacuum until sirupy. The solution was heated under water-jet vacuum to 140° and maintained between 135–145° for thirty minutes. The loss in weight was 9 g. The dark amber product was cooled and diluted with water, and decolorized with activated carbon (Darco). The sulfuric acid was removed as the barium salt by addition of barium acetate and filtering. The filtrate was concentrated under reduced pressure to a thick sirup, which was taken up in hot isopropyl alcohol, and let stand two days at room temperature. The crude yield of crystals, after washing with cold isopropyl alcohol was 33 g.; melting point, after two recrystallizations from isopropyl alcohol, was 115–116° (cor.); $[\alpha]^{27}\text{D}$ −21.9 (H_2O, $c = 2.5$) in a 2-dm. tube.

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.89; H, 7.32. Found: C, 43.9; H, 7.68. Acetin determination. Calcd. for $C_6H_8O(OH)_4$: cc. *N* alkali, 24.4. Found: cc. *N* alkali, 23.8.

Tetramethylarlitan.—Five grams of arlitan was methylated with dimethyl sulfate, caustic soda and carbon tetrachloride according to West and Holden.[24] The chloroform extract yielded on evaporation a light almost colorless oil. This oil was distilled twice in a small Widmer column. The yield was 4.9 g. A sample fractionated six times gave the following constants: $[n]^{22}\text{D}$ 1.4310; $[\alpha]^{22}\text{D}$ −38.92 (no solvent); −42.99° ($c = 4.84$, alcohol); sp. gr. 1.0658; b. p. 245–250°; b. p. 170–174° (14 mm.).

Anal. Calcd. for $C_{10}H_{20}O_5$: C, 54.47; H, 9.16; OCH_3, 56.31. Found: C, 54.33; H, 9.00; OCH_3, 56.69.

Oxidation of Tetramethylarlitan by Means of Nitric Acid.—To 5 g. of tetramethylarlitan, 35 cc. of concentrated nitric acid (d. 1.42) was added and the solution digested on a water-bath. The oxidation was allowed to proceed during the first two hours at a good rate. After three more hours the reaction appeared to be complete. One hundred cc. of water was now added and the mixture distilled *in vacuo* until after addition in all of 400 cc. of water a sample showed only a faint reaction for nitric acid. On complete evaporation a solid residue remained from which oxalic acid (0.5 g.), identified by its melting point and its insoluble calcium salt, was isolated.

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(15) R. C. Hockett, M. Conley, M. Yusem and R. I. Mason, THIS JOURNAL, **68**, 922 (1946).

(16) E. K. Bell, C. J. Carr and J. C. Krantz, Jr., *J. Phys. Chem.*, **44**, 862 (1940).

(17) E. K. Bell, C. J. Carr, W. E. Evans and J. C. Krantz, Jr., *ibid.*, **43**, 507 (1939).

(18) J. Böeseken and Couvert, *Rec. trav. chim.*, **40**, 354 (1921).

(19) W. W. Smith, N. Finkelstein and H. W. Smith, *J. Biol. Chem.*, **135**, 231 (1940).

(20) A. M. Kunkel, C. J. Carr and J. C. Krantz, Jr., *Proc. Soc. Exptl. Biol. Med.*, **42**, 438 (1939).

(21) J. C. Krantz, Jr., C. J. Carr, R. Forman and Ellis, *J. Pharm. Exptl. Therapeutics*, **67**, 187 (1939).

(22) Bleyer, Diemair and Lix, *Z. Untersuch. Lebensm.*, **65**, 37 (1933).

(23) R. M. Goepp, Jr., and K. R. Brown, *Ind. Eng. Chem.*, **30**, 1222 (1938).

(24) West and Holden, THIS JOURNAL, **56**, 930 (1934).

After most of the oxalic acid had been removed by crystallization the remainder was subjected to high-vacuum sublimation (0.1 mm.) in order to bring about complete removal of oxalic acid. After eight hours at a bath temperature of 100°, no further sublimation was noticed. The residue (0.3 g.) was a colorless sirup. Its specific rotation (c = 3, H_2O) was found to be +69°. It was acidic in reaction and formed a silver salt which was soluble in water but insoluble in ammoniacal solution.

Anal. Calcd. for $C_6H_{10}O_6$: C, 40.43; H, 5.66. Found: C, 40.78; H, 6.30.

A second experiment started with 25 g. of tetramethylarlitan and carried out in the manner described above yielded on a percentage basis the same amount of oxalic acid. The residue was transformed into its silver salt (4 g.) according to Asahina and Takimoto.[25]

This salt was treated three times with methyl iodide to produce a colorless sirup (2 g.) which showed a specific rotation of +79.4° in acetone (c = 4), *cf.* Hirst.[26] This sirup on standing for even six months did not crystallize completely.

Diamide of Dimethyl-L-threaric Acid (*d*-Dimethoxysuccinamide).—A small sample of the sirup just described was dissolved in methyl alcohol and ammonia was introduced to saturation. On standing for a short time in the ice-box crystals formed melting with decomposition at 260–265°. The specific rotation was +98.3° (c = 0.3, H_2O). Haworth, Hirst and Learner[27] give $[\alpha]_D$ +97° (H_2O, c = 0.4).

Anal. Calcd. for $C_6H_{12}O_4N_2$: N, 15.91. Found: N, 15.71, 15.73.

2,3,5,6-Tetramethylglucofuranose.—"Monoacetoneglucose" (1,2-isopropylidene-D-glucofuranose) was methylated with dimethyl sulfate to 1,2-isopropylidene-3,5,6-trimethyl-D-glucofuranose. The latter was hydrolyzed, methylated to methyl tetramethyl-D-glucofuranoside which after further hydrolysis yielded 2,3,5,6-tetramethylglucofuranose. The analysis was correct: n^{6}_{D} 1.4600; n^{17}_{D} 1.4566; n^{20}_{D} 1.4500; $[\alpha]^{24}_{D}$ −12.4 (H_2O, c = 15.0). Anderson, Charlton and Haworth[28] give n^{24}_{D} 1.4500, $[\alpha]^{20}_{D}$ −14.3° (H_2O, c = 1.26).

2,3,5,6-Tetramethylsorbitol.—Tetramethylsorbitol was prepared by reducing over Raney nickel at 1,500 lb. pressure and 135°, in aqueous alcoholic solution. The product had the following constants: n^{22}_{D} 1.4569; $[\alpha]^{24}_{D}$ −6.9° (H_2O, c = 6.1). Irvine[29] gives n_D 1.4568, $[\alpha]_D$ −6.2° in H_2O.

Anal. Calcd. for $C_{10}H_{22}O_6$: C, 50.40; H, 9.32; OCH_3, 52.03. Found: C, 50.66; H, 9.05; OCH_3, 52.00.

2,3,5,6-Tetramethyl-1,4-sorbitan from the Tetramethylsorbitol.—Twelve grams of 2,3,5,6-tetramethylsorbitol was treated with 2 cc. of 13% sulfuric acid and heated *in vacuo* for one-half hour to 135°, the temperature being measured by means of a thermometer immersed in the reaction mixture. After allowing to cool the acid was neutralized with an excess of sodium carbonate and the solution extracted by means of ether. After drying the extract over anhydrous sodium sulfate, the solvent was evaporated and the residue distilled *in vacuo*. The properties of the product were: n^{26}_{D} 1.4427; sp. gr. 1.069; $[\alpha]^{23}_{D}$ −43.0 (c = 7.08, alcohol); $[\alpha]^{23}_{D}$ −37.5° (no solvent).

Anal. Calcd. for $C_{10}H_{20}O_5$: C, 54.54; H, 9.13; OCH_3, 56.31. Found: C, 54.29; H, 9.19; OCH_3, 56.43.

Arlitan Monobenzylidenes.—Ten grams of arlitan was heated under reflux with 45 g. of benzaldehyde. After one and one-half hours the mixture was distilled *in vacuo* until most of the excess of benzaldehyde was removed. The residue was dissolved in ether, and thoroughly washed with sodium carbonate solution and water. The ether layer was separated and dried. After removal of the solvent, the residue was distilled (bath temp. 220–230°; 0.1–0.2 mm.) to produce 12 g. of a viscous sirup which partly crystallized. Fractionation with ether yielded two isomers. The more soluble isomer, after recrystallizing from methanol, melted 136–140° and showed $[\alpha]_D$ +33.72 in alcohol.

Anal. Calcd. for $C_{13}H_{16}O_5$ (mol. wt. 252.12): C, 61.88; H, 6.39. Found: C, 62.06; H, 6.44.

The less soluble isomer melts at 121–122°. It was recrystallized from ether for analysis.

Anal. Calcd. for $C_{13}H_{16}O_5$ (mol. wt. 252.12): C, 61.88; H, 6.39. Found: C, 62.14; H, 6.59.

The assistance of Dr. J. T. Sheehan in carrying out the nitric acid oxidation, and of Dr. W. Holst for certain analyses is gratefully acknowledged.

Summary

1. 1,4-Sorbitan has been synthesized by the direct acid-catalyzed anhydridizing of sorbitol.

2. The configuration has been established by comparison of the tetramethyl derivative with a preparation obtained from tetramethyl-D-glucofuranose, and by oxidation to dimethyl-L-threaric acid.

3. The trivial name arlitan is proposed for the new sorbitan.

4. D- and L-threaric acid are proposed as systematic carbohydrate names for D-(levo)- and L-(dextro)-tartaric acid.

WILMINGTON, DELAWARE RECEIVED JANUARY 29, 1946

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[25] Asahina and Takimoto, *Ber.*, **64**, 1805 (1931).

[26] Hirst, *J. Chem. Soc.*, 354 (1926).

[27] Haworth, Hirst and Learner, *ibid.*, 2435 (1927).

[28] Anderson, Charlton and Haworth, *ibid.*, 1329 (1929).

[29] Irvine, *ibid.*, **107**, 524 (1915).