[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Lead Tetraacetate Oxidations in the Sugar Group. IX.[1] The Structure of Arlitan, a Monoanhydride of Sorbitol[2]

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Previous papers from this Laboratory have reported the types of oxidation curves obtained when sugar derivatives of several classes are treated with lead tetraacetate in specially dried acetic acid under standard conditions.[1] The classes studied include hexopyranosides and anhydro-hexitols with six-membered rings, hexofuranosides and anhydro-hexitols with five-membered rings, and a number of open-chain polyalcohols. The close resemblance in oxidation behavior between glycosides and anhydro-polyols of analogous structure has pointed to the possibility of applying such oxidation procedures in the determination of the structures of polyol anhydrides of unknown constitution. In the present paper we report the successful application of the method in such a case.

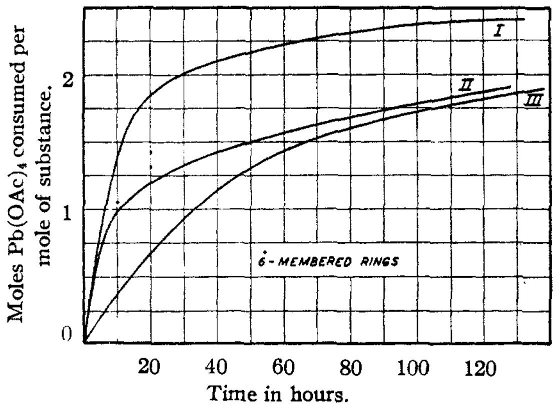

Fig. 1.—The oxidation of hexopyranosides by lead tetraacetate under standard conditions: I, methyl α-D-gulopyranoside and analogs; II, methyl α-D-galactopyranoside and analogs; III, methyl α-D-glucopyranoside and analogs.

In 1939, Soltzberg subjected sorbitol to direct dehydration by the action of sulfuric acid and from the products isolated a crystalline sorbitan[3] to which the trivial name "arlitan" was assigned. Since this compound, melting at 115° and rotating −24.5° (c, 10.000, H_2O) is not identical with either of the known monoanhydrides of sorbitol, 3,6-anhydrosorbitol,[4] or polygalitol,[5] there remain thirteen theoretically possible structures. All the possible sorbitans are listed below with an indication of the behavior to be expected of each on oxidation. Structures no. 4 and no. 12, which represent previously known substances, are marked.

TABLE I

No.	Ring position	Presence of epoxy ring	Moles of HCHO produced	Curve analogous to[a]
1	1,2	+	1	Erythritol (VI$_3$)
2	1,3	−	1	Glycerol (VI$_2$)
3	1,4	−	1	Ethyl galactofuranoside (IV)
4*	1,5	−	0	Methyl glucopyranoside (III)
5	1,6	−	0	Erythritol? (VI$_3$)
6	2,3	+	1	Glycerol (VI$_2$)
7	2,4	−	1	Ethylene glycol (VI$_1$)
8	2,5	−	0	*trans*-Cyclopentanediol[b]
9	2,6	−	0	Methyl gulopyranoside (I)
10	3,4	+	2	Glycerol (VI$_2$)
11	3,5	−	1	Ethylene glycol (VI$_1$)
12*	3,6	−	0	Methyl mannofuranoside (V)
13	4,5	+	1	Glycerol (VI$_2$)
14	4,6	−	1	Glycerol (VI$_2$)
15	5,6	+	1	Erythritol (VI$_3$)

[a] The Roman numerals identify the oxidation curves on the accompanying graphs. [b] No direct measurement of the oxidation of this substance has been made by the standard technique developed in this Laboratory. A relatively slow consumption of one mole of oxidant would be expected. However, a 2,5-anhydrohexitol having *trans* ring hydroxyls has recently been measured and found to behave according to prediction.

The observation that arlitan produces somewhat less than one molar equivalent of formaldehyde when oxidized, immediately eliminates 5, 8, 9 and 10 as possibilities and reduces the total to nine. The close resemblance of the arlitan oxidation curve to that of ethyl β-D-galactofuranoside (IV) and its wide divergence from all the other types, establishes a strong presumption that the ring of this sorbitan occupies the 1,4 position (possibility no. 3). It should be emphasized that these two determinations required only 0.25 g. of material.

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[1] Number VIII in this series, THIS JOURNAL, 66, 957 (1944).

[2] Part of the material in this paper was included in one of the same title read before the Division of Sugar Chemistry and Technology at the Detroit Meeting of the American Chemical Society in April, 1943. Some of the experimental work is taken from theses submitted by Maryalice Conley and by Milton Yusem to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy in February and in November, 1943, respectively, and from a thesis submitted by Robert I. Mason in partial fulfillment of the requirements for the degree of Bachelor of Science in January, 1943.

[3] This research, performed in the laboratories of the Atlas Powder Company, is described in an accompanying paper. The present investigation was carried out under an arrangement with Dr. R. Max Goepp, Jr., of the Atlas Powder Company and our determination of structure is published simultaneously with theirs by agreement. The work of Freudenberg, Soltzberg and Goepp holds chronological priority. The compound arlitan has been mentioned previously by Bell, Carr and Krantz, *J. Phys. Chem.*, 44, 862 (1940), and Smith, Finkelstein and Smith, *J. Biol. Chem.*, 135, 231 (1940), to whom samples were presented by the Atlas Powder Company for their investigations.

[4] Fischer and Zach, *Ber.*, 45, 456, 2068 (1912).

[5] Richtmyer and Hudson, THIS JOURNAL, 65, 64, 1477 (1943).

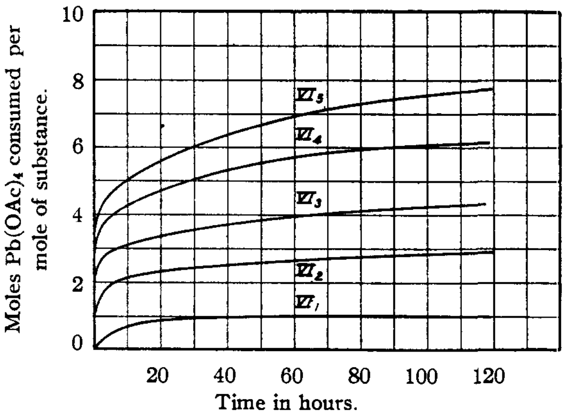
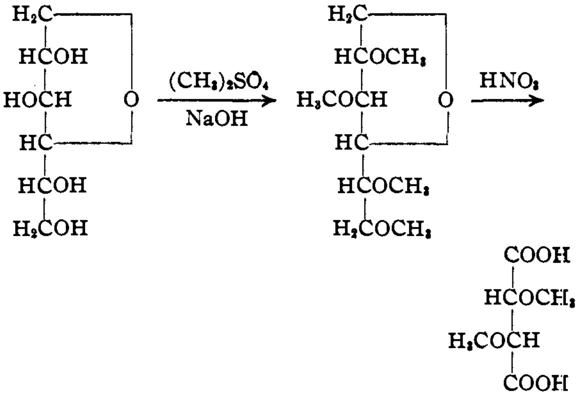


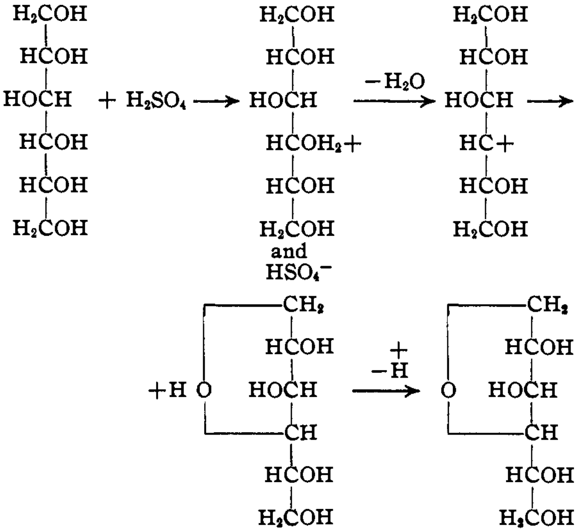
Fig. 2.—The oxidation of open-chain polyalcohols by lead tetraacetate under standard conditions: VI$_1$, ethylene glycol; VI$_2$, glycerol; VI$_3$, erythritol; VI$_4$, arabitol; VI$_5$, sorbitol, mannitol or dulcitol.

It is probable also that an epoxy ring would be detected readily by its ease of hydrolysis. The stability of arlitan would tend to eliminate 1, 6, 10, 13 and 15 as suitable structures thus further narrowing the possibilities.[3]

Although this structure assignment appears to be quite unequivocable, it was considered wise to make a confirmation by conventional methods. Therefore arlitan was fully methylated by the method of West and Holden[6] to a sirupy tetramethyl ether. On oxidation with nitric acid of density 1.42, a mixture of products was obtained from which dimethyl-L-threaric acid (*d*-dimethoxysuccinic acid) was isolated as the diamide in a yield of 22.5% of the theoretical,[7] thus confirming the observation reported in the accompanying paper.[3]



These observations establish the position of the ring in arlitan. They fail, however, to solve another problem. The action of sulfuric acid upon sorbitol is presumably to form an oxonium salt which tends to lose water in such a way as to produce a carbonium ion, which then closes the ring by coördination with an oxygen in another part of the molecule.[8] The loss of a proton on dilution completes the reaction series. In the formation of a 1,4-ether, the water loss could occur either at carbon one or four. In the latter case, a Walden inversion would be expected to occur at carbon four during the cyclization. If such an inversion occurs, the product will be an anhydrodulcitol rather than an anhydrosorbitol. The oxidation behavior of either compound would be the same so that lead tetraacetate oxidation cannot give any answer to the question whether inversion has taken place.



D-1,4-Dulcitan

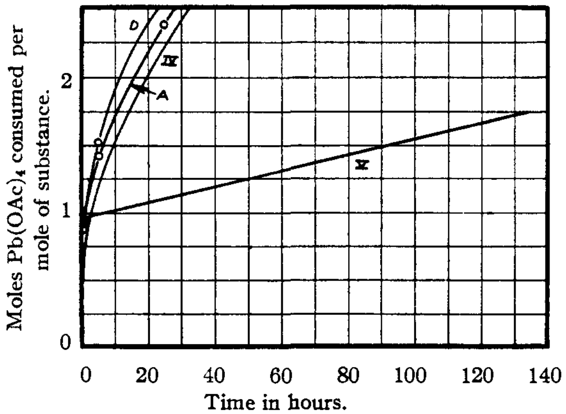


Fig. 3.—The oxidation of certain hexofuranosides and monoanhydrohexitols by lead tetraacetate under standard conditions: A, arlitan; IV, ethyl β-D-galactofuranoside; V, methyl α-D-mannofuranoside or D-3,6-anhydrosorbitol; D, D-3,6-anhydrodulcitol.

To solve this problem, we undertook to prepare an authentic sample of 3,6-anhydrodulcitol for direct comparison with arlitan. All the necessary steps in such a synthesis except the last had been reported by Haworth, Jackson and Smith[9] as follows

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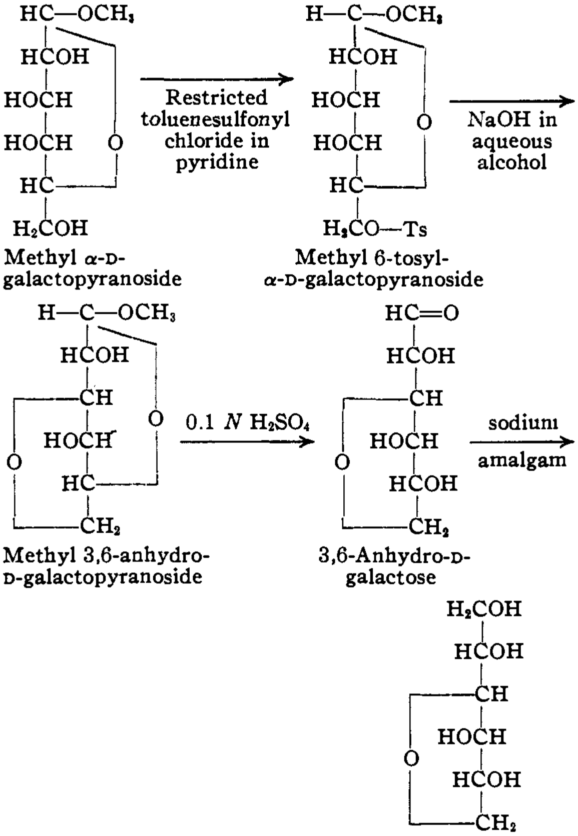
[6] West and Holden, THIS JOURNAL, 56, 930 (1934).

[7] Hockett, *ibid.*, 57, 2260 (1935).

[8] Hammett, "Physical Organic Chemistry," New York, N. Y., 1940, Chapters II, V, VI.

[9] Haworth, Jackson and Smith, *J. Chem. Soc.*, 620 (1940).



Methyl α-D-galactopyranoside

Methyl 6-tosyl-α-D-galactopyranoside

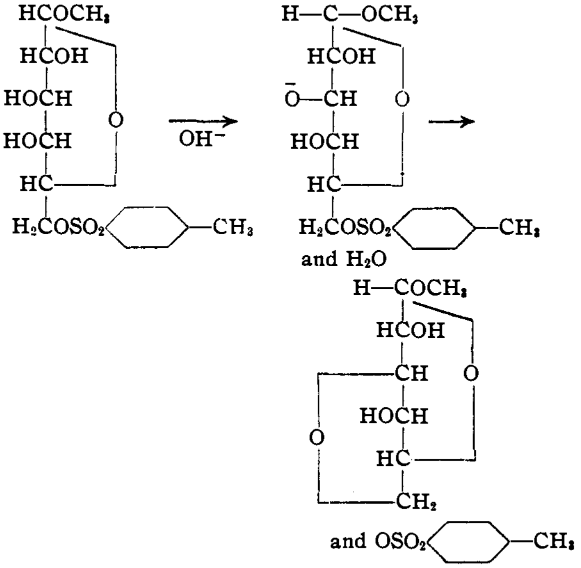
Methyl 3,6-anhydro-D-galactopyranoside

3,6-Anhydro-D-galactose

D-3,6-Anhydrodulcitol or L-1,4-anhydrodulcitol[10]

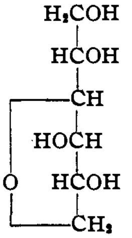
Since the validity of our conclusions regarding arlitan is dependent upon the authenticity of the 3,6-dulcitan prepared for comparison, it was important to be certain that the ring is actually in the 3,6 position. This was shown by subjecting methyl 3,6-anhydro-D-galactopyranoside to the action of lead tetraacetate. No reaction occurred until long standing had permitted acetolysis of the methyl group. A methyl 2,6- or 4,6-anhydrogalactoside would have been expected to oxidize relatively rapidly.[11] A second pertinent question is whether an inversion could have taken place at carbon three of this compound.

According to modern theory, no such inversion could occur if all bonds of carbon three remain unbroken during the reaction. An accumulation of evidence regarding the behavior of sulfonic acid esters toward alkalies has led to the opinion that during hydrolysis the bond between carbon and oxygen is the one broken.[12]

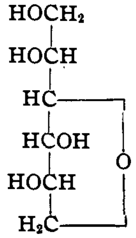


If this mechanism is correct, therefore, no inversion could occur. However, we are not dependent upon general theory for a conclusion regarding the possibility of inversion, since by the action of alkali upon methyl 6-bromo-6-desoxy-α-D-galactopyranoside, Valentin[13] has prepared a product identical in properties with the methyl 3,6-anhydro-α-D-galactopyranoside of Haworth and collaborators. In Valentin's preparation, the bonds of carbon number three cannot have been disturbed because no oxygen was removed during the reaction. Hence no inversions can have occurred and we conclude that our final product can only be 3,6-dulcitan.

This authentic reference compound will be the enantiomorph of arlitan if inversion occurred during formation of the latter substance from sorbitol. If no inversion occurred, the two substances will merely be stereoisomers



Synthetic dulcitan (D-3,6-anhydrodulcitol or L-1,4-anhydrodulcitol)



Possible structure of arlitan (L-3,6-anhydrodulcitol or D-1,4-anhydrodulcitol)

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(10) Although dulcitol itself is internally compensated many of its derivatives are capable of being resolved into optical isomers. For example, a reaction which caused formation of a 1,4-anhydride ring directly from dulcitol would produce an equal quantity of the 3,6-anhydride which is the enantiomorph. Each of these anhydrides can be given two names. The one can be named as indicated under the formula above and its enantiomorph by interchanging the D and L. Another method which has been proposed for naming such derivatives of symmetrical dulcitol is based on the concept that the unsymmetrical derivative is produced from either D- or L-galactose. This derivation can be suggested by using the name D- or L-galactitol. The substance formulated above would therefore be 3,6-anhydro-D-galactitol.

(11) Mr. Samuel Solar described the repreparation of methyl 3,6-anhydro-D-galactopyranoside and its behavior toward lead tetraacetate in a thesis submitted to the faculty of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Bachelor of Science in June, 1941.

(12) Phillips, *J. Chem. Soc.*, **123**, 44 (1923).

(13) Valentin, *Coll. Czech. Chem. Comm.*, **4**, 364 (1932); *cf.* Fischer and Zach, ref. 4.

Unfortunately the synthetic 3,6-dulcitan was obtained only as a sirup. However, both the hydrolysis of the methyl anhydrogalactoside and the reduction of the anhydrogalactose proceeded so readily that we believe the reactions to have been virtually quantitative, though the possibility of partial epimerization cannot be entirely ruled out. The yield of sirupy dulcitan was 93.6% of the theoretical on the basis of the weight of crystalline glycoside used. The substance rotated +16.1°[14] (*c* 6.572, H_2O, 22°). It was fully acetylated to a sirup which had the expected composition for a tetraacetylhexitan but which likewise failed to crystallize. Deacetylation of the purified acetate regenerated a sirupy dulcitan rotating +17.5[14] (*c* 1.428, H_2O, 22°). An oxidation by lead tetraacetate under standard conditions gave a curve of the type predicted.

A comparison of the properties of dulcitan, arlitan and their acetates indicates that the two hexitans are very probably not enantiomorphs.

TABLE II

Substance	Specific rotation[a]
Arlitan	−24.6° (*c* 10, H_2O, 26°)
D-3,6-Anhydrodulcitol	+17.5° (*c* 1.428, H_2O, 22°)
Tetraacetylarlitan	+45.9° (*c* 4.41, abs. alc., 25°)
Tetraacetyl-D-3,6-anhydrodulcitol	−16.9° (*c* 5.176, abs. alc., 22°)

[a] Reference 14.

If arlitan is not the enantiomorph of D-3,6-anhydrodulcitol, it did not suffer inversion at carbon three during formation from sorbitol and is 1,4-anhydrosorbitol.

Acknowledgments.—We thank Dr. R. Max Goepp, Jr., and Dr. Sol Soltzberg, of the Atlas Powder Company, for samples of arlitan and for a free exchange of information and suggestions. We also thank Mr. William H. Reeder, III, formerly of this Laboratory, for measuring the formaldehyde produced by oxidation of arlitan and Dr. Morris Zief for redetermination of certain oxidation curves under more strictly anhydrous conditions.

Experimental

Rate of Oxidation Measurements.—The standard technique described by Hockett, Dienes and Ramsden was employed.[15]

Tetramethylarlitan.—When twenty-five grams of arlitan was methylated almost exactly as described by West and Holden,[8] there was obtained a colorless sirup which distilled from 82–85° at 1 mm. The yield was 23.3 g. or 70% of the theoretical. The liquid rotated −38.71° (25°, no solvent), showed a specific gravity of 1.0828 at 25° and index of refraction at 25° of 1.4426 (D line of sodium).

Anal. Calcd. for $C_6H_8O(OCH_3)_4$: OCH_3, 56.4. Found: OCH_3, 55.9, 56.1.

Oxidation of Tetramethylarlitan with Nitric Acid.—A mixture of 15 g. of tetramethylarlitan and 100 cc. of nitric acid (density 1.42) was digested on a steam-bath for five hours. Water was added and distilled off under reduced pressure six times to remove most of the nitric acid. Then 4.4 g. of crystals separated on cooling the remaining sirup. These were identified as oxalic acid by melting point and their precipitation of calcium ions. The filtrate was extracted with three 20-cc. portions of alcohol-free ether. Concentration of the ether solution yielded 0.80 g. more oxalic acid and a residue weighing 2.5 g. The specific rotation of this sirup was +73.58 (*c*, 2.1742, H_2O).

Dimethyl-L-threaramide. (***d*-Dimethoxysuccinamide.**)—An ethereal solution of diazomethane was prepared from nitrosomethylurea, as described by Arndt,[16] and added in excess to an ether solution of the products of nitric acid oxidation. When evolution of nitrogen ceased, the excess ether and diazomethane were evaporated by warming on the steam-bath. A sirup remained weighing 2.7 g. and rotating[14] +78.9° (*c*, 1.254, acetone, 25°). This sirup was dissolved in 10 cc. of dry methanol and the solution was saturated with anhydrous ammonia gas. In a few minutes, fine needles separated. This product, after recrystallization from boiling water, melted about 270° (dec.) and rotated[14] +95.6° (*c* 0.4251, H_2O, 25°). The melting point of authentic dimethyl-L-threaramide, prepared by conventional means from *d*-tartaric acid, was not depressed when the two samples were mixed. The yield of amide was 2 g. or 81% if the ester was considered to be pure dimethyl dimethylthrearate. The over-all yield was 22.5% based upon tetramethylarlitan.

Determination of Formaldehyde Produced by Lead Tetraacetate Oxidation.—A sample of 0.182 g. (0.001 mole) of arlitan dissolved in 5 cc. of glacial acetic acid was dropped upon dry lead tetraacetate in an apparatus so arranged that a slow stream of dry air could be passed over the mixture, sweeping formaldehyde out through a vertical condenser that returned acetic acid to the reaction vessel, and into a receiver containing 75 cc. of 2 *N* hydrochloric acid solution saturated with 2,4-dinitrophenylhydrazine. The removal of formaldehyde was completed by heating the reaction mixture to boiling for an hour while the flow of dry air was continued at the rate of about five bubbles per second through the receiver. The formaldehyde 2,4-dinitrophenylhydrazone was filtered in a weighed crucible with a sintered glass bottom, dried at 60° and weighed. Controls were made with ethylene glycol under the same conditions. The formaldehyde recovered was equivalent to 62% of an equimolar quantity.

The apparatus and procedure used are not considered wholly satisfactory, but the observation does establish the fact that a large proportion of the arlitan molecules are cleaved at the 5,6-position.

Methyl α-D-Galactopyranoside.—Prepared as described by Hudson and Dale,[17] this substance melted at about 100° (uncor.).

Methyl 6-*p*-Toluenesulfonyl-α-D-galactopyranoside.—Prepared essentially as described by Haworth, Jackson and Smith,[9] our product melted about 180°.

Methyl 3,6-Anhydro-α-D-galactopyranoside.—Made from the methyl 6-*p*-toluenesulfonyl-α-D-galactopyranoside as described by Haworth, Jackson and Smith,[9] our product melted 136.2–137.2° (cor.) and rotated[14] about +79.5° (*c* 1.200, H_2O, 22°).

3,6-Anhydro-D-galactose.—A sample of 6.0 g. of methyl 3,6-anhydro-α-D-galactopyranoside was treated with 0.1 *N* sulfuric acid overnight at room temperature (25°). The specific rotation had then reached +29.9° and the solution showed a positive Schiff test and reduced Fehling solution at room temperature in a few seconds.

D-3,6-Anhydrodulcitol.—The solution described above was just neutralized to phenolphthalein with sodium hydroxide, made up to 150 cc. and two-thirds of the solution was treated with sodium amalgam in small portions while a rapid stream of carbon dioxide was led through and stirring was maintained. When reducing power was gone after four hours and a 100% excess of sodium amalgam over the

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[14] All rotations cited in this paper are specific rotations of the D line of sodium at the temperature indicated. Concentrations are stated as grams of substance in 100 cc. of solution.

[15] Hockett, Dienes and Ramsden, THIS JOURNAL, **65**, 1474 (1943).

[16] Arndt, "Organic Syntheses," **15**, 3 (1935).

[17] Hudson and Dale, THIS JOURNAL, **52**, 2534 (1930).

theoretical had been used the solution was made acid with sulfuric acid to convert sodium bicarbonate to sodium sulfate. After adjustment to exact neutrality, the mixture was evaporated dry (diminished pressure) and the solids were extracted repeatedly with absolute ethanol. The extracts were filtered and evaporated dry. The treatment was repeated until an ash-free sirup was obtained. A sirup so obtained rotated[14] +16.1° (*c* 6.572, H_2O, 22°) and represented a 93% yield.

Tetraacetyl-D-3,6-anhydrodulcitol.—A sample of the dulcitan was dried thoroughly and treated with a 50:50 mixture of pure pyridine and acetic anhydride. After heat evolution ceased the liquids were evaporated under reduced pressure and the remaining sirup was dissolved in chloroform and washed with dilute sodium bicarbonate and with water. On drying and evaporating the chloroform a sirup was obtained which failed to crystallize from six solvents and solvent combinations. When dried at 5 mm. and 70° for half an hour, the substance rotated[14] −16.9° (*c* 5.176, abs. alc., 22°).

Anal. Calcd. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.02. Found: C, 49.70, 50.22, 50.10; H, 5.95, 5.98, 5.69.

Deacetylation of Tetraacetyl-D-3,6-anhydrodulcitol.—The sirup was dissolved in dry methanol in which a piece of sodium the size of a pin-head had been dissolved. The mixture was boiled under reflux for ninety minutes and then a stream of carbon dioxide was passed into the solution. After filtration through decolorizing carbon, the solution was evaporated dry and heated under 2 mm. pressure at 55° for one hour after removal of most of the solvent. Part of this sample was used for a rotation measurement,[14] +17.5° (*c* 1.428, H_2O, 22°).

Rate of Oxidation of D-3,6-Anhydrodulcitol by Lead Tetraacetate.—The weighed sirup was dissolved in specially dried acetic acid in a volumetric flask. Then from a dry buret the volume of solution containing 0.041 g. of sample was measured out. The measurements were made as described by Hockett, Dienes and Ramsden.[15] The curve obtained was of the same type as that found for arlitan and ethyl β-D-galactofuranoside.

2,3,5-Tribenzoyl-6-*p*-toluenesulfonylarlitan (prepared by Elizabeth Sheffield).—To a solution of 5 g. (0.030 mole) of arlitan in 50 cc. of anhydrous pyridine at 0° was added 5.8 g. of *p*-toluenesulfonyl chloride (0.033 mole). After one-half hour at 0° and six hours at room temperature, the mixture was recooled to −7°, and 10.6 cc. (0.11 mole) of benzoyl chloride was added in small portions with vigorous shaking. After one hour at 0° and fourteen hours at room temperature, 100 cc. of ice-water was added. The precipitated oil was digested ten times with fresh 100-cc. portions of water containing a few drops of acetic acid. The oil was then separated, dissolved in chloroform and dried over anhydrous sodium sulfate. After removal of chloroform, the residue was dissolved in benzene at 30° and isopentane added to the point of turbidity. Crystals separated very slowly. Filtered, recrystallized twice as fine needles from benzene–isopentane and dried for three hours in a vacuum at 60°, the substance melted 161.5–163.0° (cor.) and rotated[14] +35.1° (*c*, 2.000, $CHCl_3$).

Anal. Calcd. for $C_{34}H_{30}O_{10}S$: C, 64.75; H, 4.75. Found: C, 64.2, 64.4; H, 5.22, 5.24.

The crystals are soluble in chloroform, benzene and pyridine.

The assigned structure is a surmise based upon the known behavior of *p*-toluenesulfonyl chloride.[18]

Summary

There are fifteen possible anhydrosorbitols of which two were previously known. A new substance of this class, arlitan, first prepared by Soltzberg of the Atlas Powder Company, has been studied under an arrangement with that company. Its behavior when oxidized with lead tetraacetate under standard conditions eliminates all of the possible structures except that containing a 1,4 ring. In the choice of this most probable structure, the rate-of-oxidation curves of many substances of known constitution have been used for comparison. The presence of a 1,4 ring is further supported by methylation and oxidation with nitric acid to *d*(+)-dimethoxysuccinic acid (*d*(+)-dimethyltartaric acid) which is identified as the diamide.

The possibility of a Walden inversion at carbon number four during anhydridization of sorbitol has been eliminated by the preparation of authentic D-3,6-anhydrodulcitol for comparison with arlitan. Since neither the anhydrohexitols nor their tetraacetates show equal and opposite rotations, it is concluded that arlitan is not the enantiomorph of D-3,6-anhydrodulcitol and therefore was formed from sorbitol without inversion. This suggests strongly that in anhydridization of sorbitol, a primary carbinol group supplies the oxygen lost as water.

A new derivative of arlitan is described.

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[18] Hockett and Downing, THIS JOURNAL, **64**, 2463 (1942).