[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Structure of Diacetone-L-fucitol (2,3,4,5-Di-isopropylidene-L-fucitol)

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In a prior publication[1] it was shown that the condensation of dulcitol and acetone by the action of gaseous hydrochloric acid led to the formation of a mixture of 2,3,4,5-di-isopropylidene-dulcitol and 2,3,5,6-di-isopropylidene-D,L-galactitol. It has now been observed that L-fucitol (6-desoxy-L-galactitol), under similar experimental conditions, condenses with acetone to give a high yield (90%) of a single crystalline di-isopropylidene-L-fucitol. This substance readily forms a monobenzoate upon arylation with benzoyl chloride in pyridine solution. This benzoylated di-isopropylidene-L-fucitol is oxidized only slowly by per-iodic acid in aqueous dioxane solution, and the consumption of oxidant corresponds to three molecular equivalents; it seems probable that the isopropylidene residues are slowly hydrolyzed in the weakly acidic solution (compare the periodic acid oxidations of α- and β-diacetone-dulcitols[1]) and the benzoyl-L-fucitol thus liberated is then oxidized in the usual manner. No formaldehyde could be detected in the oxidized solution, a fact which made it probable that the benzoyl group is attached to a primary hydroxyl group and that consequently the substance is probably 1-benzoyl-2,3,4,5-di-isopropylidene-L-fucitol. Supporting evidence for this inference was obtained when it was found that benzoyl-L-fucitol (prepared by removing the isopropylidene groups from benzoyl-di-isopropylidene-L-fucitol), upon oxidation with lead tetraacetate in glacial acetic acid solution, consumed three molecular equivalents of oxidant in one hour, due to the oxidation of the benzoyl-L-fucitol, and a further two equivalents upon long standing, due to the secondary oxidation of the two molecular equivalents of formic acid[2] produced in the primary oxidation of the benzoyl-L-fucitol. The absence of formaldehyde as an oxidation product was again noted. These results thus support the view that the benzoyl group is attached to a primary hydroxyl group, and that the substances concerned have the structures that have been inferred. Definitive proof of this conclusion was obtained through the following reactions: the diacetone compound (I) was converted to 1-tosyl-2,3,4,5-di-isopropylidene-L-fucitol (II) which in turn was transformed to 1-iodo-2,3,4,5-di-isopropylidene-L-fucitol (III) by treatment with sodium iodide in acetone solution at 100°. The iodo compound was reduced with hydrogen and Raney nickel in alkaline solution to 1,6-bis-desoxy-2,3,4,5-di-isopropylidene-dulcitol (IV) which, upon removal of the isopropylidene residues, yielded 1,6-bis-desoxy-dulcitol (V). This substance, upon oxidation with sodium periodate, consumed three molecular equivalents of oxidant and formed two molecular equivalents of formic acid. Upon oxidation with per-iodic acid and estimation of acetaldehyde by the procedure developed by Nicolet and Shinn[3] it yielded two molecular equivalents of acetaldehyde. A 1,6-bis-desoxy-dulcitol would be expected to follow the reaction course $CH_3(CHOH)_4CH_3 + 3HIO_4 = 2CH_3CHO + 2HCOOH + 3HIO_3 + H_2O$. The data agree with this equation and no applicable structure other than the one postulated corresponds with these measurements.

A further independent and conclusive proof of the structure of di-isopropylidene-L-fucitol follows from the observation that 1,6-di-iodo-2,3,4,5-di-isopropylidene-dulcitol[1] could be reduced by hydrogen and Raney nickel in alkaline solution to 1,6-bis-desoxy-2,3,4,5-di-isopropylidene-dulcitol which was identical with the compound (IV) prepared in the series of reactions already described, starting from di-isopropylidene-L-fucitol (I).

We are indebted to Mr. George L. Keenan of the Food and Drug Administration of the Federal Security Agency, for the determination of the optical crystallographic properties of 1,6-bis-desoxy-2,3,4,5-di-isopropylidene-dulcitol and to Dr. B. H. Nicolet and Mr. L. A. Shinn, of the Bureau of Dairy Industry, U. S. Department of Agriculture, for assistance in the acetaldehyde determinations.

Experimental

2,3,4,5-Di-isopropylidene-L-fucitol.—A suspension of 10.0 g. of L-fucitol in 95 cc. of acetone was cooled in an ice-bath and 5 cc. of acetone, which had been saturated at 0°

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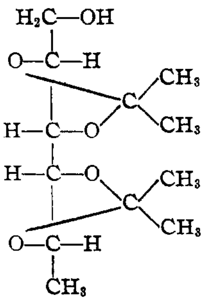
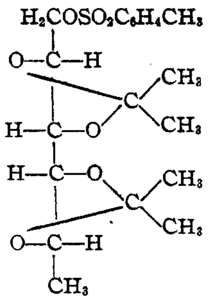
[1] Hann, Maclay and Hudson, THIS JOURNAL, **61**, 2432 (1939). The conventions which we use regarding the names dulcitol and galactitol have been explained in that article.

[2] Grosheintz, *ibid.*, **61**, 3381 (1939).

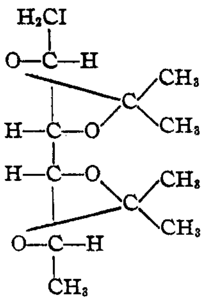
[3] Nicolet and Shinn, *J. Biol. Chem.*, **138**, 91 (1941); THIS JOURNAL, **63**, 1456 (1941).



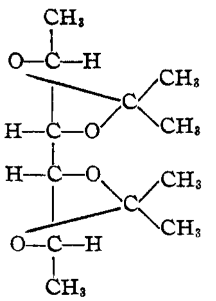
2,3,4,5-Di-isopropylidene-L-fucitol (I)



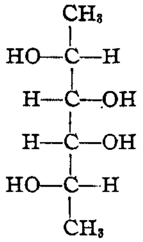
1-Tosyl-2,3,4,5-di-isopropylidene-L-fucitol (II)



1-Iodo-2,3,4,5-di-isopropylidene-L-fucitol (III)



1,6-Bis-desoxy-2,3,4,5-di-isopropylidene-dulcitol (IV)



1,6-Bis-desoxy-dulcitol (V)

with dry gaseous hydrochloric acid, was added. The reaction mixture was agitated at 20° until the L-fucitol dissolved completely (two hours). The next day, the solution was stirred with 40 g. of basic lead carbonate for one hour, the lead chloride and carbonate were removed by filtration, and the filtrate was concentrated to a dry crystalline residue in the presence of some basic lead carbonate. The reaction product was dissolved in 50 cc. of acetone and the solution, after clarification by filtration, was concentrated to a thick sirup which gradually deposited thin plates. The precipitate (9.5 g., m. p. 54–59°) was separated by filtration and the filtrate concentrated to yield an additional 3.8 g. of crystalline product. The total yield was therefore 13.3 g. (90%). The di-isopropylidene-L-fucitol was very soluble in the usual organic solvents and was recrystallized with a direct recovery of 50% from one part of 50% alcohol. It was obtained in the form of thin rectangular plates which melted at 59–60° (cor.) and had a specific rotation of +11.7° (*c*, 0.94) in absolute alcohol.[4]

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.51; H, 9.00. Found: C, 58.48; H, 9.01.

1-Acetyl-2,3,4,5-di-isopropylidene-L-fucitol.—A solution of 5.0 g. of 2,3,4,5-di-isopropylidene-L-fucitol in a mixture of 10 cc. of pyridine and 25 cc. of acetic anhydride was allowed to stand overnight at 20° and then poured upon crushed ice. The precipitated acetyl derivative crystallized in a yield of 5.0 g. (85%). It was recrystallized from 10 parts of 50% alcohol and obtained in the form of thin plates which melted at 46–47° and showed a specific rotation of +26.1° (*c*, 0.85) in chloroform.

Anal. Calcd. for $C_{14}H_{24}O_6$: C, 58.31; H, 8.39; CH_3CO, 14.9. Found: C, 58.30; H, 8.26; CH_3CO, 14.7.

1-Benzoyl-2,3,4,5-di-isopropylidene-L-fucitol.—To an ice-cold solution of 5.0 g. of 2,3,4,5-di-isopropylidene-L-fucitol in 20 cc. of pyridine, 3.0 cc. (1.2 molecular equivalents) of benzoyl chloride was added dropwise. After forty-two hours at room temperature the reaction mixture was poured into 400 cc. of ice water and the crystalline benzoate separated by filtration. The yield was 7.1 g. (quantitative). The compound crystallized from its solution in 10 parts of 60% alcohol in clusters of fine needles which showed a melting point of 56.5 to 58° (cor.) and a rotation of +18.7° (*c*, 0.84) in chloroform.

Anal. Calcd. for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48; C_6H_5CO, 30.0. Found: C, 65.28; H, 7.45; C_6H_5CO, 29.7.

Per-iodic Acid Oxidation of 1-Benzoyl-2,3,4,5-di-isopropylidene-L-fucitol.—To a solution of 0.2497 g. of 1-benzoyl-2,3,4,5-di-isopropylidene-L-fucitol in 18 cc. of purified dioxane, 4.95 cc. of 0.576 *M* per-iodic acid (4.00 molecular equivalents) was added and the volume adjusted to 25 cc. with purified dioxane. Analysis of 5-cc. sub-samples at the expiration of one, twenty-two, forty-nine, one hundred and forty-one, and three hundred and thirty-eight hours, indicated that 0.05, 0.61, 1.25, 2.54 and 2.80 molecular equivalents had been consumed at 20°. The hydrolysis of the acetone groups evidently occurred slowly and the final consumption of the oxidant approached the expected value of 3.00 molecular equivalents for a 1-benzoyl-L-fucitol.

1-Benzoyl-L-fucitol.—A solution of 7.0 g. of 1-benzoyl-2,3,4,5-di-isopropylidene-L-fucitol in 100 cc. of 80% acetic acid was refluxed for one-half hour, then diluted with 300 cc. of cold water and allowed to stand at 5° overnight. The 1-benzoyl-L-fucitol (4.8 g., 89%) which had crystallized was separated by filtration and recrystallized from 50 parts of 25% acetic acid. The pure compound was obtained in the form of long needles which melted at 177–178° (cor.) and had a specific rotation of +4.30° (*c*, 0.82) in absolute pyridine.

Anal. Calcd. for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71; C_6H_5CO, 38.9. Found: C, 57.73; H, 6.59; C_6H_5CO, 38.8.

Lead Tetraacetate Oxidation of 1-Benzoyl-L-fucitol.—To a solution of 0.1162 g. of 1-benzoyl-L-fucitol in 25 cc. of glacial acetic acid, 66.65 cc. of 0.0516 *M* lead tetraacetate glacial acetic acid solution (8.00 molecular equivalents) was added and the volume adjusted to 100 cc. with glacial acetic acid. Analysis of 5-cc. sub-samples at the expiration of one, twenty-five, ninety-seven, and one hundred and sixty-nine hours, indicated that 2.94, 4.18, 4.98 and 5.19 molecular equivalents of oxidant had been consumed. The oxidation of the 1-benzoyl-L-fucitol should require three molecular equivalents of oxidant. The consumption of 2.94 equivalents of oxidant in the first hour indicated that the glycol groupings had been oxidized rapidly. The slow secondary oxidation was probably due to the reducing action of the two moles of formic acid produced in the reaction. Grosheintz[2] has shown that formic acid is quantitatively oxidized to carbon dioxide and water in lead tetraacetate–glacial acetic acid solution. The total consumption of oxidant was therefore in agree-

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[4] All of the crystalline compounds described in the experimental part were recrystallized to constant melting point and specific rotation, $[\alpha]^{20}\mathrm{D}$; *c* is the concentration in 100 cc. of solution; the tube length was 4 dm.

ment with the expected consumption of 5.00 molecular equivalents.

1-Benzoyl-2,3,4,5-tetraacetyl-L-fucitol.—A solution of 2.0 g. of 1-benzoyl-L-fucitol in a mixture of 50 cc. of pyridine and 50 cc. of acetic anhydride was allowed to stand overnight at room temperature. The reaction mixture was then poured into 250 cc. of ice water and the crystalline reaction product removed by filtration. The yield was 3.2 g. (quantitative). The compound deposited from its solution in 10 parts of alcohol in the form of small plates which melted at 116–117° (cor.) and exhibited a specific rotation of +18.6° (*c*, 0.84) in chloroform.

Anal. Calcd. for $C_{21}H_{26}O_{10}$: C, 57.54; H, 5.96. Found: C, 57.52; H, 5.99.

Pentabenzoyl-L-fucitol.—This compound was obtained in quantitative yield by the benzoylation of 1-benzoyl-L-fucitol with benzoyl chloride in pyridine solution in the usual manner. The substance deposited from its solution in 50 parts of alcohol in clusters of long needles. It melted at 149–150° (cor.) and showed a specific rotation of −5.96° (*c*, 0.87) in chloroform.

Anal. Calcd. for $C_{41}H_{34}O_{10}$: C, 71.71; H, 4.99; C_6H_5CO, 76.5. Found: C, 71.70; H, 5.13; C_6H_5CO, 76.1.

1-Benzoyl-tritosyl-L-fucitol.—A solution of 3.5 g. (4.8 molecular equivalents) of *p*-toluene-sulfonyl chloride in 5 cc. of pyridine was added slowly to an ice-cold solution of 1 g. of benzoyl-L-fucitol in 10 cc. of pyridine. The reaction mixture was held at 0° for one-half hour, then for five days at room temperature (23–24°) and finally warmed to 40° for twenty-four hours and then poured into 350 cc. of ice water. The gummy precipitate which formed was separated by filtration and dissolved in 75 cc. of warm alcohol. Water was added to the solution to a slight turbidity and upon standing overnight at room temperature, 0.6 g. (22%) of a fine powder was deposited. The substance was recrystallized from 50 parts of alcohol and was obtained in small prisms which melted at 155–157° (cor.) and exhibited a specific rotation of +13.8° (*c*, 0.86) in chloroform. This melting point and rotation were not changed by two further recrystallizations from alcohol.

Anal. Calcd. for $C_{34}H_{36}O_{12}S_3$: C, 55.72; H, 4.95; S, 13.12. Found: C, 55.80; H, 4.97; S, 13.06.

1-Benzoyl-2,3,4,5-tetratosyl-L-fucitol.—The mother liquor from which the 0.6 g. of impure 1-benzoyl-tritosyl-L-fucitol (above) had been separated was treated with 100 cc. of water and it deposited a sticky sirup. The aqueous portion was decanted and the sirup dissolved in 25 cc. of warm alcohol. As the solution cooled droplets of a viscid sirup settled out and gradually crystallized. The product (yield 1.0 g., 30%) was recrystallized from 50 parts of alcohol from which clusters of prisms formed. The pure tetratosylate melted at 143–145° (cor.) and showed a specific rotation of +18.0° (*c*, 0.90) in chloroform.

Anal. Calcd. for $C_{41}H_{42}O_{14}S_4$: C, 55.51; H, 4.77; S, 14.46. Found: C, 55.55; H, 4.84; S, 14.27.

1-Tosyl-2,3,4,5-di-isopropylidene-L-fucitol.—A solution of 5 g. of *p*-toluenesulfonyl chloride in 10 cc. of pyridine was added dropwise to an ice-cold solution of 5.0 g. of 2,3,4,5-di-isopropylidene-L-fucitol in 10 cc. of pyridine and the reaction mixture, after standing for forty-two hours at 25°, was poured upon crushed ice. The crystalline 1-tosyl derivative, which precipitated in a yield of 7.2 g. (89%), was recrystallized from 10 parts of 60% alcohol and was obtained in the form of long needles which melted at 78–79° (cor.) and rotated +19.7° (*c*, 0.82) in chloroform.

Anal. Calcd. for $C_{19}H_{28}O_7S$: C, 56.98; H, 7.05; S, 8.01. Found: C, 57.04; H, 7.02; S, 7.93.

1-Iodo-2,3,4,5-di-isopropylidene-L-fucitol.—A solution of 5.0 g. of 1-tosyl-2,3,4,5-di-isopropylidene-L-fucitol and 5.6 g. (3 molecular equivalents) of sodium iodide in 100 cc. of acetone was heated at 100° in a pressure bottle for one hour. The sodium *p*-toluene sulfonate which had deposited (2.5 g., quantitative) was removed by filtration and the acetone was evaporated by an air current. The dark sirupy residue, after treatment with 25 cc. of water and a few drops of sodium thiosulfate solution to remove sodium iodide and a small amount of free iodine, was cooled to 5° and it gradually crystallized. The yield was 3.6 g. (82%). The crude crystalline product was dissolved in 8 parts of alcohol and water added just to turbidity. Upon standing at 0° elongated prisms of the pure compound, which melted at 35–36° (cor.) and showed a specific rotation +28.9° (*c*, 0.80) in chloroform, were readily obtained.

Anal. Calcd. for $C_{12}H_{21}O_4I$: C, 40.46; H, 5.94. Found: C, 40.62; H, 5.90.

1,6-Bis-desoxy-2,3,4,5-di-isopropylidene-dulcitol.—A suspension of 0.5 g. of freshly prepared Raney nickel in 10 cc. of methyl alcohol was added to a solution of 2.5 g. of 1-iodo-2,3,4,5-diisopropylidene-L-fucitol in a mixture of 20 cc. of methanol and 5 cc. of a 10% solution of sodium hydroxide in methanol. The reaction mixture was agitated vigorously while hydrogen under a slight positive pressure was introduced from a reservoir which permitted measurement of the volume of the gas absorbed. The theoretical amount of hydrogen, 158 cc. (S. T. P.), was taken up in the first one-half hour and only 2 cc. in the second half-hour. The catalyst was removed by filtration and the alkaline methanol solution was neutralized by a current of carbon dioxide and then concentrated *in vacuo* to dryness. The dry residue was extracted with three 25-cc. portions of ether and upon evaporation of the solvent the crude reduction product was obtained as a crystalline powder which melted at 60–63° (cor.). The yield was 1.5 g. (94%). The 1,6-bis-desoxy-di-isopropylidene-dulcitol was deposited from its solution in 10 parts of isopropyl alcohol as prisms which melted at 62 to 63.5° (cor.). The compound was optically inactive in chloroform solution (*c*, 0.82). It was noticeably volatile at room temperature. It may be sublimed readily and the sublimed substance melted at 63–64° (cor.).

Anal. Calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.70; H, 9.63.

1,6-Bis-desoxy-dulcitol.—A solution of 2.5 g. of 1,6-bis-desoxy-2,3,4,5-di-isopropylidene-dulcitol in 100 cc. of 80% acetic acid was refluxed for three hours and the solvent then removed by concentration *in vacuo* at 50°. The dry residue was recrystallized from 40 parts of absolute alcohol and yielded 0.6 g. (38%) of small prisms which melted at 183–184° (cor.). The compound was optically inactive in absolute alcohol solution.

Anal. Calcd. for $C_6H_{14}O_4$: C, 47.98; H, 9.40. Found: C, 48.11; H, 9.37.

Sodium Periodate Oxidation of 1,6-Bis-desoxy-dulcitol.—To an ice-cold solution of 0.2196 g. of 1,6-bis-desoxy-dulcitol in 30 cc. of water was added 8.35 cc. of 0.574 *M* sodium periodate (3.3 molecular equivalents). After standing at 0° for one-half hour, the solution was allowed to warm to room temperature and the volume was adjusted to 50 cc. with water. Analysis of 5-cc. sub-samples at the expiration of one, two, three, and twenty hours indicated that 2.97, 3.01, 3.03 and 3.06 molecular equivalents of oxidant had been consumed. At the expiration of twenty hours the titration of a 5-cc. sub-sample required 2.92 cc. of 0.1 *N* sodium hydroxide (using methyl red as indicator), equivalent to 2.00 molecular equivalents of formic acid. The oxidation of 1,6-bis-desoxy-dulcitol should consume three molecular equivalents of sodium periodate and produce two molecular equivalents of formic acid.

Determination of the Acetaldehyde Produced in the Oxidation of 1,6-Bis-desoxy-dulcitol by Per-iodic Acid.—A 10-cc. aliquot (0.0847 millimole) of a solution of 0.0318 g. of 1,6-bis-desoxy-dulcitol in 25 cc. of water was oxidized by per-iodic acid and the acetaldehyde produced was determined by the procedures described by Nicolet and Shinn.[3] The consumption of 0.02 *N* iodine (16.48 cc.) corresponded to 0.1648 millimole of acetaldehyde, equivalent to 1.95 moles of acetaldehyde per mole of 1,6-bis-desoxy-dulcitol. As previously indicated, the expected production of acetaldehyde was two molecular equivalents.

1,6-Bis-desoxy-2,3,4,5-di-isopropylidene-dulcitol from 1,6-Di-iodo-2,3,4,5-di-isopropylidene-dulcitol.—A sample of 2.5 g. of 1,6-di-iodo-2,3,4,5-di-isopropylidene-dulcitol[1] was reduced with hydrogen and Raney nickel by the procedure employed for the reduction of 1-iodo-2,3,4,5-di-isopropylidene-L-fucitol. The absorption of hydrogen was 241 cc. (S. T. P.), the theoretical volume being 232 cc. (S. T. P.). The yield of 1,6-bis-desoxy-2,3,4,5-di-isopropylidene-dulcitol was 1.2 g. (quantitative). The recrystallized compound was optically inactive and melted at 62–63° (cor.). A mixed melting point with the reduction product from 1-iodo-2,3,4,5-di-isopropylidene-L-fucitol showed no depression. As would be expected, the substance was converted to 1,6-bis-desoxy-dulcitol upon refluxing with 80% acetic acid for three hours. The identity of the latter compound with that obtained starting from 2,3,4,5-di-isopropylidene-L-fucitol was established through optical crystallographic data by Mr. George L. Keenan. He reported that the substance, from both sources, under the microscope *in ordinary light* showed refractive indices of $n_\alpha = 1.500$, $n_\beta = 1.518$, $n_\gamma = 1.528$, $n_\gamma - n_\alpha = 0.028$, all ±0.002. *In parallel polarized light* (*crossed nicols*) the extinction is inclined on the rods and the sign of elongation is negative. *In convergent polarized light* (*crossed nicols*) partial biaxial figures are seen on many of the rods and plates, one axis usually being perpendicular to them.

Summary

The condensation of acetone and L-fucitol by the action of dry hydrochloric acid gas has been shown to produce a single di-isopropylidene-L-fucitol in high yield. Evidence has been obtained from the per-iodic acid oxidation of benzoyl-di-isopropylidene-L-fucitol, and from the lead tetraacetate oxidation of the benzoyl-L-fucitol obtained by its acid hydrolysis, that the benzoyl group in these derivatives is attached to a primary hydroxyl group. Proof that di-isopropylidene-L-fucitol is 2,3,4,5-di-isopropylidene-L-fucitol has been established by formation from the diacetal of a tosyl derivative which was converted to an iodo compound reducible in alkaline solution by hydrogen and Raney nickel to 1,6-bis-desoxy-2,3,-4,5-di-isopropylidene-dulcitol; the latter substance was hydrolyzed to 1,6-bis-desoxy-dulcitol, which upon per-iodic acid oxidation formed *two equivalents* of acetaldehyde and *two equivalents* of formic acid; these analytical results limit the structure of the diacetal to that of 2,3,4,5-di-isopropylidene-L-fucitol. Further confirmation of this structure was obtained by reducing catalytically the known 1,6-di-iodo-2,3,4,5-di-isopropylidene-dulcitol to 1,6-bis-desoxy-2,3,4,5-di-isopropylidene-dulcitol which proved to be identical with the compound prepared from 2,3,4,5-di-isopropylidene-L-fucitol.

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