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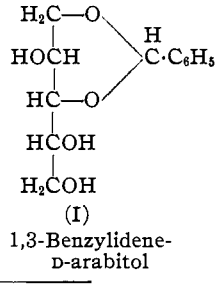
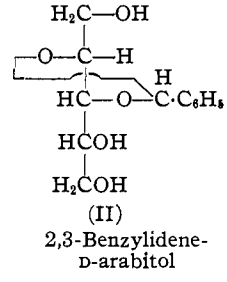
The Isomeric 1,3- and 2,3-Benzylidene-D-arabitols

BY W. T. HASKINS, RAYMOND M. HANN AND C. S. HUDSON

In 1894 Emil Fischer[1] prepared a monobenzylidene-L-arabitol melting at 152° (cor.) from L-arabitol and benzaldehyde through the condensing action of concentrated hydrochloric acid which had been saturated with gaseous hydrochloric acid. At the time of discovery of the compound methods were not available for the determination of the position of the benzylidene linkage in such acetals, but recently Steiger and Reichstein[2] have shown that the enantiomorphous benzylidene-D-arabitol is oxidized by lead tetraacetate to a sirupy product considered to be benzylidene-D-threose since upon mild acid hydrolysis it is converted in a yield of 95% into D-threose. This fact, as pointed out by Steiger and Reichstein, limits the structure of the acetal to either that of 1,3-benzylidene-D-arabitol (I) or 2,3-benzylidene-D-arabitol (II), since these are the only acetal structures of D-arabitol which can yield a derivative of the tetrose sugar under the oxidative conditions employed.



(I)
1,3-Benzylidene-D-arabitol



(II)
2,3-Benzylidene-D-arabitol

In the present article we describe the synthesis and proof of structure of 2,3-benzylidene-D-arabitol (II). The synthesis of the new acetal was accomplished through the use of intermediates of known structure in which the possibility of the benzaldehyde reacting with the primary hydroxyl groups of D-arabitol was excluded. The starting material employed, namely, 1,5-dibenzoyl-D-arabitol, was prepared by the selective benzoylation of D-arabitol at positions one and five. The structure of this dibenzoate was established through a study of its oxidation with lead tetraacetate. A 1,5-dibenzoyl-pentitol should reduce two molecular equivalents of this reagent and produce one equivalent of formic acid and two equivalents of benzoyl-glycolic aldehyde. The oxidation of the new dibenzoyl-D-arabitol proceeded with the consumption of 1.94 and 2.02 molecular equivalents of oxidant in thirty and sixty minutes, respectively, and from the oxidized solution it was possible to isolate a yield of 57% of the crystalline semicarbazone of benzoyl-glycolic aldehyde; the fact that this yield is greater than 50% proves that both primary hydroxyl groups are benzoylated and the dibenzoate is therefore 1,5-dibenzoyl-D-arabitol. The 1,5-dibenzoyl-D-arabitol upon agitation with benzaldehyde and fused zinc chloride at room temperature formed the 1,5-dibenzoate of a monobenzylidene-D-arabitol and the latter substance, upon

(1) Fischer, *Ber.*, **27**, 1535 (1894). The original communication does not state whether D- or L-arabitol was employed, but it was undoubtedly the latter alcohol, since D-arabitol was first prepared by Ruff in 1899 (*ibid.*, **32**, 555 (1899)).

(2) Steiger and Reichstein, *Helv. Chim. Acta*, **19**, 1016 (1936).

debenzoylation yielded a crystalline monobenzylidene-D-arabitol, which melted at 81–83° (cor.) and showed a specific rotation $[\alpha]^{20}D$ of +18.1° in chloroform. The method of synthesis limits the possible structures of this acetal to those of 2,3-, 2,4- or 3,4-benzylidene-D-arabitol. By treatment with glycol-splitting reagents the 2,3-acetal would yield one molecular equivalent each of benzylidene-D-threose and formaldehyde, while the 2,4-acetal would not be attacked and the 3,4-acetal would form benzylidene-D-erythrose and formaldehyde. The new benzylidene-D-arabitol, upon oxidation with aqueous sodium periodate, consumed 1.05 molecular equivalents of oxidant and from the oxidized solution the crystalline dimethone derivative of formaldehyde was isolated in a yield of 74%; the 2,4-benzylidene structure is thus excluded and the choice lies between the 2,3- and 3,4-structures. In further experiments the sirupy oxidation product, which could conceivably be either 2,3-benzylidene-D-threose or 2,3-benzylidene-D-erythrose, was hydrolyzed to remove the benzylidene moiety and a quantitative yield of sirupy tetrose sugar was obtained; it was characterized as D-threose by conversion (1) to its crystalline isopropylidene derivative, (2) by oxidation with nitric acid to L-tartaric acid, and (3) by reduction to the corresponding crystalline alcohol, D-threitol. The conversion to D-threose decides the question; the new acetal is 2,3-benzylidene-D-arabitol. While these results constitute a definitive proof of the structure of the new benzylidene-D-arabitol [m. p. 81–83° (cor.)] and would appear at first glance to justify the assignment of a 1,3-acetal structure to the known benzylidene-D-arabitol melting at 152°, they do not exclude the possibility that the latter substance may also possess a 2,3-acetal structure. As Emil Fischer[3] has pointed out, the condensation of a polyhydroxy compound with benzaldehyde introduces a new asymmetric carbon atom (the carbonyl carbon of the benzylidene moiety) into the molecule and the difference in physical properties of the two benzylidene-D-arabitols could conceivably be due either to the position or to the stereo structure of the benzylidene group. A decision of this question was sought through treatment of the crystalline tribenzoyl derivatives of the isomeric benzylidene-D-arabitols with a 2% sulfuric acid acetylating mixture; previous experience has shown that this reagent causes the substitution of acetyl groups on those hydroxyl groups which are concerned in the acetal linkage and it would be expected that if the 2,3-acetal linkage were present in both compounds they should both yield 2,3-diacetyl-1,4,5-tribenzoyl-D-arabitol. It was found that the 1,4,5-tribenzoyl-2,3-benzylidene-D-arabitol that was prepared from the new 2,3-benzylidene-D-arabitol melting at 81–83° (cor.) gave a quantitative yield of a sirupy 1,4,5-tribenzoyl-2,3-diacetyl-D-arabitol which rotated $[\alpha]^{20}D$ +19.1° in chloroform; in contrast, the tribenzoyl derivative of the benzylidene-D-arabitol of Steiger and Reichstein gave a quantitative yield of a crystalline product, presumably 2,4,5-tribenzoyl-1,3-diacetyl-D-arabitol, which melted at 65–66° (cor.) and rotated $[\alpha]^{20}D$ −8.2° in chloroform. The wide divergence in physical properties of these tribenzoyl-diacetyl-D-arabitols would seem to exclude the possibility that the two tribenzoyl-benzylidene-D-arabitols from which they are derived are stereo isomers and we therefore conclude that the benzylidene-D-arabitol of Steiger and Reichstein is 1,3-benzylidene-D-arabitol. Its older enantiomorph, which Emil Fischer prepared, becomes 1,3-benzylidene-L-arabitol.

We express our appreciation to Dr. A. T. Ness for performing the microchemical analyses in connection with this study.

Experimental

1,5-Dibenzoyl-D-arabitol.—A solution of 50 g. of D-arabitol in 500 cc. of absolute pyridine was cooled to 0° in an ice–salt mixture and 76 cc. of benzoyl chloride (two molecular equivalents) was added to the stirred solution dropwise at such a rate that the temperature of the solution did not rise above 5°. The reaction mixture was allowed to stand for two hours at room temperature, the pyridine was removed by concentration *in vacuo* (bath temperature, 50°), and the sirupy residue was poured into 1 liter of ice water; the slightly gummy solid which formed was dissolved in 400 cc. of alcohol and as the solution cooled it deposited the dibenzoate (60 g., 51%) as clusters of small prisms. The compound, after recrystallization from 6 parts of alcohol, showed a melting point of 131–132° (cor.) and a specific rotation $[\alpha]^{20}D$ of +8.4° in pyridine (*c*, 0.81).[4] It is soluble in pyridine and in hot alcohol, moderately soluble in acetone, and insoluble in chloroform, ether and water.

Anal. Calcd. for $C_{19}H_{20}O_7$: C, 63.32; H, 5.59; C_6H_5CO, 58.3. Found: C, 63.42; H, 5.64; C_6H_5CO, 58.5.

(3) Fischer, *Ber.*, **27**, 1532 (1894). Cf. Haskins, Hann and Hudson, THIS JOURNAL, **64**, 137 (1942).

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

1,5-Dibenzoyl-2,3,4-triacetyl-D-arabitol.—A solution of 2.0 g. of 1,5-dibenzoyl-D-arabitol in a mixture of 10 cc. of pyridine and 10 cc. of acetic anhydride was allowed to stand for eighteen hours at room temperature; the mixture was poured into ice water and the precipitate which formed (2.6 g., 96%) was recrystallized from 6 parts of alcohol, from which it was deposited as needles melting at 102–103° (cor.) and rotating $[\alpha]^{20}D$ +31.0° in chloroform (*c*, 0.84). The compound is soluble in ether, pyridine and warm alcohol and insoluble in water, petroleum ether and cold alcohol.

Anal. Calcd. for $C_{25}H_{26}O_{10}$: C, 61.72; H, 5.39. Found: C, 61.65; H, 5.45.

Lead Tetraacetate Oxidation of 1,5-Dibenzoyl-D-arabitol.—(1) A solution of 1.026 g. of 1,5-dibenzoyl-D-arabitol in 100 cc. of 0.0696 *M* lead tetraacetate–glacial acetic acid solution (2.44 molecular equivalents) was adjusted to a volume of 120 cc. with glacial acetic acid. Analysis of 5-cc. subsamples at the expiration of thirty and sixty minutes, and eighteen hours showed that 1.94, 2.02 and 2.30 molecular equivalents of oxidant, respectively, had been consumed at 20°. The expected consumption, in accordance with the reaction course $C_6H_5COOCH_2(CHOH)_3CH_2OOCC_6H_5 + 2Pb(OOC\cdot CH_3)_4 = 2C_6H_5COOCH_2CHO + HCOOH + 2Pb(OOC\cdot CH_3)_2 + 2CH_3COOH$ was two molecular equivalents. The increased consumption of oxidant after eighteen hours presumably was due to a secondary oxidation of the formic acid produced in the primary oxidation.[5]

(2) A 50-cc. aliquot of the above solution was removed after the oxidation had proceeded for one hour and it was heated on the steam-bath for one hour with 1.0 g. of semicarbazide hydrochloride and 2.0 g. of sodium acetate; the cooled reaction mixture was filtered to remove the precipitated lead chloride and the filtrate was freed of lead by treatment with hydrogen sulfide; the lead-free solution was concentrated *in vacuo* to dryness and the dry residue was extracted with cold water to remove the sodium acetate. The precipitate of fine needles (0.3 g., 57%) of benzoyl-glycolic aldehyde semicarbazone which remained showed a melting point of 194–195° (cor.) in agreement with Aoyama's[6] recorded value and a mixed melting point with benzoyl-glycolic aldehyde semicarbazone prepared by the lead tetraacetate oxidation of 1,6-dibenzoyl-dulcitol showed no depression.

1,5-Dibenzoyl-2,3-benzylidene-D-arabitol.—A mixture of 10 g. of 1,5-dibenzoyl-D-arabitol, 10 g. of powdered fused zinc chloride and 20 cc. of benzaldehyde was agitated at room temperature for one hour, at which time the solution of the dibenzoate was complete. The reaction mixture was allowed to stand for three days during which period it set to a magma; the mass was thinned with 20 cc. of alcohol and the crystals were separated by filtration; a further crop of crystalline material was obtained by adding water to the filtrate. The total yield was 9.1 g. (73%). The compound, upon recrystallization from 4 parts of alcohol, formed needles which melted at 108–109° (cor.) and rotated $[\alpha]^{20}D$ +12.6° in chloroform (*c*, 0.85). The substance is soluble in pyridine, ether, acetone and warm alcohol; it is insoluble in petroleum ether and water.

Anal. Calcd. for $C_{26}H_{24}O_7$: C, 69.63; H, 5.39; C_6H_5CO, 46.9. Found: C, 69.52; H, 5.51; C_6H_5CO, 47.4.

1,5-Dibenzoyl-4-acetyl-2,3-benzylidene-D-arabitol.—A solution of 1.0 g. of 1,5-dibenzoyl-2,3-benzylidene-D-arabitol in a mixture of 5 cc. of pyridine and 5 cc. of acetic anhydride was allowed to stand overnight at 25°; the crystalline precipitate (1.1 g., quantitative) which formed upon pouring the reaction mixture into ice water was recrystallized from 5 parts of alcohol as clusters of cottony needles. The compound is insoluble in water and petroleum ether, but dissolves readily in acetone, pyridine and chloroform. It melted at 73–75° (cor.) and rotated $[\alpha]^{20}D$ +2.1° in chloroform (*c*, 1.01).

Anal. Calcd. for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.60; H, 5.41.

1,4,5-Tribenzoyl-2,3-benzylidene-D-arabitol.—This compound was prepared by the further benzoylation of 1,5-dibenzoyl-2,3-benzylidene-D-arabitol in pyridine solution with benzoyl chloride. It crystallized from its solution in 5 parts of alcohol in the form of needles, which melted at 101–103° (cor.) and rotated $[\alpha]^{20}D$ −14.6° in chloroform (*c*, 0.82).

Anal. Calcd. for $C_{33}H_{28}O_8$: C, 71.73; H, 5.11; C_6H_5CO, 57.1. Found: C, 71.93; H, 5.15; C_6H_5CO, 56.9.

2,3-Benzylidene-D-arabitol.—To an ice-cold solution of 5.4 g. of 1,5-dibenzoyl-2,3-benzylidene-D-arabitol in 50 cc. of chloroform, 5 cc. of 0.2 *N* sodium methylate solution was added and the reaction mixture was allowed to stand at 5° for eighteen hours. The solution was then concentrated to a volume of 15 cc. and diluted with 15 cc. of petroleum ether; the gummy precipitate which formed was dissolved in 30 cc. of warm chloroform and upon cooling the solution, the acetal crystallized in the form of fine needles. The yield was 2.6 g. (90%). The compound, which is moderately soluble in acetone and alcohol, was recrystallized from 10 parts of chloroform; it melted at 81–83° (cor.) and a further recrystallization from 3 parts of acetone did not alter this melting point; its specific rotation $[\alpha]^{20}D$ in absolute alcohol (*c*, 0.80) was +10.8° and in pyridine (*c*, 0.81) it was +18.1°.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.83; H, 6.71.

Sodium Periodate Oxidation of 2,3-Benzylidene-D-arabitol.—(1) To a solution of 0.1184 g. of 2,3-benzylidene-D-arabitol in 10 cc. of water, 2.0 cc. of 0.388 *M* sodium periodate solution (1.57 molecular equivalents) was added and the volume was adjusted to 25 cc. with water. The analysis of 5-cc. subsamples at the expiration of one, two and one-half and twenty-four hours showed that 1.05, 1.05 and 1.11 molecular equivalents of oxidant had been consumed. The expected consumption for a 2,3-benzylidene-D-arabitol is one molecular equivalent.

(2) An aqueous solution (25 cc.) containing 0.1000 g. of 2,3-benzylidene-D-arabitol and 2.0 cc. of 0.388 *M* sodium periodate solution was allowed to stand for one hour at room temperature; the solution was then neutralized to methyl red by addition of saturated aqueous sodium bicarbonate and 60 cc. of 0.4% dimethone reagent was added; an immediate precipitation of fine needles of formal-dimethone occurred; the mixture was allowed to stand for twenty-four hours at 5° and the precipitate

(5) Grosheintz, THIS JOURNAL, **61**, 3381 (1939).

(6) Aoyama, *J. Pharm. Soc. Japan*, **47**, 539 (1927).

(0.0902 g., 74%) was separated by filtration; the formal-dimethone melted at 188–190° (cor.) and a mixed melting point with authentic formal-dimethone showed no depression of this value.

Isopropylidene-D-threose from 2,3-Benzylidene-D-arabitol.—To a solution of 5.0 g. of 2,3-benzylidene-D-arabitol in 100 cc. of water, 50 cc. of 0.442 *M* sodium periodate solution (1.06 molecular equivalents) was added. After one hour a solution of 2.8 g. of barium chloride dihydrate in 25 cc. of water was added and the insoluble barium iodate and periodate were separated by filtration. The filtrate was concentrated *in vacuo* in the presence of 1.0 g. of washed barium carbonate and the sirupy residue, after drying by successive addition and evaporation of three-25 cc. portions of absolute alcohol, was dissolved in absolute alcohol and filtered to remove the insoluble barium salts; the filtrate was concentrated *in vacuo* to a dry sirup (4.7 g., theory for 2,3-benzylidene-D-threose, 4.3 g.). The sirup did not crystallize. It was dissolved in 50 cc. of 10% acetic acid and the solution was refluxed for one hour; the solvent and part of the liberated benzaldehyde were removed by concentration *in vacuo* and the residual sirup was dissolved in 15 cc. of water and extracted with three 10-cc. portions of ether to remove the remaining benzaldehyde; the aqueous layer was concentrated to a dry sirup (2.5 g., theory for D-threose, 2.5 g.). The sirup was dissolved in 50 cc. of acetone containing 0.2 cc. of concentrated sulfuric acid and the solution was agitated with 10 g. of anhydrous copper sulfate for forty-eight hours; the reaction mixture was filtered and the filtrate was agitated with 5.0 g. of anhydrous potassium carbonate for eighteen hours; the solid was removed by filtration and the filtrate was concentrated *in vacuo* in the presence of 0.2 g. of potassium carbonate to a dry crystalline residue; an ether extract of the residue, upon evaporation, deposited 2.5 g. (76%) of crystalline isopropylidene-D-threose which, after one recrystallization from 5 parts of ether, melted at 83–84° (cor.) and showed a specific rotation $[\alpha]^{20}D$ of −15.1° in acetone (*c*, 0.80) in agreement with the recorded values[6] of 84° and −15.27°, respectively.

L-Tartaric Acid from Isopropylidene-D-threose.—Two grams of isopropylidene-D-threose was converted to L-tartaric acid by oxidation with nitric acid in accordance with the procedure of Steiger and Reichstein. The yield of crystalline L-tartaric acid obtained was 0.7 g. (37%). The compound, after recrystallization by solution in 2 parts of dioxane and the addition of 2 parts of ether, showed a melting point of 168–169° (cor.) and a specific rotation $[\alpha]^{20}D$ of −14.8° in water (*c*, 2.0). A mixed melting point with authentic L-tartaric acid showed no depression. The specific rotation of a 2.0% solution of L-tartaric acid, calculated by the formula of Pribram and Glücksmann,[7] is −14.98°.

D-Threitol from 2,3-Benzylidene-D-arabitol.—The sirupy 2,3-benzylidene-D-threose obtained by the sodium periodate oxidation of 5.0 g. of 2,3-benzylidene-D-arabitol was dissolved in 50 cc. of alcohol and reduced with hydrogen and Raney nickel at a pressure of 110 atmospheres at room temperature (25°) for twenty hours. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to a non-reducing sirup, presumably 2,3-benzylidene-D-threitol. The sirup was hydrolyzed as directed for 2,3-benzylidene-D-threose and the aqueous benzaldehyde-free solution of D-threitol thus obtained was concentrated to a dry crystalline residue; a solution of the crystalline material in 15 cc. of absolute alcohol deposited D-threitol (1.6 g., 64%) in the form of long needles. The compound, after recrystallization from 6 parts of absolute alcohol, melted at 88–89° (cor.) and showed a specific rotation $[\alpha]^{20}D$ +4.6° in aqueous solution (*c*, 0.84) in agreement with the values of 88° and +4.0°, respectively, recorded for D-threitol by Maquenne and Bertrand.[8] The D-threitol was further characterized by conversion to dibenzylidene-D-threitol. This compound crystallized from 25 parts of dioxane or 300 parts of alcohol as fine needles which melted at 231° (cor.) in agreement with the melting point reported by Maquenne and Bertrand. The specific rotation of the diacetal has not been previously recorded; in pyridine solution (*c*, 0.80) it showed a specific rotation $[\alpha]^{20}D$ of −90.2°.

1,3-Benzylidene-D-arabitol.—On passing a rapid stream of dry hydrochloric acid gas into a suspension of 30.0 g. of D-arabitol in 25 cc. of benzaldehyde at room temperature the D-arabitol dissolved completely in ten minutes. The reaction mixture was allowed to stand for eighteen hours during which period it became a magma of crystals; the mass was broken up and kept for twenty-four hours in an evacuated desiccator containing potassium hydroxide and sulfuric acid; the product was then successively triturated with ether, dilute sodium bicarbonate solution and water. The yield of 1,3-benzylidene-D-arabitol, which upon one recrystallization from 4 parts of alcohol, gave a product showing the correct melting point of 151–152°, was 40.0 g. (84%). In our hands the original method of Fischer, in which concentrated hydrochloric acid saturated with dry hydrochloric acid gas is used as a condensing agent, gave yields of only 10–11% of the acetal. The specific rotation $[\alpha]^{20}D$ of the purified substance, not recorded heretofore, was found to be −7.6° in pyridine (*c*, 2.0).

1,3-Benzylidene-2,4,5-tribenzoyl-D-arabitol.—The benzoylation of 4.5 g. of 1,3-benzylidene-D-arabitol in pyridine solution by benzoyl chloride gave a quantitative yield (10.3 g.) of the tribenzoate. The compound is soluble in chloroform, ether, acetone and warm alcohol, slightly soluble in cold alcohol and insoluble in petroleum ether and water. Upon recrystallization from 10 parts of alcohol it formed prisms, which melted at 137–138° (cor.) and rotated $[\alpha]^{30}D$ −133.8° in chloroform (*c*, 0.84).

Anal. Calcd. for $C_{33}H_{28}O_8$: C, 71.73; H, 5.11; C_6H_5CO, 57.1. Found: C, 71.60; H, 5.17; C_6H_5CO, 56.8.

1,3-Diacetyl-2,4,5-tribenzoyl-D-arabitol.—A solution of 4.0 g. of 1,3-benzylidene-2,4,5-tribenzoyl-D-arabitol in 25 cc. of an acid acetylating solution (prepared by adding 1 cc. of concentrated sulfuric acid dropwise to an ice-cold mixture of 35 cc. of acetic anhydride and 15 cc. of acetic acid) was allowed to stand at 20° for twenty-four hours and then poured upon crushed ice. The sirupy reaction product was extracted with chloroform and the washed and dried extract was again concentrated to a sirup. A solution of the sirup in warm alcohol deposited fine needles of 1,3-diacetyl-2,4,5-tribenzoyl-D-arabitol as it cooled. The yield was 3.8 g. (95%). The compound, after recrystal-

(7) Pribram and Glücksmann, *Monatsh.*, **19**, 136 (1898).

(8) Maquenne and Bertrand, *Bull. soc. chim.*, [3] **25**, 740 (1901).

lization from 4 parts of methyl alcohol, melted at 65–66° (cor.) and rotated $[\alpha]^{20}D$ −8.2° in chloroform (*c*, 1.0).

Anal. Calcd. for $C_{30}H_{28}O_{10}$: C, 65.69; H, 5.15; saponification, 0.1047 g. requires 9.54 cc. 0.1 *N* sodium hydroxide. Found: C, 65.58; H, 5.16; saponification, 0.1047 g. consumed 9.47 cc. 0.1 *N* sodium hydroxide.

2,3-Diacetyl-1,4,5-tribenzoyl-D-arabitol.—This substance was prepared from 2,3-benzylidene-1,4,5-tribenzoyl-D-arabitol and the acid acetylating mixture. It was obtained as a sirup which gave correct carbon, hydrogen and saponification analyses for a diacetyl-tribenzoyl-D-arabitol. The fact that the specific rotation $[\alpha]^{20}D$ of the sirup in chloroform, namely, +19.1°, was different in sign and magnitude from that (−8.2°) of the isomeric 1,3-diacetyl-2,4,5-tribenzoyl-D-arabitol described in the preceding paragraph would seem to exclude the possibility that the tribenzoyl-benzylidene-D-arabitols from which the diacetates are derived are stereoisomers and we accordingly designate them as structural isomers.

Anal. Calcd. for $C_{30}H_{28}O_{10}$: C, 65.69; H, 5.15; saponification, 0.1164 g. requires 10.61 cc. 0.1 *N* sodium hydroxide. Found: C, 65.63; H, 5.24; saponification, 0.1164 g. consumed 10.41 cc. 0.1 *N* sodium hydroxide.

Summary

A new benzylidene-D-arabitol has been obtained by the debenzoylation of the 1,5-dibenzoyl-benzylidene-D-arabitol that is obtained by condensing 1,5-dibenzoyl-D-arabitol with benzaldehyde under the catalytic action of fused zinc chloride. The new acetal has been shown to be 2,3-benzylidene-D-arabitol since it is oxidized by sodium periodate to a sirupy product, presumably 2,3-benzylidene-D-threose, which gives a quantitative yield of D-threose upon acid hydrolysis. It has been shown that the acetal can be converted into a crystalline 1,4,5-tribenzoyl-2,3-benzylidene-D-arabitol which is different from the isomeric crystalline tribenzoyl-benzylidene-D-arabitol obtained by the benzoylation of the known benzylidene-D-arabitol of Steiger and Reichstein; these tribenzoates, upon treatment with an acid acetylating mixture, are transformed into two different isomeric tribenzoyl-diacetyl-D-arabitols. These facts indicate that the two benzylidene-D-arabitols are position rather than stereo isomers and lead to the conclusion that the known benzylidene-D-arabitol of Steiger and Reichstein, which also yields D-threose upon oxidation with lead tetraacetate, is 1,3-benzylidene-D-arabitol. The substance which Emil Fischer prepared is the enantiomorphic 1,3-benzylidene-L-arabitol.

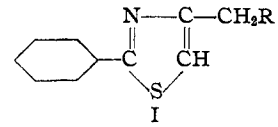
BETHESDA, MARYLAND RECEIVED MAY 27, 1943

[CONTRIBUTION NO. 285 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Conversion of 2-Phenyl-4-chloromethylthiazole to 2-Phenyl-4-hydroxymethyl-5-chlorothiazole

BY ERNEST H. HUNTRESS AND KARL PFISTER, 3RD[1]

In the course of an investigation of certain 2-phenylthiazole-4,5-dicarboxylic acid derivatives, samples of the hitherto unreported 2-phenylthiazole-4-carboxylic acid became necessary. In view of the ready accessibility of 2-phenyl-4-chloromethylthiazole (I, R = Cl) by condensation of equivalent amounts of thiobenzamide and *sym*-dichloroacetone,[2] conversion of this compound to the desired acid by oxidation of the 4-chloromethyl side chain seemed an unequivocal synthesis for the desired acid. By the use of aqueous chromic–sulfuric acid mixture on the corresponding alcohol, the desired 2-phenylthiazole-4-carboxylic acid was finally obtained although in low yield.



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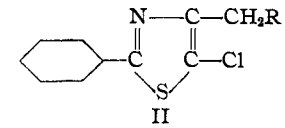

II

During our study of alternative oxidants for this purpose, however, the observation was made that when 2-phenyl-4-chloromethylthiazole was boiled with dilute aqueous nitric acid there could be isolated in 57.5% yield a neutral compound still containing halogen. The work described in this paper proves that this unexpected product is the hitherto unknown 2-phenyl-4-hydroxymethyl-5-chlorothiazole (I, R = OH). This paper also reports that similar treatment of 2-phenylthiazole-4-carboxylic acid chloride yields 2-phenyl-5-chlorothiazole-4-carboxylic acid. Such surprising changes in the location of the halogen substituent do not appear previously to have been observed in the thiazole series.

(1) This paper is constructed from part of a dissertation submitted in September, 1942, by Karl Pfister, 3rd, to the Faculty of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Hooper and Johnson, THIS JOURNAL, **56**, 484 (1934).