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D,L-1,3:2,4-Dimethylene-adonitol and 2,4-Methylene-adonitol

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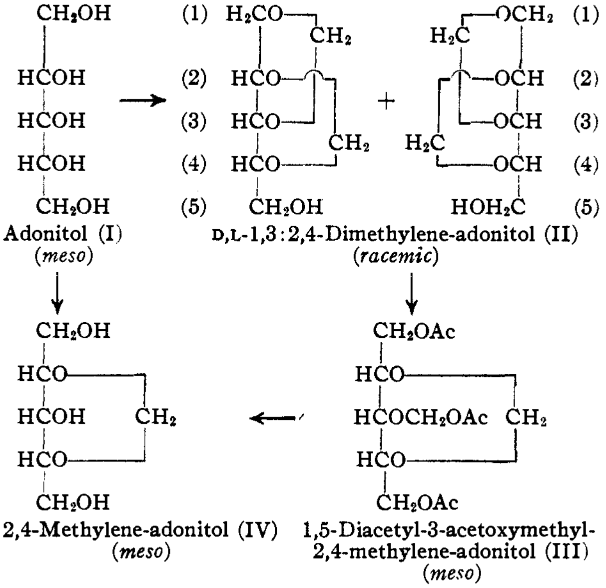
In 1896 Schulz and Tollens[1] condensed adonitol with aqueous formaldehyde through the action of concentrated hydrochloric acid and obtained a methylene derivative melting at 145°. Combustion analysis, molecular weight determination and the fact that the compound formed a monobenzoyl derivative (m. p. 104°) showed that the acetal was a monomeric dimethylene-adonitol. As pointed out by Schulz and Tollens, it was not possible at the time to decide which of the five hydroxyls of adonitol was present in the dimethylene-adonitol.

In continuation of our studies on the structures of the cyclic acetals of the sugar alcohols, we have now determined the structure of the dimethylene-adonitol and also that of a monomethylene-adonitol which was isolated in the form of a monohydrate from the mother liquor of the diacetal preparation.

The dimethylene-adonitol, which was prepared essentially according to the procedure of Schulz and Tollens, melted at 150–151° and yielded a monobenzoyl derivative which melted at 107–108°. It also formed crystalline mono-α-naphthyl carbamyl, acetyl and tosyl derivatives. The last-named substance, upon being heated in an acetonylacetone solution of sodium iodide at 80° for four hours, was converted to an iodo-desoxydimethylene-adonitol. This experimental finding is an indication by the Oldham–Rutherford rule[2] that the tosyl group is attached to a primary hydroxyl group and that therefore the diacetal itself is D,L-1,2,3,4-dimethylene-adonitol, a racemic mixture. Evidence supporting this conclusion was obtained when it was found that the limited acetolysis of the diacetal yielded a diacetylacetoxymethyl-methylene-adonitol (m. p. 92–93°). This result is in agreement with that expected, since previous experience has shown that the limited acetolysis of a 1,2,3,4-dimethylene-pentitol (for example, 1,3:2,4-dimethylene-xylitol[3]) proceeds in its initial stage with the rupture of that acetal linkage formed through the primary hydroxyl group at position one; the compound which is formed as a result of the cleavage is apparently immediately acetylated and the product which is isolated is a diacetyl-acetoxymethyl-methylene-pentitol. It is obvious that the isolation of an acetolyzed product of this composition and formula does not prove the specific position of all the cyclic acetal linkages, since the possible position isomers of a 1,2,3,4-dimethylene-adonitol, namely, 1,2:3,4-, 1,3:2,4- and 1,4:2,3-dimethylene-adonitols, will presumably form three isomeric diacetyl-acetoxymethyl-methylene-adonitols upon limited acetolysis. A definitive proof that the dimethylene-adonitol melting at 150–151° is the 1,3:2,4-isomer (II) was obtained when it was found that the saponification of the above-mentioned diacetyl-acetoxymethyl-methylene-adonitol (m. p. 92–93°) (III) that is obtained from it yields a monomethylene-adonitol (IV) (crystallizing as a monohydrate, m. p. 85–86°) which is not oxidized by sodium periodate and therefore contains no α-glycol grouping; the only structure of a pentitol monoacetal which conforms with this limitation is that of a 2,4-monoacetal and hence the methylene adonitol is 2,4-methylene-adonitol (IV), a *meso* structure; the dimethylene-adonitol must have one of its acetal linkages at position three because its only free hydroxyl group is a primary one, and hence it possesses the structure of D,L-1,3:2,4-dimethylene-adonitol (II).



Adonitol (I)
(*meso*)

D,L-1,3:2,4-Dimethylene-adonitol (II)
(*racemic*)

2,4-Methylene-adonitol (IV)
(*meso*)

1,5-Diacetyl-3-acetoxymethyl-2,4-methylene-adonitol (III)
(*meso*)

The 2,4-methylene-adonitol monohydrate was also obtained from the mother liquor of the dimethylene-adonitol preparation. It was converted to crystalline triacetyl, tribenzoyl, triphenylcarbamyl and tritosyl derivatives by customary reactions. The last named substance, as would be expected, is convertible to a 1,5-di-iodo-1,5-didesoxy-3-tosyl-2,4-methylene-adonitol, a *meso* structure, upon heating its solution in acetonylacetone with sodium iodide at 80° for twenty-four hours. The halogenated derivative was in turn converted to 1,5-didesoxy-3-tosyl-2,4-methylene-adonitol (*meso*) by reduction in alkaline solution with hydrogen and Raney nickel.

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(1) Schulz and Tollens, *Ann.*, **289**, 24 (1896).

(2) Oldham and Rutherford, THIS JOURNAL, **54**, 366 (1932).

(3) Hann, Ness and Hudson, *ibid.*, **66**, 670 (1944).

Experimental

2,4-Methylene-adonitol and D,L-1,3:2,4-Dimethylene-adonitol.—A solution of 20.0 g. of adonitol in a mixture of 20 cc. of concentrated hydrochloric acid and 20 cc. of 37% aqueous formaldehyde was heated at 100° for two hours, then allowed to cool to 25°, diluted with 50 cc. of alcohol and placed in a refrigerator for eighteen hours. The precipitate of 1,3:2,4-dimethylene-adonitol (3.2 g.; m. p. 149–151°) was separated by filtration and the filtrate was concentrated *in vacuo* to a sirup which was dried by the successive addition and evaporation of two 50-cc. portions of absolute alcohol, and dissolved in 90 cc. of absolute alcohol; on standing at 5° for forty-eight hours a further crop (0.9 g.) of diacetal deposited from the solution, making the yield 4.1 g. (18%). The compound was recrystallized from 15 parts of alcohol and formed needles which melted at 150–151°; Schulz and Tollens record a melting point of 145°.

Anal. Calcd. for $C_7H_{12}O_5$: C, 47.72; H, 6.87. Found: C, 47.77; H, 6.73.

The alcohol mother liquor was concentrated to 30 cc. and cooled to 5° for several hours; the crop of crystalline 2,4-methylene-adonitol (9.2 g.; m. p. 77–80°) which deposited was separated by filtration and further crops of 4.7 g. (m. p. 76–81°) and 1.2 g. (m. p. 75–80°) were obtained by successive concentration of the mother liquor to volumes of 15 and 7.5 cc., respectively. The total yield of monomethylene acetal, which crystallized in the form of a monohydrate, was 15.1 g. (63%). The product was recrystallized from 2.5 parts of alcohol as prisms which melted at 85–86°; it is readily soluble in cold water and pyridine, warm methyl and ethyl alcohols and ethyl acetate, and nearly insoluble in cold acetone and chloroform.

Anal. Calcd. for $C_6H_{12}O_5 \cdot H_2O$: C, 39.56; H, 7.75; H_2O, 9.89. Found: C, 39.61; H, 7.74; H_2O, 10.05.

Derivatives of D,L-1,3:2,4-Dimethylene-adonitol.—(a) A solution of 2.0 g. of D,L-1,3:2,4-dimethylene-adonitol in a mixture of 30 cc. of pyridine and 20 cc. of acetic anhydride was allowed to stand at room temperature for eighteen hours and then poured into ice and water; when the excess anhydride had decomposed the solution was extracted with chloroform in the usual manner and the crystalline precipitate which was obtained by concentration of the extract was recrystallized from 10 parts of alcohol. The D,L-*5-acetyl-1,3:2,4-dimethylene-adonitol* formed needles which melted at 108–109°; it is readily soluble in chloroform, acetone, ethyl acetate and pyridine and relatively insoluble in water. The yield was 2.4 g. (96%).

Anal. Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.47; CH_3CO, 19.7. Found: C, 49.66; H, 6.49; CH_3CO, 19.5.

(b) D,L-*5-Benzoyl-1,3:2,4-dimethylene-adonitol* was obtained in quantitative yield (1.6 g.) upon benzoylation of 1.0 g. of 1,3:2,4-dimethylene-adonitol in pyridine solution with benzoyl chloride. It was recrystallized from 10 parts of alcohol as needles which were readily soluble in chloroform, ethyl acetate, acetone and pyridine and insoluble in water. The benzoate melted at 107–108°, slightly higher than the 104° recorded by Schulz and Tollens.[1]

(c) D,L-*5-Tosyl-1,3:2,4-dimethylene-adonitol* was obtained in a yield of 1.5 g. (79%) by the action of *p*-toluenesulfonyl chloride and pyridine on 1.0 g. of D,L-1,3:2,4-dimethylene-adonitol. It was recrystallized from 10 parts of absolute alcohol as glistening platelets which melted at 117–118°; it is soluble in cold chloroform and acetone, warm methyl and ethyl alcohols and pyridine and relatively insoluble in cold methyl and ethyl alcohols and water.

Anal. Calcd. for $C_{14}H_{18}O_7S$: C, 50.90; H, 5.49; S, 9.70. Found: C, 50.91; H, 5.44; S, 9.47.

D,L-5-Iodo-5-desoxy-1,3:2,4-dimethylene-adonitol.—A solution of 5.4 g. of D,L-5-tosyl-1,3:2,4-dimethylene-adonitol and 5.4 g. of sodium iodide in 54 cc. of acetonylacetone[4] was heated at 80° for four hours and then cooled and poured into 250 cc. of ice-cold water. The precipitated D,L-5-iodo-5-desoxy-1,3:2,4-dimethylene-adonitol (4.7 g.; quantitative) was recrystallized from 20 parts of absolute alcohol as fine needles melting at 119–120°. The substance is readily soluble in acetone, ethyl acetate and ether and relatively insoluble in chloroform, toluene and water.

Anal. Calcd. for $C_7H_{11}O_4I$: C, 29.39; H, 3.88; I, 44.36. Found: C, 29.55; H, 4.06; I, 44.26.

D,L-5-Desoxy-1,3:2,4-dimethylene-adonitol.—A solution of 6.0 g. of D,L-5-iodo-5-desoxy-1,3:2,4-dimethylene-adonitol in a mixture of 250 cc. of methyl alcohol and 14.7 cc. of 1.715 *N* barium methylate solution (1.2 molecular equivalents) was agitated with Raney nickel and hydrogen under slight positive pressure; in ten minutes 505 cc. of hydrogen, measured at 25° and 758 mm., had been absorbed and in the next hour only 10 cc. more was taken up (theory, 511 cc. at 25° and 758 mm.). The catalyst was removed by filtration and on concentrating the filtrate to 25 cc. the desoxy diacetal crystallized; the precipitate (1.55 g.) was separated by filtration and a further 1.55 g. of the same product (total yield 91%) was obtained by concentrating the mother liquor. The compound was recrystallized from 16 parts of methyl alcohol as glistening plates which melted at 100–101°; it is soluble in ether, chloroform, benzene, acetone and warm petroleum ether.

Anal. Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.43; H, 7.36.

D,L-5-(α-Naphthylcarbamyl)-1,3:2,4-dimethylene-adonitol.—A solution of 0.9 g. of 1,3:2,4-dimethylene-adonitol and 1 cc. of α-naphthyl isocyanate in 20 cc. of pyridine was heated under reflux for two hours; the cooled solution was filtered to remove a small amount (0.25 g.) of *sym*-di-α-naphthyl urea and the filtrate was evaporated by an air current. The solid reaction product (1.8 g.; quantitative) was recrystallized from 60 parts of methyl alcohol as needles which melted at 172–173°. The urethan is soluble in cold acetone, chloroform, ethyl acetate and acetic acid and insoluble in toluene and water.

Anal. Calcd. for $C_{18}H_{19}O_6N$: C, 62.60; H, 5.54; N, 4.06. Found: C, 62.76; H, 5.51; N, 4.09.

1,5-Diacetyl-3-acetoxymethyl-2,4-methylene-adonitol (*meso*).—A solution of 2.0 g. of D,L-1,3:2,4-dimethylene-adonitol in 10 cc. of an ice-cold acetolyzing solution (prepared by adding 1.0 cc. of concentrated sulfuric acid dropwise to an ice-cold mixture of 70 cc. of acetic anhydride and 30 cc. of glacial acetic acid) was allowed to stand at 0° for ten minutes and then poured into 300 cc. of ice-cold water. The precipitate (0.7 g.; m. p. 89–91°), which deposited in the solution upon allowing it to stand for several hours at 5°, was separated by filtration and the filtrate was neutralized with potassium carbonate and extracted with three 50-cc. portions of chloroform; the washed and dried extract was evaporated to a crystalline residue (2.0 g.) which was recrystallized from 12 cc. of alcohol and yielded a further 1.3 g. of product (m. p. 88–90°) to make the yield 2.0 g. or 55%. The compound was recrystallized from 10 parts of alcohol as fine needles which melted at 92–93°. It is soluble in cold chloroform, acetone, ethyl acetate and warm alcohol and nearly insoluble in cold alcohol and water.

Anal. Calcd. for $C_{13}H_{20}O_8$: C, 48.75; H, 6.29; saponification, 0.1701 g. substance requires 15.93 cc. 0.1 *N* alkali (3 saponifiable groups). Found: C, 48.84; H, 6.33; saponification, 0.1701 g. substance consumed 15.80 cc. 0.1 *N* NaOH.

2,4-Methylene-adonitol from 1,5-Diacetyl-3-acetoxymethyl-2,4-methylene-adonitol.—To an ice-cold solution of 1.6 g. of 1,5-diacetyl-3-acetoxymethyl-2,4-methylene-adonitol in 10 cc. of chloroform, 3 cc. of 0.2 *N* sodium methylate solution was added and the mixture was allowed to stand at 5°. After several days the small prisms (0.7 g.; m. p. 84–86°) which had crystallized were recrystallized from 5 parts of alcohol; the product then melted at 85–86° and it did not depress the melting point of 2,4-methylene-adonitol monohydrate. Its composition was confirmed by an analysis.

Anal. Calcd. for $C_6H_{12}O_5 \cdot H_2O$: C, 39.56; H, 7.75. Found: C, 39.55; H, 7.85.

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[4] Murray and Purves, This Journal, 62, 3195 (1940).

Stability of 2,4-Methylene-adonitol against Oxidation by Sodium Periodate.—To a solution of 0.2004 g. of 2,4-methylene-adonitol monohydrate in 10 cc. of water at 20°, 6.20 cc. of 0.432 *M* sodium periodate (2.5 molecular equivalents) was added and the volume was adjusted to 25 cc. with water. Analysis of 5-cc. sub-samples at the expiration of one and forty-eight hours showed that none of the sodium periodate had been consumed. The failure of this reagent to oxidize the methylene-adonitol indicates that its structure does not include an α-glycol grouping. The only possible structure for a cyclic monoacetal of a pentitol which conforms to this limitation is that of a 2,4-acetal; methylene-adonitol is therefore 2,4-methylene-adonitol.

Derivatives of 2,4-Methylene-adonitol.—(a) A solution of 2.0 g. of 2,4-methylene-adonitol monohydrate in a mixture of 10 cc. pyridine and 10 cc. acetic anhydride was allowed to stand at 25° for eighteen hours. The reaction mixture was then poured over crushed ice and the solution which resulted was extracted with chloroform; the washed extract was evaporated to a sirup which was dissolved in a mixture of ether and petroleum ether and on cooling the solution in "dry-ice," crystallization of the triacetate took place. The *1,3,5-triacetyl-2,4-methylene-adonitol* was recrystallized from 2.5 parts of alcohol as small prisms which melt at 50–51°; the compound is soluble in chloroform, acetone, ethyl acetate, acetic acid and pyridine and insoluble in cold water. The yield was 2.6 g. (81%).

Anal. Calcd. for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25; CH_3CO, 44.5. Found: C, 49.57; H, 6.44; CH_3CO, 44.2.

(b) The *1,3,5-tribenzoyl-2,4-methylene-adonitol* (2.0 g.; 77%) which was obtained by the benzoylation of 1.0 g. of 2,4-methylene-adonitol monohydrate in pyridine solution by benzoyl chloride (2.9 cc.; 4.5 molecular equivalents) was recrystallized from 10 parts of alcohol and obtained in the form of needles which melted at 109–110°; the tribenzoate is soluble in acetone, chloroform, ethyl acetate and dioxane and insoluble in water.

Anal. Calcd. for $C_{27}H_{24}O_8$: C, 68.06; H, 5.08; C_6H_5CO, 66.2. Found: C, 68.26; H, 4.94; C_6H_5CO, 65.9.

(c) To an ice-cold solution of 2.0 g. of 2,4-methylene-adonitol monohydrate in 20 cc. of pyridine 9.2 g. (4.4 molecular equivalents) of *p*-toluenesulfonyl chloride was added and the reaction mixture was allowed to stand at 25° for forty-eight hours. The *1,3,5-tritosyl-2,4-methylene-adonitol* (3.6 g.; 52%), which precipitated upon pouring the mixture upon crushed ice, was recrystallized from 20 parts of absolute alcohol as small prisms which melted at 126–127°. The compound is readily soluble in cold chloroform, acetone and ethyl acetate, warm ether and toluene; it is relatively insoluble in cold ether and toluene and insoluble in water.

Anal. Calcd. for $C_{27}H_{30}O_{11}S_3$: C, 51.74; H, 4.82; S, 15.35. Found: C, 51.70; H, 5.00; S, 15.42.

1,5-Dibenzoyl-2,4-methylene-adonitol.—A solution of 1.0 g. of 2,4-methylene-adonitol in 5 cc. of pyridine was cooled in ice and 1.2 cc. (2.0 molecular equivalents) of benzoyl chloride was added dropwise; the reaction mixture was allowed to stand at 20° for forty-eight hours and then poured over crushed ice. The precipitated product (0.3 g.; 15%) was recrystallized from 15 parts of alcohol as fine needles which melted at 165–166°.

Anal. Calcd. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41; C_6H_5CO, 56.4. Found: C, 64.57; H, 5.58; C_6H_5CO, 56.1.

1,3,5-Triphenylcarbamyl-2,4-methylene-adonitol.—To a solution of 2.0 g. of 2,4-methylene-adonitol monohydrate in 15 cc. of pyridine, 6.6 cc. (5.5 molecular equivalents) of phenyl isocyanate was added; the reaction mixture became hot and a noticeable evolution of carbon dioxide occurred. The solution was heated under reflux for two hours and as it cooled a magma of needles resulted; the mass was thinned with 30 cc. of ether, the crystalline precipitate (5.7 g.), presumably a mixture, was separated by filtration and recrystallized from 65 parts of acetone. The 1.4 g. (24%) of 1,3,5-triphenylcarbamyl-2,4-methylene-adonitol which deposited from the acetone solution melted at 231–232° and the value was unchanged by further recrystallization. The substance is soluble in warm ethyl acetate, dioxane and methyl alcohol and nearly insoluble in warm chloroform, toluene and water. The pyridine–ether filtrate contains the *sym*-diphenyl urea formed from the molecule of water in the 2,4-methylene-adonitol hydrate and 2.1 g. (theory 2.3 g.) of this substance, melting at 239–240°, was obtained by evaporating the filtrate to dryness and recrystallizing the crystalline residue from alcohol.

Anal. Calcd. for $C_{27}H_{27}O_5N_3$: C, 62.18; H, 5.22; N, 8.06. Found: C, 62.16; H, 5.39; N, 8.04.

1,5-Di-iodo-1,5-didesoxy-3-tosyl-2,4-methylene-adonitol.—A solution of 1.0 g. of 1,3,5-tritosyl-2,4-methylene-adonitol and 1.0 g. (4.2 molecular equivalents) of sodium iodide in 10 cc. of acetonylacetone was allowed to stand at 80° for twenty-four hours; the cooled solution was poured into 100 cc. of ice-cold water and the precipitated reaction product was recrystallized from 70 parts of absolute alcohol. The 1,5-di-iodo-1,5-didesoxy-3-tosyl-2,4-methylene-adonitol forms glistening platelets which melt at 164–165°; the compound is readily soluble in acetone, chloroform, dioxane, ethyl acetate and toluene and insoluble in water. The yield was 0.8 g. (quantitative).

Anal. Calcd. for $C_{13}H_{16}O_5SI_2$: C, 29.01; H, 3.00; S, 5.96. Found: C, 29.13; H, 3.13; S, 5.71.

1,5-Didesoxy-3-tosyl-2,4-methylene-adonitol.—A suspension of 1.0 g. of finely ground 1,5-di-iodo-1,5-didesoxy-3-tosyl-2,4-methylene-adonitol and 2.0 g. of Raney nickel in a mixture of 100 cc. of methyl alcohol and 2.6 cc. of 1.715 *N* barium methylate solution (1.1 molecular equivalents) was agitated in a glass bottle under a slight positive pressure of hydrogen. In ten minutes 81 cc. of hydrogen (theory 90 cc.) at 27° and 750 millimeters was taken up. At this stage the reduction was interrupted and 3.3 g. more of the dihalogenated acetal and an additional 2.0 g. of Raney nickel were added; upon resumption of the reduction it was found that 320 cc. of hydrogen was absorbed in fifteen minutes and no further absorption occurred in an additional thirty minutes; the total hydrogen which reacted was therefore 401 cc. at 27° and 750 millimeters, 390 cc. being the theoretical amount under these conditions. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to dryness; the reaction products were extracted with 50 cc. of cold water to remove barium salts, and the undissolved 1,5-didesoxy-3-tosyl-2,4-methylene-adonitol (2.1 g.; 91%; m. p. 63–64°) was recrystallized from 5 parts of alcohol as small prisms. The compound, which is readily soluble in acetone, chloroform and pyridine and relatively insoluble in water, melts at 64–65°.

Anal. Calcd. for $C_{13}H_{18}O_5S$: C, 54.53; H, 6.34; S, 11.20. Found: C, 54.71; H, 6.52; S, 11.11.

Appreciation is expressed to Mr. Harry W. Diehl for assistance in preparing some of the compounds, to Dr. Arthur T. Ness for performing the microchemical analyses and to Dr. H. M. Wuest, of Hoffmann LaRoche, Inc., for furnishing a supply of adonitol.

Summary

The limited acetolysis of the dimethylene-adonitol of Schulz and Tollens yields a diacetyl-acetoxymethyl-methylene-adonitol which upon saponification forms a methylene-adonitol that is not oxidized by aqueous sodium periodate. This fact limits the structure of the monoacetal to that of 2,4-methylene-adonitol; proof that the diacetal is D,L-1,3:2,4-dimethylene-adonitol is presented. Several derivatives of the mono- and diacetals are described.

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