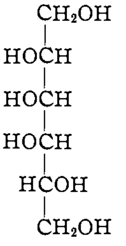
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

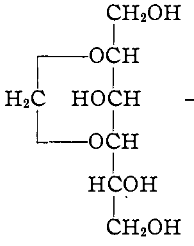
Some Methylene Acetals of D-Talitol[1]

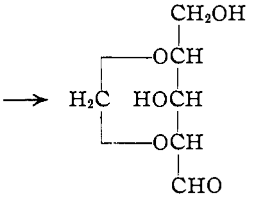
BY RAYMOND M. HANN, W. T. HASKINS AND C. S. HUDSON

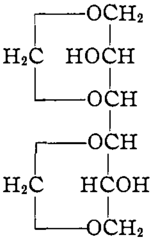
In previous publications we have shown that the positions of attachment of the methylene groups in the cyclic acetals of polyhydric alcohols exhibit regularities that can be summarized by simple generalizations.[2] These so-called "rules" have been found to hold in the cases of two pentitols (adonitol[3] and xylitol[4]), five hexitols (sorbitol,[5] mannitol,[6] dulcitol,[7] iditol[8] and allitol[9]), two 6-desoxyhexitols (epirhamnitol[10] and rhamnitol[11]) and one heptitol (gluco-*gulo*-heptitol[12]). The present research concerns the preparation of methylene acetals of the last remaining hexitol (D-talitol), the determination of their structures, and an inquiry as to whether the rules apply to them.

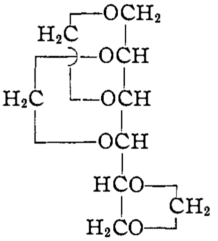
When D-talitol (I) was allowed to react with formaldehyde by the slow evaporation at 25° of a solution of the hexitol in aqueous 37% formaldehyde and concentrated hydrochloric acid, four crystalline acetals could be isolated and they were obtained in pure condition fairly readily by fractional crystallization. Two of them constitute the major products of the reaction; one of these is a monomethylene-D-talitol (II) (m. p. 144–145°); $[\alpha]^{20}\text{D}$ in water, −4.2°), the yield of which is 57%, and the other is a dimethylene-D-talitol (III) (m. p. 182–183°; $[\alpha]^{20}\text{D}$ −41.2° in water), the yield of it being 12%. The remaining two products occur in very minor amounts, the yields of each being about 2%; they are a second dimethylene-D-talitol (m. p. 261–262°; $[\alpha]^{60}\text{D}$ −1.0° in water) which proves to possess the 2,3,-4,5-structure, and a trimethylene-D-talitol (IV) (m. p. 118–119°; $[\alpha]^{20}\text{D}$ −32.1° in water). The total yield of crystalline acetals was thus about 73% of theoretical; the sirupy residual material was not further investigated.

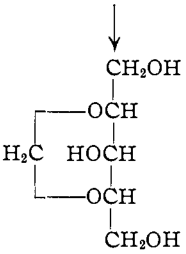

(I)
D-Talitol


(II)
Monomethylene-D-talitol
(m. p. 144–145°)


(V)
2,4-Methylene-D-ribose


(III)
First dimethylene-D-talitol
(m. p. 182–183°)


(IV)
Trimethylene-D-talitol
(m. p. 118–119°)


(VI)
2,4-Methylene-adonitol

The Structure of Monomethylene-D-talitol (II).—The oxidation of this substance by an excess of sodium metaperiodate reduces one molecular equivalent of the oxidant and generates one molecular equivalent of formaldehyde; these data show that the acetal possesses only one pair of contiguous hydroxyl groups and that one hydroxyl of this pair is of primary type; these specifications restrict the ring of monomethylene-D-talitol to the 2,4 or the 3,5 position. Choice between these possibilities was made by the reduction with hydrogen and Raney nickel of the sirupy monomethylene-pentose which is produced by the oxidation; the reduction product was the known 2,4-methylene-adonitol (VI),[3] a *meso* structure, and this result proves that the sirupy monomethylene-pentose is 2,4-methylene-D-ribose (V) and that the talitol acetal is 2,4-methylene-D-talitol, since a 3,5-methylene-D-talitol would have yielded a 2,4-methylene-D-lyxose and an optically active 2,4-methylene-D-arabitol by the indicated series of reactions.

It was not sought to isolate the intermediate 2,4-methylene-D-ribose in this investigation but we call attention to this method of access to it; by the similar periodate oxidation of 2,4-methylene-D,L-allitol, Wolfrom, Lew and Goepp[9] evidently produced the related 2,4-methylene-D,L-ribose in solution.

The Structure of the First Dimethylene-D-talitol (III).—This dimethylene-D-talitol is not oxidized by sodium metaperiodate, a behavior

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[1] Presented before the Division of Sugar Chemistry and Technology at the Chicago meeting of the American Chemical Society, September 9–13, 1946.

[2] Hann and Hudson, THIS JOURNAL, **66**, 1909 (1944).

[3] Hann and Hudson, *ibid.*, **66**, 1906 (1944).

[4] Hann, Ness and Hudson, *ibid.*, **66**, 670 (1944).

[5] Ness, Hann and Hudson, *ibid.*, **66**, 665 (1944); Hann, Wolfe and Hudson, *ibid.*, **66**, 1898 (1944).

[6] Ness, Hann and Hudson, *ibid.*, **65**, 2215 (1943).

[7] Haskins, Hann and Hudson, *ibid.*, **64**, 132 (1942); Hann, Haskins and Hudson, *ibid.*, **64**, 986 (1942); **64**, 1614 (1942).

[8] Hann and Hudson, *ibid.*, **67**, 602 (1945).

[9] Wolfrom, Lew and Goepp, *ibid.*, **68**, 1445 (1946). They prepared two crystalline methylene acetals of allitol and proved that their structures are those of 2,4-methylene-D,L-allitol and 2,4:3,5-dimethylene-allitol.

[10] Ness, Hann and Hudson, *ibid.*, **66**, 1901 (1944); **66**, 1235 (1944).

[11] Haskins, Hann and Hudson, *ibid.*, **67**, 1800 (1945).

[12] Hann, Ness and Hudson, *ibid.*, **68**, 1769 (1946).

which indicates that its two free hydroxyl groups are not contiguous. Its crystalline ditosyl derivative is recovered unchanged in nearly quantitative yield when it is heated with sodium iodide in acetone solution at 100° for two hours, indicating that the tosyl groups are attached to secondary hydroxyl groups. The foregoing two conclusions limit the structure of the diacetal to those of 1,2:4,6-, 1,3:5,6- and 1,3:4,6-dimethylene-D-talitol (III). The fact that unsymmetrical hexitol diacetals of the type of the first two mentioned, possessing a six atom and a five atom ring, have not been encountered in our previous work, leads us to the provisional supposition that the product in hand is the 1,3:4,6-diacetal. Additional evidence that each of the terminal carbon atoms is involved in the acetal rings was obtained by treating the diacetal with an acid acetolyzing reagent; the sirupy product which was produced, presumably 1,2,5,6-tetraacetyl-3,4-di-(acetoxymethyl)-D-talitol, yielded D-talitol and formaldehyde upon deacetylation; these reactions are analogous to those exhibited by the known 1,3:4,6-dimethylene-dulcitol.[13] Although the evidence favors the probability of the 1,3:4,6-dimethylene-D-talitol structure, it does not definitely exclude the 1,2:4,6 and 1,3:5,6 structures.

The Structure of the Second Dimethylene-D-talitol (m. p. **261–262°**).—This crystalline diacetal, which was obtained in very minor amount (2%), is of remarkably low solubility in all common solvents, and this property probably accounts for its having been detected at all. It is not oxidized by glycol-splitting reagents, which indicates that its two free hydroxyl groups are not contiguous. It formed a crystalline ditosyl derivative, the two tosyloxy groups of which were replaceable by iodine through refluxing the nearly insoluble substance for one hour with a solution of sodium iodide in acetic anhydride. The resulting diiodo compound was readily reduced to a didesoxy-dimethylene-D-talitol. The foregoing evidence leads us to assign to the second dimethylene diacetal the structure of 2,3,4,5-dimethylene-D-talitol. Present evidence does not prove the structural arrangement of the two acetal groups. If one may follow analogy with the known 2,4:3,5-dimethylene-sorbitol (or -iditol) preference would be given to the 2,4:3,5-dimethylene-D-talitol arrangement.

The Structure of Trimethylene-D-talitol (IV).—The second minor crystalline product of the condensation was found by its analysis to be a trimethylene-D-talitol. It was isolated from the direct condensation of the hexitol and formaldehyde in only one experiment and in a yield of only 2%, but it is readily obtainable in a yield of 55% by condensing 2,4-methylene-D-talitol with aqueous formaldehyde and concentrated hydrochloric acid, a result which led to the surmise that it contains one of its three acetal groups attached in the 2,4-position. When the triacetal was treated with an acid acetolyzing solution a crystalline product was obtained which gave a correct analysis for a diacetyl-di-(acetoxymethyl)-monomethylene hexitol, and the deacetylation of this substance yielded 2,4-methylene-D-talitol and formaldehyde. This evidence leads us to ascribe the structure of 1,3:2,4:5,6-trimethylene-D-talitol to the original acetal, and that of 1,6-diacetyl-3,5-di-(acetoxymethyl)-2,4-methylene-D-talitol to the compound that was produced from it by the acid acetolysis reaction.

Discussion of the Structures.—Applying to the configuration of D-talitol (I) the previously recorded generalizations[2] correlating the configurations of polyhydric alcohols with the structures of benzylidene and methylene acetals derived from them, it is to be expected that the condensation of this hexitol with formaldehyde in strongly acid aqueous solution will result in the prominent formation of the 2,4-acetal, since only the hydroxyl groups at positions 2 and 4 are secondary ones which are *cis* in configuration and β in position and thus represent the most favored configuration. Other acetal structures which appear from the rules to be favored are those involving the 1,3-, 4,6- and 2,5- hydroxyl groups. The favored 2,4 acetal ring obviously conflicts with a 4,6 acetal ring and likewise with a 2,5 ring. With the possible exception of the second dimethylene-D-talitol (m. p. 261–262°), for which the 2,3; 4,5- structure seems to be valid, none of the isolated four methylene acetals of D-talitol contains the 2,5-acetal ring and it is probable that it does not occur even in this dimethylene acetal, the structure of which is probably that of a 2,4:3,5-dimethylene-D-talitol, as previously mentioned. The form that the rules have taken in the past indicates that this 2,5 ring, which has so far been found only in the mannitol and 6-desoxymannitol series, might also occur in the iditol and talitol series. However, it has not been detected in the crystalline products obtained from these hexitols and therefore its formation may be a special characteristic of the mannitol asymmetric configuration. In the talitol series, the isolation of its 2,4-methylene acetal and its 1,3:4,6-dimethylene diacetal as the major products, the yields being 57 and 12%, respectively, agrees with the predictions that can be made from the rules. The 1,3:2,4 combination, which appears to be one that might be formed, has not yet been detected in the structure of a dimethylene talitol, but it is present in the 1,3:2,4:5,6-trimethylene-D-talitol (IV) that has been isolated. It is possible, of course, that the 1,3:2,4-dimethylene acetal may constitute a part of the considerable quantity of non-crystalline products (27%) from the methylenation. It is of interest that the 1,3:2,4:5,6-trimethylene-D-talitol has a structure like that of the known 1,3:2,4:5,6-trimethylene-D-sorbitol,

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[13] Ness, Hann and Hudson, THIS JOURNAL, **65**, 2219 (1943).

that 2,4-methylene-D-talitol is analogous to 2,4-methylene-D-sorbitol, and that 1,3:4,6-dimethylene-D-talitol is analogous to 1,3:4,6-dimethylene-dulcitol. The formation of a 2,3,4,5-dimethylene-D-talitol would not be expected by the rules. The amount of it which was isolated, namely, 2%, was in marked contrast to the yield of 97% of the 2,4:3,5-dimethylene acetal from L-iditol,[8] a hexitol in which the pairs of secondary groups in positions 2,4 and 3,5 are *cis* in configuration and β in position, a highly favored arrangement for acetal formation, as previously mentioned. The configuration of allitol is likewise favorable for the formation of a 2,4:3,5-dimethylene acetal and this is the structure which Wolfrom, Lew and Goepp[9] have established for the diacetal that they obtained.

We would mention in conclusion, as a matter of importance in the history of the general theory of the asymmetric carbon atom, that sorbitol and talitol are the only hexitols that are derivable by simple reduction, in each case, from two different aldohexoses; the same conclusion applies of course to the corresponding glucosaccharic and talomucic dibasic acids. This mathematical theorem was first derived by Van't Hoff from the application of requirements of geometrical symmetry to his theory. It was used later by Emil Fischer[14] as an essential part of his proof of the configuration of glucose, after he had found that saccharic acid results from the oxidation of either glucose or gulose. Later, he showed that sorbitol is obtained by the reduction of either glucose or gulose. He also made talomucic acid and talitol from talose and then Levene and Jacobs[15] showed that talomucic acid is also derivable from altrose. The present reduction of altrose to talitol rounds out the full experimental verification of the predictions of the Van't Hoff mathematical theorem. All the hexitols and hexaric acids are known, the relationships of them to all the aldohexoses have been established, and throughout the completed series the theorem has found confirmation in all respects.

Acknowledgments.—We are indebted to Dr. N. K. Richtmyer for supplying the α-D-altropyranose pentaacetate used in the preparation of D-talitol and to Dr. A. T. Ness for carrying out the sodium metaperiodate oxidations and the microchemical analyses.

Experimental

D-Talitol from α-D-Altropyranose Pentaacetate.—The considerable quantity of D-talitol that was used in this investigation was prepared by the reduction of D-altrose with hydrogen and Raney nickel. The D-altrose was prepared in sirupy form by the catalytic deacetylation of pure crystalline α-D-altropyranose pentaacetate, which in turn was made from methyl α-D-glucopyranoside by the directions that were published lately from this Laboratory.[16] Crystalline D-talitol can be obtained in this way from α-D-altropyranose pentaacetate in good yield (82%); however, it was found unnecessary in the present work to crystallize the hexitol since its methylene acetals can be made from the sirupy D-talitol.

A suspension of 50 g. of α-D-altropyranose pentaacetate in a mixture of 200 ml. of methanol and 1 ml. of *N* sodium methylate was agitated for one hour at 20–25°. Following the addition of 1 ml. of *N* hydrochloric acid to the clear solution and removal of the methyl alcohol and methyl acetate by distillation *in vacuo*, the sirupy residue of D-altrose containing a trace of sodium chloride was dissolved in 250 ml. of water and the aqueous solution was transferred to a bomb and agitated with hydrogen and Raney nickel under 127 atmospheres pressure at 98° for seven hours. The solution was filtered to remove the catalyst, and the filtrate, which was nonreducing to Fehling solution, was concentrated *in vacuo* to a very thick sirup. The solution of the sirup in 30 ml. of methyl alcohol was seeded with D-talitol and allowed to stand for several days at 5°. The precipitate of crystalline D-talitol (19.0 g.; 82%) was recrystallized from 5 parts of methyl alcohol and it melted at 87–88°[17] and rotated $[\alpha]^{20}\text{D}$ +3.2° in water (*c*, 1.78) in agreement with the recorded values of 86° and $[\alpha]^{18}\text{D}$ +3.05°, respectively, which Bertrand and Bruneau[18] reported for D-talitol made by the reduction of D-talose with sodium amalgam.

Anal. Calcd. for $C_6H_{14}O_6$: C, 39.56; H, 7.75. Found: C, 39.56; H, 7.60.

Methylenation of D-Talitol.—The D-talitol sirup that was obtained by the deacetylation and subsequent reduction of a second lot of 50 g. of α-D-altropyranose pentaacetate was dissolved in a mixture of 35 ml. of concentrated hydrochloric acid and 35 ml. of 37% aqueous formaldehyde solution, and the reaction mixture was allowed to evaporate in a desiccator containing calcium chloride, sodium hydroxide pellets and several small beakers of concentrated sulfuric acid. Crystalline material began to precipitate after seven days and after fourteen days the magma was thinned by the addition of 10 ml. of absolute alcohol. Following the evaporation of this alcohol (three days) a second 10 ml. was added and the evaporation repeated. The nearly solid residue, 24 g., was triturated with 50 ml. of water and the undissolved crystalline material (1.7 g.) was separated by filtration and washed with three 10-ml. portions of water. This 1.7 g. of product was recrystallized from 50 ml. of water and yielded 0.5 g. (2%) of needles melting at 257–259°, which were later shown to possess the structure of a 2,3,4,5-dimethylene-D-talitol, and 1.1 g. of an isomeric 1,3:4,6-dimethylene-D-talitol (III) crystallizing in the form of prisms and melting at 179–184°. The aqueous filtrate from the trituration of the original crude mixture was concentrated to 35 ml. and a further portion, 2.0 g., of this second dimethylene acetal (III) was obtained to make the total yield of this substance 3.1 g. (12%). The mother liquor from which the dimethylene acetals had been thus removed was concentrated to a sirup which crystallized upon successive addition and evaporation *in vacuo* of two 25-ml. portions of absolute alcohol. The crystals were dissolved in 100 ml. of hot absolute alcohol and as the solution cooled it deposited 7.0 g. of 2,4-methylene-D-talitol (II) mixed with a small amount of dimethylene-D-talitols. Second (6.5 g.) and third (0.5 g.) fractions of the same compound were obtained by concentrating the alcohol mother liquor to 50 and 20 ml., respectively (14 g., 57% total yield). The residual sirup could not be crystallized.

In one experiment it was possible to isolate in the earlier crystalline fractions a small amount (0.6 g.) of the 1,3:2,4:5,6-trimethylene-D-talitol (IV) melting at 118–119° and rotating $[\alpha]^{20}\text{D}$ −32.1°, which is described later as

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[14] E. Fischer, *Ber.*, **24**, 1836, 2683 (1891).

[15] Levene and Jacobs, *Ber.*, **43**, 3141 (1910).

[16] Richtmyer and Hudson, THIS JOURNAL, **63**, 1727 (1941).

[17] All of the crystalline compounds that are described were recrystallized to constant melting point and specific rotation $[\alpha]^{20}\text{D}$; *c* is the concentration in grams in 100 cc. of solution; the tube length was 4 dm. The melting points were determined with the stem of the thermometer immersed in the heated bath.

[18] Bertrand and Bruneau, *Bull. soc. chim.*, [4] **3**, 496 (1908).

resulting from the action of concentrated hydrochloric acid and 37% aqueous formaldehyde solution on 2,4-methylene-D-talitol.

The separation of pure 2,4-methylene-D-talitol (II) from the crude product containing 1,3:4,6-dimethylene-D-talitol (III) as the principal impurity was accomplished by dissolving the crude reaction product in 2 parts of warm water, cooling the solution to 25°, seeding it with 1,3:4,6-dimethylene-D-talitol (III) and allowing it to stand at 5° for several days. The prisms of the crystallized dimethylene acetal were separated by filtration and the filtrate was concentrated to one-half of its volume and diluted with 4 to 5 volumes of acetone; the 2,4-methylene-D-talitol (II) crystallized in nearly pure condition.

Evidence that the Dimethylene-D-talitol Melting at 261–262° is 2,3,4,5-Dimethylene-D-talitol

The dimethylene-D-talitol melting at 257–259° was recrystallized from 70 parts of boiling water and formed long, narrow, thin plates which melted at 261–262°. The compound is only slightly soluble in hot pyridine and nearly insoluble in hot methyl cellosolve. By working rapidly and using a jacketed 4-dm. polariscope tube through which warm water was circulated it was possible to determine the specific rotation $[\alpha]^{60}\text{D}$ as −1.0° in water (*c*, 0.41).

Anal. Calcd. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.62; H, 6.85.

Stability of the 2,3,4,5-Dimethylene-D-talitol (m. p. 261–262°) against Oxidation by Sodium Metaperiodate.—To a solution of 0.2083 g. of the dimethylene-D-talitol in 175 ml. of water at 25°, 10.0 ml. (4.30 molecular equivalents) of 0.434 *M* sodium metaperiodate was added and the volume was adjusted to 200 ml. with water. Analysis of 20-ml. aliquots at the expiration of one, four and forty-eight hours showed that none of the sodium periodate had been reduced. The failure of this reagent to oxidize the dimethylene-D-talitol indicates that its structure does not include an α-glycol grouping.

1,6-Ditosyl-2,3,4,5-dimethylene-D-talitol.—A mixture of 0.5 g. of the dimethylene-D-talitol and 1.0 g. of *p*-toluenesulfonyl chloride in 25 ml. of pyridine was heated on the steam-bath for thirty minutes and then allowed to stand at 25° for forty-six hours. The crystalline precipitate which formed upon pouring the reaction mixture into 50 ml. of ice-cold water was separated by filtration and recrystallized from 10 parts of pyridine as small granular prisms which melted at 204–206° and rotated $[\alpha]^{20}\text{D}$ +2.8° in acetonyl acetone (*c*, 0.45). The compound is soluble in hot pyridine, moderately soluble in acetonyl acetone, and only slightly soluble in chloroform, alcohol, ether, petroleum ether and hot acetone.

Anal. Calcd. for $C_{22}H_{26}O_{10}S_2$: C, 51.35; H, 5.09; S, 12.46. Found: C, 51.26; H, 4.95; S, 12.34.

1,6-Didesoxy-1,6-diiodo-2,3,4,5-dimethylene-D-talitol.—A mixture of 1.1 g. of the previously described 1,6-ditosyl-dimethylene-D-talitol and 1.1 g. of sodium iodide was heated under reflux with 30 ml. of acetic anhydride. The ditosylate dissolved readily and precipitation of sodium *p*-toluenesulfonate was observed shortly after complete solution had taken place. After one hour the suspension was cooled to 5°; a quantity of needles, differing in appearance from the plates of sodium *p*-toluenesulfonate, crystallized from the reaction mixture. The precipitate was filtered on a Büchner funnel and washed with water to remove the sodium *p*-toluenesulfonate. The yield of water-insoluble product was 0.8 g. and it was combined with an additional 0.1 g. recovered from the acetic anhydride filtrate (total yield 0.9 g., quantitative) and recrystallized by solution in 30 parts of warm chloroform and addition of 60 parts of hexane. The pure compound melted at 219–220° and rotated $[\alpha]^{20}\text{D}$ +3.1° in dioxane (*c*, 0.42). It is soluble in hot acetonyl acetone, moderately soluble in dioxane and sparingly soluble in methyl and ethyl alcohols, water, ether, petroleum ether, pyridine, chloroform and acetone. The ready and quantitative replacement of the tosyloxy group by iodine under the relatively mild experimental conditions is accepted as strong evidence, although not as a conclusive proof, that the tosyl groups of the ditosyl-dimethylene-D-talitol are attached through the primary hydroxyl groups at positions one and six. (Compare the behavior of the ditosyl derivative of the dimethylene-D-talitol (III) melting at 182–183°.)

Anal. Calcd. for $C_8H_{12}O_4I_2$: C, 22.55; H, 2.84; I, 59.28. Found: C, 22.68; H, 2.76; I, 59.45.

1,6-Didesoxy-2,3,4,5-dimethylene-D-talitol.—A suspension of 1.0 g. of 1,6-didesoxy-1,6-diiodo-2,3,4,5-dimethylene-D-talitol and 0.6 g. of Raney nickel in a mixture of 50 ml. of methyl alcohol and 0.97 ml. (4 molecular equivalents) of diethylamine was agitated in a glass container under a slight positive pressure of hydrogen. In fifteen minutes, 116 ml. of hydrogen (theoretical 116 ml.) at 28° and 759 millimeters pressure was taken up, and no further absorption was noted during a second fifteen minutes. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to 20 ml.; the reduction product (0.32 g.) crystallized spontaneously. Further concentration of the mother liquor to 5 ml. gave an additional 0.07 g. of the same material to make the total yield 0.39 g. (95%). The compound was recrystallized from 60 parts of methyl alcohol; it formed long brittle needles which melted at 165–166° (sublimation being noted at 155°) and rotated $[\alpha]^{20}\text{D}$ +2.0° in chloroform (*c*, 0.43). It is soluble in acetone, ether, dioxane, chloroform, warm alcohol and hexane and sparingly soluble in water and cold methyl and ethyl alcohols.

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.99; H, 7.90.

1,6-Diacetyl-2,3,4,5-dimethylene-D-talitol.—A mixture of 0.5 g. of 2,3,4,5-dimethylene-D-talitol, 5 ml. of pyridine and 5 ml. of acetic anhydride was heated on the steam-bath for one hour. The crystalline product (0.7 g., quantitative) which precipitated upon the addition of 25 ml. of ice-cold water to the cooled reaction mixture was recrystallized from 70 parts of absolute alcohol and formed flat elongated prisms which melted at 177–178° and rotated $[\alpha]^{20}\text{D}$ −0.5° in chloroform (*c*, 0.55). In pyridine (*c*, 0.44) or acetone (*c*, 0.45) solutions no rotation could be detected; the substance is also soluble in ether, ethyl acetate and dioxane and relatively insoluble in water, petroleum ether and cold alcohol.

Anal. Calcd. for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25; CH_3CO, 29.7. Found: C, 49.81; H, 6.37; CH_3CO, 29.5.

1,6-Dibenzoyl-2,3,4,5-dimethylene-D-talitol.—A suspension of 0.5 g. of 2,3,4,5-dimethylene-D-talitol in a mixture of 5 ml. of pyridine and 1 ml. of benzoyl chloride was heated on the steam-bath for thirty minutes. The precipitate (1.0 g., quantitative) which crystallized upon the addition of 25 ml. of ice-cold water to the reaction mixture was separated by filtration and recrystallized by solution in 15 parts of chloroform and the addition of 15 parts of ether. The dibenzoate crystallized as fine needles which melted at 188–189° and rotated $[\alpha]^{20}\text{D}$ +1.0° in chloroform (*c*, 0.86); it is moderately soluble in chloroform, pyridine and boiling absolute alcohol and nearly insoluble in ether, petroleum ether, cold alcohol and acetone.

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35; C_6H_5CO, 50.7. Found: C, 63.71; H, 5.36; C_6H_5CO, 50.4.

Evidence that the Dimethylene-D-talitol (III) Melting at at 182–183° is 1,3:4,6-Dimethylene-D-talitol

The dimethylene-D-talitol which melted at 179–184° as isolated from the methylenation mixture was readily purified by recrystallization from 16 parts of alcohol; it crystallized in well-formed prisms which melted at 182–183° and rotated $[\alpha]^{20}\text{D}$ −41.2 in water (*c*, 0.81).

Anal. Calcd. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.59; H, 6.85.

Stability of the Dimethylene-D-talitol, m. p. 182–183°, against Oxidation by Sodium Metaperiodate.—To a solution of 0.2183 g. of the dimethylene-D-talitol in 25 ml. of water at 25°, 10.0 ml. (4.10 molecular equivalents) of

0.434 *M* sodium metaperiodate was added and the volume was adjusted to 50 ml. with water. Analysis of 10-ml. aliquots at the expiration of one, four and forty-eight hours showed that none of the periodate had been reduced, a result which indicates that the dimethylene-D-talitol does not possess an α-glycol grouping as part of its structure.

2,5-Ditosyl-1,3:4,6-dimethylene-D-talitol.—A solution of 2.09 g. of dimethylene-D-talitol, m. p. 182–183°, and 4.1 g. (2.2 molecular equivalents) of *p*-toluenesulfonyl chloride in 20 ml. of pyridine was allowed to stand for forty-eight hours at 25° and then poured upon crushed ice. The crystalline precipitate which formed (4.5 g.; 90% yield) was recrystallized by solution in 20 parts of hot acetone and addition of 40 parts of hot alcohol. As the solution cooled it deposited the ditosyl diacetal as clusters of elongated prisms. The pure compound melted at 193–194° and rotated $[\alpha]^{20}\text{D}$ −27.9° in chloroform (*c*, 0.94). The ditosylate was recovered unchanged and in nearly quantitative yield upon heating 2.0 g. of it with 2.0 g. of sodium iodide in 25 ml. of acetone at 100° for two hours in a pressure bottle. It was also unchanged upon heating in acetonyl acetone solution with sodium iodide for forty-eight hours at 80°, conditions which have been shown to bring about a quantitative replacement by iodine of a tosyloxy group attached to a primary carbon atom. Our interpretation of these experimental results is that both tosyl groups are attached through secondary hydroxyl groups. The only cyclic diacetal structures of D-talitol which can fulfill the conditions of possessing two free secondary hydroxyl groups and resisting oxidation by sodium metaperiodate are the 1,2:4,6, 1,3:5,6 and 1,3:4,6 diacetal structures. For reasons previously stated in the theoretical section we favor the 1,3:4,6 structure which is analogous to that of the 1,3:4,6-dimethylenedulcitol[7] of Weber and Tollens.[19] As described in a following paragraph, its acetate shows a behavior analogous to that of 2,5-diacetyl-1,3:4,6-dimethylene-dulcitol[6] toward the sulfuric acid acetolyzing reagent.

Anal. Calcd. for $C_{22}H_{26}O_{10}S_2$: C, 51.35; H, 5.09; S, 12.46. Found: C, 51.29; H, 5.20; S, 12.31.

2,5-Diacetyl-1,3:4,6-dimethylene-D-talitol.—One gram of 1,3:4,6-dimethylene-D-talitol was slowly (ninety minutes) dissolved by agitation in a mixture of 5 ml. of pyridine and 5 ml. of acetic anhydride. Upon standing at 25° overnight spontaneous crystallization of the diacetyl derivative occurred; the suspension was poured upon crushed ice and the precipitate (1.2 g.; 86%) was separated by filtration and recrystallized from 40 parts of absolute alcohol as glistening thin plates which melted at 190–191° and rotated $[\alpha]^{20}\text{D}$ −27.5° in chloroform (*c*, 0.82). The compound is readily soluble in chloroform, acetone and ethyl acetate and relatively insoluble in water, cold methyl and ethyl alcohols and petroleum ether.

Anal. Calcd. for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25; CH_3CO, 29.7. Found: C, 49.79; H, 6.29; CH_3CO, 29.3.

D-Talitol from 2,5-Diacetyl-1,3:4,6-dimethylene-D-talitol.—A solution of 1.0 g. of 2,5-diacetyl-1,3:4,6-dimethylene-D-talitol in 5.0 ml. of an ice-cold acetolyzing solution (prepared by adding 1.0 ml. of concentrated sulfuric acid dropwise to an ice-cold mixture of 70 ml. of acetic anhydride and 30 ml. of glacial acetic acid) was allowed to stand for thirty minutes at 25° and then poured into 100 ml. of ice-cold water. After one hour the solution was neutralized by the cautious addition of solid sodium bicarbonate and extracted with three 25-ml. portions of chloroform. The chloroform extract was washed with water, dried with calcium chloride, and evaporated to a dry sirup. The sirup (1.4 g.; theoretical, 1.7 g.), which presumably consisted of 1,2,5,6-tetraacetyl-3,4-di-(acetoxymethyl)-D-talitol, could not be induced to crystallize. It was dissolved in 10 ml. of methyl alcohol, 0.5 ml. of 0.1 *N* sodium methylate was added, and the solution allowed to stand at 5° for eighteen hours; the reaction mixture was neutralized by the addition of 1 ml. of 0.1 *N* sulfuric acid, filtered to separate the sodium sulfate and the filtrate was evaporated to a sirup which had a strong odor of formaldehyde. This sirup was dried by the successive addition and evaporation of three 5-ml. portions of absolute alcohol and then dissolved in 5 ml. of warm methyl alcohol. The solution was cooled and seeded with D-talitol and upon standing at 5° for several hours the deposition of 0.3 g. (50%) of D-talitol melting at 85–86° and rotating $[\alpha]^{20}\text{D}$ +3.2° in water (*c*, 0.82) occurred. The melting point of the compound was not depressed upon admixture with authentic D-talitol. The recovery of the hexitol rather than a monomethylene-D-talitol is to be expected if both of the cyclic acetal linkages of the dimethylene-D-talitol are formed in part through primary hydroxyl groups. (Compare the saponification product of acetolyzed 1,3:2,4:5,6-trimethylene-D-talitol which is described later.)

2,4-Methylene-D-talitol and Some of Its Derivatives

2,4-Methylene-D-talitol.—The 2,4-methylene-D-talitol was recrystallized from 10 parts of absolute alcohol as very small glistening needles which melted at 144–145° and rotated $[\alpha]^{20}\text{D}$ −4.2° in water (*c*, 1.2). It is soluble in cold water, hot acetone and ethyl acetate and nearly insoluble in ether, chloroform and cold acetic acid.

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.29; H, 7.27. Found: C, 43.31; H, 7.27.

1,3,5,6-Tetraacetyl-2,4-methylene-D-talitol.—A solution of 1.0 g. of 2,4-methylene-D-talitol in a mixture of 5 ml. of acetic anhydride and 5 ml. of pyridine was allowed to stand at 25° for eighteen hours and then poured into ice-cold water. The product was extracted from the aqueous solution with three 25-ml. portions of chloroform and the washed extract was dried over calcium chloride and evaporated to a sirup. The sirup was dissolved in 10 ml. of ether and upon the addition of 10 ml. of hexane the reaction product crystallized as clusters of elongated prisms. The yield was 1.9 g. (quantitative). The compound was recrystallized by solution in 15 parts of ether and the addition of 15 parts of hexane or 2 parts of alcohol. It melted at 67–68° and rotated $[\alpha]^{20}\text{D}$ +37.8° in chloroform (*c*, 0.94). It is soluble in ether, chloroform, hot alcohol and acetone and nearly insoluble in petroleum ether and water.

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; CH_3CO, 47.5. Found: C, 49.66; H, 6.12; CH_3CO, 47.7.

1,3,5,6-Tetrabenzoyl-2,4-methylene-D-talitol.—The tetrabenzoate was obtained in quantitative yield (3.2 g.) by the benzoylation of 1.0 g. of 2,4-methylene-D-talitol in pyridine solution. It was recrystallized from 10 parts of alcohol and formed fine needles which melted at 122–123° and rotated $[\alpha]^{20}\text{D}$ +8.1° in chloroform (*c*, 0.94). It is soluble in chloroform, ether, acetone and warm alcohol and nearly insoluble in water, petroleum ether and cold alcohol.

Anal. Calcd. for $C_{35}H_{30}O_{10}$: C, 68.84; H, 4.95; C_6H_5CO, 68.9. Found: C, 68.82; H, 5.12; C_6H_5CO, 69.0.

Sodium Metaperiodate Oxidation of 2,4-Methylene-D-talitol.—To an ice-cold solution of 0.2070 g. of 2,4-methylene-D-talitol in 25 ml. of water, 10 ml. (4.07 molecular equivalents) of 0.434 *M* sodium metaperiodate was added; the solution was allowed to come to room temperature (22°) and the volume adjusted to 50 ml. with water. Analysis of 5-ml. aliquots at the expiration of one, four and forty-eight hours showed that 0.87, 0.95 and 0.96 molecular equivalents, respectively, of oxidant had been consumed. After the oxidation had been completed (six hours), a 5-ml. aliquot of the oxidation solution was poured into 200 ml. of 0.4% dimethone solution; the reaction mixture, upon preservation at 5° for forty-eight hours, deposited 0.0310 g. of formal-dimethone, which is 99% of that expected if one molecular equivalent of formaldehyde was produced as an oxidation product.

2,4-Methylene-adonitol from 2,4-Methylene-D-talitol.—To an ice-cold solution of 3.0 g. of 2,4-methylene-D-talitol in 150 ml. of water, 37.4 ml. (1.05 molecular equivalents) of 0.434 *M* sodium metaperiodate solution was added and the reaction mixture was allowed to stand at

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[19] Weber and Tollens, *Ann.*, **299**, 316 (1898).

0° for one hour and thereafter at 20° for eighteen hours. A solution of 2.0 g. of barium chloride dihydrate in 10 ml. of water was added, and, following the removal of the insoluble barium salts by filtration, the filtrate was concentrated *in vacuo* in the presence of 2.0 g. of barium carbonate to a sirup. The dry residue which was obtained by the successive addition and evaporation of two 25-ml. portions of absolute alcohol to this sirup was extracted with four 10-ml. portions of absolute alcohol and the combined extracts were evaporated and yielded 4.0 g. of a clear sirup. The sirup, which was strongly reducing to Fehling solution, could not be induced to crystallize. It was transferred to a bomb with 50 ml. of water, 0.6 g. of Raney nickel was added and the mixture was agitated with hydrogen under a pressure of 107 atmospheres at 99° for five hours. The catalyst was separated by filtration and the filtrate, which was nonreducing to Fehling solution and exhibited no rotation, was concentrated *in vacuo* to a thick sirup. A solution of the sirup in 5 ml. of warm alcohol deposited 2.2 g. (79%) of 2,4-methylene-adonitol monohydrate as it cooled. The methylene-pentitol melted at 84–85° and it showed no rotation in aqueous solution (*c*, 0.80); the melting point was not depressed upon admixture with an authentic sample of 2,4-methylene-adonitol monohydrate.[3] Further confirmation of the identity of the compound with 2,4-methylene-adonitol was obtained by converting it to the tribenzoate, which melted at 109–110° and no depression of this value was noted upon making a mixed melting point determination with authentic 1,3,5-tribenzoyl-2,4-methylene-adonitol.

Reactions of 1,3:2,4:5,6-Trimethylene-D-talitol

1,3:2,4:5,6-Trimethylene-D-talitol from 2,4-Methylene-D-talitol.—A solution of 5.0 g. of 2,4-methylene-D-talitol in a mixture of 10 ml. of 37% aqueous formaldehyde and 10 ml. of concentrated hydrochloric acid was evaporated in a desiccator containing concentrated sulfuric acid and small beakers of sodium hydroxide pellets. After five days the pasty mass of crystals was again suspended in a mixture of 5 ml. of formaldehyde and 5 ml. of concentrated hydrochloric acid and the evaporation was repeated. The solid residue was reconcentrated in the same desiccator with two 10-ml. portions of absolute alcohol and when dry was dissolved in 10 ml. of warm water. The solution upon cooling deposited 1.9 g. of cottony needles which melted at 117–119°; this melting point was not depressed upon admixture with the trimethylene-D-talitol obtained by condensation of D-talitol with aqueous formaldehyde and concentrated hydrochloric acid. The aqueous mother liquor was concentrated to a sirup and upon further treatment with formaldehyde and concentrated hydrochloric acid it yielded 1.2 g. more of the same compound. The total yield was therefore 3.1 g. (55%). The trimethylene-D-talitol was recrystallized from 10 parts of methyl alcohol or 2.5 parts of water as fine needles which melted at 118–119° and rotated $[\alpha]^{20}\mathrm{D}$ −32.1° in water (*c*, 0.42). It is very soluble in hot water, moderately soluble in acetone and alcohol at 25° and nearly insoluble in cold water, ether and petroleum ether.

Anal. Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.62; H, 6.57.

1,6-Diacetyl-3,5-di-(acetoxymethyl)-2,4-methylene-D-talitol.—A solution of 1.6 g. of 1,3:2,4:5,6-trimethylene-D-talitol in 5 ml. of an ice-cold acetolyzing solution (prepared by adding 0.5 ml. of concentrated sulfuric acid dropwise to an ice-cold mixture of 70 ml. of acetic anhydride and 30 ml. of acetic acid) was allowed to stand for ten minutes in an ice-bath and poured into 100 ml. of ice-cold water. The mixture, which contained oily droplets in suspension, was neutralized by the addition of solid sodium bicarbonate, and upon standing at 5° the sirupy phase crystallized. The crude product, 1.8 g., which was slightly sticky, was dissolved in 50 ml. of ether, the solution was filtered through a carbon mat, and 50 ml. of hexane was added to the filtrate. The precipitate of fine needles (1.2 g.; 39%) was recrystallized from 80 parts of ether by the addition of 80 parts of hexane. The product melted at 90–91° and rotated $[\alpha]^{20}\mathrm{D}$ +22.5° in chloroform (*c*, 0.44) and these constants were not changed by further recrystallizations. The 1,6-diacetyl-3,5-di-(acetoxymethyl)-2,4-methylene-D-talitol is soluble in alcohol, acetone, chloroform and pyridine, moderately soluble in ether and nearly insoluble in water and petroleum ether.

Anal. Calcd. for $C_{17}H_{26}O_{12}$: C, 48.34; H, 6.20; CH_3CO, 40.8. Found: C, 48.34; H, 6.25; CH_3CO, 40.7.

2,4-Methylene-D-talitol from 1,6-Diacetyl-3,5-di-(acetoxymethyl)-2,4-methylene-D-talitol.—To an ice-cold solution of 1.0 g. of 1,6-diacetyl-3,5-di-(acetoxymethyl)-2,4-methylene-D-talitol in 25 ml. of chloroform, 1.0 ml. of 1 *N* sodium methylate was added and the mixture was allowed to stand at 5° for eighteen hours. The chloroform was evaporated and the sirupy residue was dissolved in 10 ml. of absolute alcohol and the solution neutralized by the addition of 1 *N* sulfuric acid. The sodium sulfate was separated by filtration and the filtrate was evaporated to a sirup; the reaction product (0.3 g.; 65%) crystallized from a warm solution of the sirup in a few ml. of absolute alcohol as needles which melted at 143–144° and rotated $[\alpha]^{20}\mathrm{D}$ −4.0° in water (*c*, 0.80). The melting point of the compound was not depressed in a mixed melting point determination with authentic 2,4-methylene-D-talitol.

Summary

The reduction of D-altrose by hydrogen and Raney nickel is a convenient way of preparing the rather rare D-talitol. Four crystalline acetals of D-talitol have been isolated through the reaction of this hexitol with formaldehyde, using concentrated hydrochloric acid as catalyst. The main products are a 2,4-methylene-D-talitol and a 1,3:4,6-dimethylene-D-talitol. A 2,3,4,5-dimethylene-D-talitol and a 1,3:2,4:5,6-trimethylene-D-talitol were obtained in yields of about 2%, but the trimethylene acetal can be produced in large yield by starting with the monomethylene-D-talitol. The experimental evidence which leads to these assignments of structure is presented. The structures of the methylene acetals derived from D-talitol conform with the empirical rules that have been found to apply to the structures of the methylene and benzylidene acetals of many other polyhydric alcohols.

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