CYCLIC METHYLENE ACETAL STABILITIES IN DIANHYDRO-HEXITOLS¹

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ABSTRACT

Ring closure at the 1,4-3,6-positions in monomethylenated mannitol and iditol imparts considerable lability to the cyclic methylene acetal group. The two derivatives, 1,4-3,6-dianhydro-2,5-methylene-D-mannitol and 1,4-3,6-dianhydro-2,5-methylene-D-iditol, are easily cleaved at the 2,5-methylene positions by highly dilute acid and differ distinctly in this respect from 2,5-methylene-D-mannitol.

The cyclic methylene acetal bridge in 2,5-methylene-D-mannitol (I) is quite stable to dilute acids. The methylene bridge does not cleave unless rather drastic acid treatment is carried out. In comparison to benzylidene and ethylidene acetals and isopropylidene ketals methylene acetals are surprisingly stable. It is therefore valid to assume that the acetal ring in 2,5-methylene-D-mannitol is a low energy structure. Sterically, the mannitol carbon chain can fold in such a manner as to diminish distortion within the methylene carbon valence bonds. Benzylidene, ethylidene, and isopropylidene groups are in reality methylene groups in which one phenyl, one methyl, and two methyl groups replace hydrogen atoms respectively. Folding of the carbon chain may be more difficult, owing to steric forces, so that the inherent energy may be large enough to make benzylidene, ethylidene, and isopropylidene acetals act in a normal manner, that is, they are unstable in acidic solution.

Mannitol and iditol readily form fused tetrahydrofuran rings as shown by the formation of 1,4-3,6-dianhydro-D-mannitol (II) (1, 4) and 1,4-3,6-dianhydro-L-iditol (III) (2, 6). These dianhydrohexitols (II) and (III) have been prepared by the above-mentioned authors by means of simple acid-catalyzed dehydration of D-mannitol and L-iditol respectively. The 1,4-3,6-dianhydro rings in the mannitol (II) and iditol (III) derivatives are fused tetrahydrofuran systems that are *cis*-oriented, thus imparting considerable stability to the two substances, (II) and (III).

A methylene acetal bridge across C-2 and C-5 in (II) and (III) should be under considerable strain inasmuch as the valence bond angular distortion cannot be diminished by folding of the rigid tetrahydrofuran ring structures. 1,4-3,6-Dianhydro-2,5-methylene-D-mannitol (IV) and 1,4-3,6-dianhydro-2,5methylene-D-iditol (V) were synthesized to compare the stability of the methylene acetals in the latter two dianhydrohexitols, (IV) and (V), to the identical group in 2,5-methylene-D-mannitol (I). The mannitol derivative(IV) proved to be very labile to 0.001 N hydrochloric acid and even to hot water. The iditol derivative (V) required somewhat more drastic treatment to cleave the acetal ring. Hot water had no effect whatsoever and 0.01 N, but not 0.001 N, hydrochloric acid cleaved the acetal ring in a few minutes. Although

- ¹ Manuscript received May 11, 1953.
- Contribution from the Research Institute, Montreal General Hospital, Montreal, Quebec.
 - In charge, Division of Organic Chemistry.

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Ts = p-Toluenesulphonyl

the iditol derivative (V) was less labile than the mannitol derivative (IV), both were extremely labile when compared to 2,5-methylene-D-mannitol (I).

Saponification of 2,5-methylene-1,6-ditosyl-D-mannitol (VI) with alcoholic potassium hydroxide or sodium methoxide solution yielded a dianhydromethylene hexitol. It is now generally accepted that detosyloxylation followed by ring closure occurs through the transitory formation of a carbonium cation. Ring closure occurs when the transitory carbonium cation has a hydroxyl or presumptive hydroxyl group in a *trans* position and the ring closes on the side of the molecule where the reacting hydroxyl group is situated. Therefore the dianhydromethylene hexitol can be formulated either 1,4-3,6-dianhydro-2,5-methylene-D-mannitol (IV) or 1,3-4,6-dianhydro-2,5-methylene-Dmannitol (VII). The latter structure can be dismissed on steric grounds. Removal of the methylene group with either hot water or 0.001 N hydrochloric acid yielded a product identical with the known isomannide. It is unlikely that a methylene acetal group can shift under the experimental conditions used to prepare the dianhydromethylene mannitol. This is therefore further unequivocal proof of the 1,4-3,6-dianhydro-D-mannitol (II) structure for isomannide.

The iditol derivative was prepared by sodium methoxide saponification of 1,6-dibenzoyl-2,5-methylene-3,5-ditosyl-D-mannitol (VIII). Again, for the same reasons as above, it is only possible to formulate the hexitol derivative as 1,4-3,6-dianhydro-2,5-methylene-D-iditol (V). Removal of the methylene acetal with 0.01 N hydrochloric acid yielded a product that was identical with the known isoidide. This then is additional proof for the 1,4-3,6-dianhydro ring structure for isoidide.

EXPERIMENTAL

2,5-Methylene-1,6-ditosyl-D-mannitol (VI)

2,5-Methylene-D-mannitol (5) (50 gm.) was dissolved in hot pyridine (500 cc.). The solution was cooled (0°C.) and *p*-toluenesulphonyl chloride (100 gm.), dissolved in pyridine (200 cc.), was added over a period of 30 min. with stirring. The reaction mixture was then allowed to stand overnight at room temperature and was finally concentrated *in vacuo* to remove most of the pyridine. The remaining sirupy mass was suspended in a large volume of cold water and the sirup soon crystallized. It was filtered, washed well with cold water, and air-dried. The crude product was recrystallized once from methanol after decolorizing with charcoal. An additional recrystallization gave 94 gm. (73%) of a pure product melting at 148–149°C. and rotating (α)^{20°c.} -22.8°. These constants agreed with those found by Haskins, Hann, and Hudson (3).

A sample of the above (3 gm.) was dissolved in pyridine (20 cc.), p-toluenesulphonyl chloride (2.4 gm.) was added, and the solution allowed to stand 72 hr. at 40°C. The reaction mixture was cooled to 20°C. and then added to a large volume of cold water. The product separated as an oil and it slowly solidified. After the solid had been allowed to stand overnight it was broken up, filtered, and washed with cold water. The air-dried material was recrystallized from 99% ethanol and after desiccation it weighed 3.3 gm. (68%) and melted at 176–177°C. A mixed melting point determination with authentic 2,5-methylene-1-3,4,6-tetratosyl-D-mannitol was not depressed.

1,4-3,6-Dianhydro-2,5-methylene-D-mannitol (IV)

Sodium Methoxide Method

2,5-Methylene-1,6-ditosyl-D-mannitol (20 gm.) was dissolved in chloroform (200 cc.). A sodium methoxide solution (50 cc.) containing 1.9 gm. sodium was added and, within one minute, a gel formed. The gel was soon replaced by glistening crystals of sodium p-toluenesulphonate. The small excess of sodium methoxide was converted to sodium carbonate by means of carbon dioxide and the separated salts removed by filtration. The slightly colored filtrate was concentrated *in vacuo* and the gummy residue mixed with hot chloroform (100 cc.). The turbid solution was filtered and the solvent again removed *in vacuo* at 30°C. The solid residue was dissolved in hot ether (300 cc.) and the ethereal solution was decolorized with charcoal, then filtered. The filtrate was concentrated to one-half volume and cooled to -20° C. Long needlelike crystals separated in a yield of 5 gm. (80%). They were recrystallized twice more when the melting point of 84–85°C. became constant and the rotation was (α)_{24°C}. 133.7° (CHCl₃; c, 10.4304; 1, 2).

Potassium Hydroxide Method

2,5-Methylene-1,6-ditosyl-D-mannitol (20 gm.) was dissolved in ethanolic potassium hydroxide (5.3 gm. in 250 cc.). The highly alkaline reaction mixture became neutral to phenolphthalein on heating under reflux. Heating was continued an additional 30 min. and the mixture was then concentrated *in vacuo* at 30°C. The gummy mass was thinned with chloroform (300 cc.) and the mixture filtered to remove potassium *p*-toluenesulphonate in quantitative yield. The chloroform solution was then concentrated *in vacuo* and the residual solid dissolved in hot ether (300 cc.) and the latter solution decolorized with activated charcoal. The solution, after filtration, was concentrated to one-half volume and on cooling to -20° C. needlelike crystals separated in a yield of 5.6 gm. (90%). An additional recrystallization from ether gave a pure product melting at 84–85°C. and rotating (α)_p^{24°c.} 133.2° (CHCl₃; *c*, 8.631; 1, 2). A mixed melting point determination with a sample of the substance obtained by the sodium methoxide method, above, was not depressed.

Anal. Calc. for C7H10O4; C, 53.16; H, 6.33. Found: C, 53.09; H, 6.46.

Methylenation of 1,4-3,6-Dianhydro-D-mannitol (II)

1,4-3,6-Dianhydro-D-mannitol (4 gm.) was dissolved in anhydrous dioxane (175 cc.) containing paraldehyde (5 gm.) and anhydrous calcium sulphate (20 gm.). The mixture was heated in a sealed bomb tube in a steam bath for 10 hr. The tube was cooled to 20°C. and the contents removed in the fume cabinet. Chloroform (380 cc.) was added and the mixture filtered. The filter was washed with a little chloroform and the combined filtrates concentrated to dryness *in vacuo*. A sirup resulted which was partially soluble in ether and it was therefore heated under reflux with anhydrous ether (300 cc.) for one hour. The ethereal solution was decanted from the undissolved sirup and the latter was triturated with a little ethyl acetate. The sirup crystallized immediately and after one recrystallization from ethyl acetate it weighed 2 gm. (50% recovery) and melted at 87–88°C. A mixed melting point determination with authentic 1,4-3,6-dianhydro-D-mannitol was not depressed.

The ethereal solution, above, was concentrated to about 75 cc. and filtered from a faint turbidity. The clear, colorless solution was cooled to -20° C. and crystals which separated in a yield of 1.2 gm. (27%) melted at 84–85°C. A mixed melting point determination with 1,4-3,6-dianhydro-2,5-methylene-D-mannitol obtained above was not depressed.

Acetolysis of 1,4-3,6-Dianhydro-2,5-methylene-D-mannitol (IV)

1,4-3,6-Dianhydro-2,5-methylene-D-mannitol (1 gm.) was added to an acetolyzing (5) mixture (5 cc.) at 0°C. The solid dissolved immediately and

the solution was allowed to stand 18 hr. at 5°C. The reaction mixture was added slowly with stirring to an excess of cold (5°C.) saturated potassium bicarbonate solution. The aqueous solution was then concentrated to dryness *in vacuo* at 15°C. The dry residue was extracted with warm chloroform (100 cc.) and after filtration, the solvent was removed *in vacuo*. The remaining colorless sirup was distilled at 130–133°C. at 0.08 mm. and gave 0.9 gm. of a viscous sirup. This yield was equivalent to 64% based on 2,5-diacetyl-1,4-3,6dianhydro-D-mannitol. The specific rotation was $(\alpha)_{p}^{23^{\circ}c}$. 119.8° (CHCl₃; *c*, 1.602; 1, 2) and refractive index $\eta_{p}^{23^{\circ}c}$. 1.4840. A few drops of the product when heated with dilute hydrochloric acid did not give a test for formaldehyde, signifying that the methylene acetal was cleaved by the acetolyzing mixture.

The presumed 2,5-diacetyl-1,4-3,6-dianhydro-D-mannitol (0.6 gm.) was dissolved in chloroform (25 cc.). Sodium methoxide solution (5 cc. of 0.01 N) was added and the solution allowed to stand overnight at 5°C. Carbon dioxide gas was passed in and the mixture was then concentrated *in vacuo*. The dry residue was heated with a small volume of ethyl acetate. The latter solution was concentrated to one-half volume and after cooling to -10° C. the concentrate was inoculated with a crystal of 1,4-3,6-dianhydro-D-mannitol. Immediate crystallization occurred and the product was recrystallized once more from ethyl acetate yielding 0.39 gm. (77%) and melting at 87.5-88°C. A mixed melting point determination with authentic 1,4-3,6-dianhydro-D-mannitol was not depressed.

Effect of Hot Water on 1,4-3,6-Dianhydro-2,5-methylene-D-mannitol (IV)

1,4-3,6-Dianhydro-2,5-methylene-D-mannitol (1 gm.) was dissolved in distilled water (25 cc.) and the solution was distilled slowly through a 150 mm. glass column. The distillate was collected in an excess of ice-cold 2,4-dinitrophenylhydrazine hydrochloride solution. Immediate precipitation of formalde-hyde-2,4-dinitrophenylhydrazone occurred and distillation was continued until 15 cc. distillate was collected. The water was replaced and distillation continued. This process was repeated six times so that practically all the formaldehyde was removed. The voluminous 2,4-dinitrophenylhydrazone was filtered, washed with a little water, and air-dried. The yield was 1.2 gm. (89%) and the melting and mixed melting points with an authentic sample were $164-167^{\circ}C$.

The above was repeated but the distillate was added to an excess of 5,5dimethyl-1,3-cyclohexanedione. The dimethone of formaldehyde separated in nearly quantitative yield and melted at 187–189°C. A mixed melting point determination with an authentic sample showed 188–189°C.

The residues in both distilling flasks were combined and concentrated to dryness *in vacuo* and the gummy product dissolved in a small volume of hot ethyl acetate. The slightly colored solution was decolorized with charcoal, filtered, and then allowed to cool. The crystalline product that separated was removed by filtration and it was recrystallized once more giving 1.3 gm. (77%) melting at 87–88°C. This proved to be 1,4-3,6-dianhydro-D-mannitol as determined by a mixed melting point.

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1,4-3,6-Dianhydro-2,5-dibenzoyl-D-mannitol

1,4-3,6-Dianhydro-2,5-methylene-D-mannitol (1V) (2 gm.) was dissolved in 0.001 N hydrochloric acid (75 cc.) and the solution distilled *in vacuo* at 50°C. The sirupy residue was dried by distilling ethanol from it. This was repeated four times. The partially crystalline mass was then dissolved in anhydrous pyridine (25 cc.), the solution cooled to 0°C., and benzoyl chloride (4 cc.) was added. The reaction mixture was allowed to stand for two hours at 24°C., then concentrated *in vacuo*. The remaining sirup was mixed with cold water and after it had been allowed to stand overnight at 5°C. the sirup solidified. The air-dried material was dissolved in about 20 cc. ethanol and the solution decolorized with charcoal. The solution was cooled and crystallization occurred. Two additional recrystallizations from ethanol raised the melting point to 131–132°C. and rotation to $(\alpha)_{\rm p}^{24°c.}$ 224.8° (CHCl₃; *c*, 0.6649; 1, 2). Fletcher and Goepp (2) report m.p. 132.0–132.4°C. and $(\alpha)_{\rm p}^{20°c.}$ 225.7° (CHCl₃).

1,6-Dibenzoyl-2,5-methylene-3,4-ditosyl-D-mannitol (VIII)

1,6-Dibenzoyl-2,5-methylene-D-mannitol (5) (25.2 gm.) was dissolved in anhydrous pyridine (90 cc.). The solution was cooled to 0°C. and *p*-toluenesulphonyl chloride (26.4 gm.) was added. The reaction mixture was allowed to stand for three days at 40°C. and then concentrated *in vacuo* to remove most of the pyridine. The dark-brown residue was mixed with a large volume of cold water and the sirup soon solidified. The solid mass was broken up, filtered, and washed with cold water. The air-dried crude material was recrystallized from methanol yielding perfect hexagonal plates. The partially purified material was recrystallized once more from the same solvent and the yield was 40.6 gm. (91%). It melted at 112–113°C. and rotated $(\alpha)_{\rm p}^{24°c.}$ 13.7° (CHCl₃; 1, 2; *c*, 7.2828).

Anal. Calc. for C₃₅H₃₄S₂O₁₂; C, 59.15; H, 4.78; S, 9.01. Found: C, 59.21; H, 4.83; S, 9.0.

1,4-3,6-Dianhydro-2,5-methylene-D-iditol (V)

1,6-Dibenzoyl-2,5-methylene-3,4-ditosyl-D-mannitol (VIII) (27.3 gm.) was dissolved in dry chloroform (200 cc.). Sodium metal (1.8 gm.) was dissolved in methanol (65 cc.) and the solution was added to the chloroform solution. The mixture was allowed to stand at room temperature (24°C.) for 24 hr. The slight excess of sodium methoxide was converted to carbonate with carbon dioxide gas and the mixture filtered to remove the sodium salts. The filtrate was concentrated *in vacuo* at 40°C., the residue was dissolved in chloroform (100 cc.), and the solution treated with decolorizing charcoal to remove a trace of color and turbidity. The colorless sirup that remained after solvent removal was dissolved in a little ethyl acetate and crystallization occurred after several hours' standing at room temperature. The crystalline mass was recrystallized from ethyl acetate and it weighed 4.6 gm. (76%), melted at 83-84°C., and rotated (α)^{22°c.}_D -152.1° (CHCl₃; 1, 2; *c*, 0.4108). Mixed melting point determinations with 1,4-3,6-dianhydro-2,5-methylene-D-mannitol and with isomannide were depressed over 20°C.

Anal. Calc. for C₇H₁₀O₄; C, 53.16; H, 6.33. Found: C, 53.11; H, 6.41.

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Effect of Hot Water on 1,4-3,6-Dianhydro-2,5-methylene-D-iditol (V)

The above (V) (0.5 gm.) was heated under reflux for two hours with distilled water (50 cc.) in a stream of nitrogen. The gas was passed through cold (5°C.) water (250 cc.). Formaldehyde could not be detected. The water was then removed from the reaction mixture *in vacuo* at 50° C. and the sirup, after drying with ethanol, was dissolved in a small volume of ethyl acetate. The solution was seeded and after two hours, crystals of 1,4-3,6-dianhydro-2,5-methylene-D-iditol (V) separated as shown by a mixed melting point determination with an authentic sample.

Effect of Dilute Hydrochloric Acid on 1,4-3,6-Dianhydro-2,5-methylene-D-iditol (V)

The above (V) (0.5 gnl) was dissolved in 0.001 N hydrochloric acid (50 cc.). A stream of nitrogen was passed through the solution, while it was heated under reflux for 30 min. The gas was passed into cold (5°C.) water (250 cc.). A test for formaldehyde was negative. The solution was then taken up with more hydrochloric acid to give a normality of 0.01 N and heating continued. Formaldehyde was detected after 10 min. by means of 2,4-dinitrophenylhydrazine hydrochloride. The acidic solution was then concentrated in vacuo at 50°C. and the remaining colorless sirup was dried by distilling ethanol from it. The dried sirup was dissolved in a small volume of ethyl acetate and allowed to stand overnight at 22°C. after which tufts of crystals separated. After filtration and desiccation the yield was 0.18 gm. (40%) and the product melted at 63-64°C. A mixed melting point determination with authentic 1,4-3,6-dianhydro-D-iditol was not depressed.

1,4-3,6-Dianhydro-2,5-dibenzoyl-p-iditol

The filtrate from the above isolation of 1,4-3,6-dianhydro-D-iditol was concentrated *in vacuo* and the resulting sirup (0.23 gm.) dissolved in anhydrous pyridine (4 cc.). The solution was cooled to 0°C. and benzoyl chloride (0.5 cc.) was added. The reaction mixture was allowed to stand overnight at 22°C., then poured into cold water (50 cc.). Cold saturated potassium bicarbonate solution was added to dissolve benzoic acid and the sirup solidified after standing for three days at 5°C. The solid was broken up, filtered, and washed. It was dried in air and recrystallized twice from butanol-1. The yield was 0.34 gm. and the product melted at 110-111° and rotated $(\alpha)_{p}^{22^{\circ}c.}$ -140.6° (CHCl₃; 1, 2; c, 0.7724). The reported (1) constants for the enantimorph are m.p. 111.0–111.3°C. and $(\alpha)_{p}^{25.2°c.}$ 141.9° (CHCl₃).

ACKNOWLEDGMENT

We are greatly indebted to the Sugar Research Foundation for a grant-inaid.

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