lized from 90% alcohol and then from boiling water, m. p. 186–187°, yield, 3.5 g.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.88. Found: C, 70.67; H, 6.38.

1-(*p*-Acetoxyphenyl)-2,6-dicarbethoxy-4-carbethoxymethyl-cyclohexanedione-3,5 (III).—Equimolar quantities of 1-(*p*-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5, ethyl bromoacetate and sodium ethoxide in absolute alcohol were mixed with dry ether and the mixture refluxed for two hours. After acidifying, the solvents were removed by distillation under reduced pressure. Residues were washed with cold water, filtered off and dissolved in alcohol. Solution evaporated gave crystals and a yellowish glassy material which looked like supercooled liquid. Residues recrystallized twice from boiling water gave crystals, m. p. 168°. Continued heating after melting caused a rise of the melt in the capillary at 178°.

Anal. Calcd. for $C_{24}H_{28}O_{10}$: C, 60.53; H, 5.88. Found: C, 60.65; H, 5.65.

Acknowledgment.—The author wishes to express his appreciation and thanks to Dean Charles M. McConn of Washington Square College and to Professor Arthur C. DeGraff of the Department of Therapeutics, for the arrangement which made it possible for him to do this work in the Laboratory of the Department of Therapeutics. The interest and coöperation of Dr. DeGraff and Dr. Robert A. Lehman are gratefully acknowledged.

Summary

Crystalline 4-acetoxybenzalmalonic diethyl ester, m. p. 67–68°, was prepared from acetoxybenzaldehyde and diethyl malonate in acetic anhydride, using dry hydrogen chloride as condensing agent.

The preparation of 1-(*p*-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5, of 4-acetoxyphenyl-cyclohexanedione-3,5 and of 1-(*p*-acetoxyphenyl)-2,6-dicarbethoxy-4-carbethoxymethyl-cyclohexanedione-3,5 is described. These are used as starting materials for further synthesis of substitutes for digitalis glycosides.

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

1,3:2,5-Dimethylene-L-rhamnitol and Some of its Derivatives

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

According to the recently published relationship[1] between the configurations of the polyhydric alcohols and the structures of the methylene and benzylidene cyclic acetals derived from them, it would be expected that L-rhamnitol, which is 6-desoxy-L-mannitol, would form a methylene cyclic acetal comparable in structure with that formed from L-mannitol. Since formaldehyde has been shown[2] to condense with the D-form of the hexitol to yield 1,3:2,5:4,6-trimethylene-D-mannitol it is to be expected that L-rhamnitol will form a 1,3:2,5-dimethylene-L-rhamnitol, the 4,6-acetal linkage being incapable of formation because of the presence of the 6-desoxy group in the rhamnitol. Weber and Tollens[3] condensed formaldehyde with L-rhamnitol and obtained a crystalline dimethylene-L-rhamnitol; from it a crystalline monobenzoate was prepared. Nothing has been known in the past regarding the structure of the diacetal. In the present communication we supply definitive proof that it is indeed 1,3:2,5-dimethylene-L-rhamnitol (I), the structure that is to be expected. The compound was prepared essentially by the procedure of Weber and Tollens; improvements in the method of isolation and purification of the product resulted in yields of about 75%, whereas these authors reported that only a "few grams" of dimethylene-L-rhamnitol were obtained from thirty grams of L-rhamnitol. Upon treatment with a sulfuric acid acetolyzing solution, the dimethylene-L-rhamnitol was transformed to a diacetyl-acetoxymethyl-monomethylene-L-rhamnitol (II). In the light of previous experience, the result indicated that the ruptured acetal linkage was formed through the primary hydroxyl group at position one of the L-rhamnitol. The diacetyl-acetoxymethyl-monomethylene-L-rhamnitol was saponified by methyl alcoholic barium methylate and yielded a monomethylene-L-rhamnitol that melted at 124–125° and rotated $[\alpha]^{20}D$ +62.1° in water. This monoacetal, as will be seen in the continuation, was shown to be 2,5-methylene-L-rhamnitol (III). The 2,5-structure of the monoacetal limited the position of the second methylene group in the diacetal to the 1,3-, the 1,4-, or the 3,4-position. The previous evidence obtained from the action of the acetolyzing solution on the diacetal, which indicated the presence of an acetal linkage at position 1, permitted a provisional elimination of the 3,4-type of acetal linkage. This was confirmed later by a rigorous proof that the 1,3-acetal linkage is present.

A conclusive proof of the structure of 2,5-methylene-L-rhamnitol (III) was obtained by correlating its structure with that of 2,5-methylene-D-mannitol.[2] The 2,5-methylene-D-mannitol was converted to the monotosyl derivative (IV) by treatment with one molecular equivalent of *p*-toluenesulfonyl chloride in pyridine solution. Because of the symmetry of the mannitol molecule it is immaterial whether the primary hydroxyl group at the one or the six position reacts with

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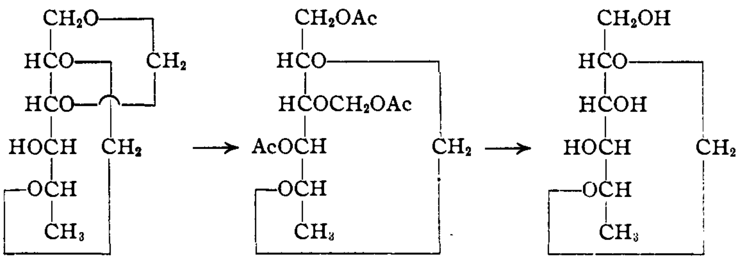
[1] Hann and Hudson, THIS JOURNAL, **66**, 1909 (1944).

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

[3] Weber and Tollens, *Ann.*, **299**, 321 (1898).

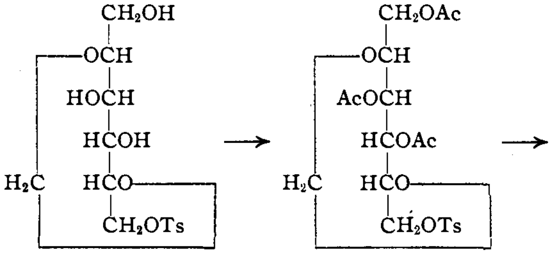


(I) 1,3:2,5-Dimethylene-L-rhamnitol

(II) 1,4-Diacetyl-3-acetoxymethyl-2,5-methylene-L-rhamnitol

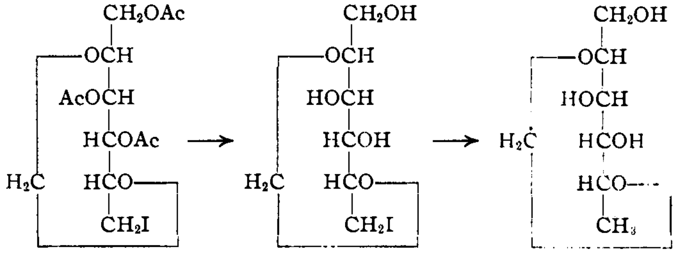
(III) 2,5-Methylene-L-rhamnitol

the reagent since they are equivalent; however, it would be expected that some 1,6-ditosyl-2,5-methylene-D-mannitol would be formed when both primary hydroxyls on the same molecule reacted, and such was found to be the case. The crude product was a mixture consisting of approximately two parts of the monotosyl derivative to one part of the ditosyl derivative. They were readily separated by fractional crystallization from ethylene dichloride in which the monotosyl compound is considerably less soluble; the yields were low, 27% for the monotosyl derivative and 17% for the 1,6-ditosyl-2,5-methylene-D-mannitol. Since previous experience[4] has shown that iodination, under the usual conditions of the Oldham–Rutherford technique,[5] of tosyl compounds possessing also free hydroxyl groups, gave low yields of the expected desoxy-iodo derivative, the 6-(*syn.*1)-tosyl-2,5-methylene-D-mannitol (IV) was acetylated and the crystalline 1,3,4-triacetyl-6-tosyl-2,5-methylene-D-mannitol (V) thus formed was heated for two hours with sodium iodide in acetone solution. The 1,3,4-triacetyl-6-desoxy-6-iodo-2,5-methylene-D-mannitol (VI), which was obtained in quantitative yield, was deacetylated with barium methylate and the 6-desoxy-6-iodo-2,5-methylene-D-mannitol (VII) was reduced with hydrogen in the presence of Raney nickel to 6-desoxy-2,5-methylene-D-mannitol (VIII). This compound melted at 124–125° and rotated $[\alpha]^{20}\text{D}$ $-61.9°$ in aqueous solution, and hence it is the enantiomorph of 2,5-methylene-L-rhamnitol (III) (m. p. 124–125°; $[\alpha]^{20}\text{D}$ $+62.1°$ in water). The two enantiomorphs form a crystalline racemate which melts at 123–124° and is devoid of rotation.



(IV) 6-(*syn.*1)-Tosyl-2,5-methylene-D-mannitol

(V) 1,3,4-Triacetyl-6-tosyl-2,5-methylene-D-mannitol



(VI) 1,3,4-Triacetyl-6-desoxy-6-iodo-2,5-methylene-D-mannitol

(VII) 6-Desoxy-6-iodo-2,5-methylene-D-mannitol

(VIII) 6-Desoxy-2,5-methylene-D-mannitol

Confirmation of the structural relationship of the 2,5-methylene-L-rhamnitol and the known 2,5-methylene-D-mannitol was also obtained by conversion of the fully tosylated derivative of the latter compound and that of 2,5-methylene-L-rhamnitol to enantiomorphous 1,6-didesoxy-3,4-ditosyl-2,5-methylene hexitol derivatives. The 1,3,4,6-tetratosyl derivative of 2,5-methylene-D-mannitol (IX) was transformed to 1,6-didesoxy-1,6-diiodo-3,4-ditosyl-2,5-methylene-D-mannitol (X) by heating it with sodium iodide in acetonylacetone[6] at 80° for six hours and this dihalogenated compound was reduced with hydrogen in the presence of Raney nickel to 1,6-didesoxy-3,4-ditosyl-2,5-methylene-D-mannitol (XI) (m. p. 119–120°; $[\alpha]^{20}\text{D}$ $+15.7°$ in chloroform). Following the same series of reactions, but starting with the 1,3,4-tritosyl derivative of 2,5-methylene-L-rhamnitol (XII), it was possible to isolate 1-desoxy-1-iodo-3,4-ditosyl-2,5-methylene-L-rhamnitol (XIII) which upon reduction formed 1-desoxy-3,4-ditosyl-2,5-methylene-L-rhamnitol (XIV), the enantiomorph of the previously described 1,6-didesoxy-3,4-ditosyl-2,5-methylene-D-mannitol (XI), as shown by its analysis, identical melting point, 119–120°, and the magnitude and sign of its rotation, $[\alpha]^{20}\text{D}$ $-15.3°$ in chloroform. This enantiomorphous pair of compounds also forms a racemate, which melts at 138–139° and shows no rotation.

The oxidation of the monomethylene-L-rhamnitol in aqueous solution by sodium periodate also yielded results in agreement with its 2,5-acetal structure. Only slightly more than one molecular equivalent of the oxidant was reduced and no formaldehyde or formic acid was produced. The

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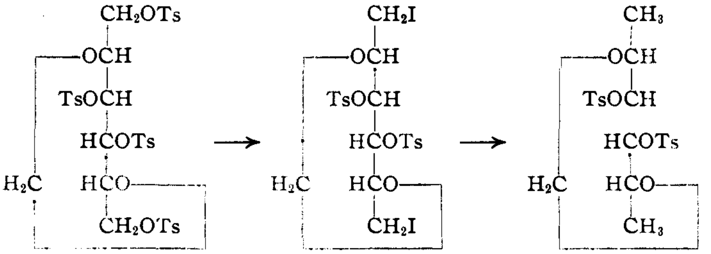
(4) Ness, Hann and Hudson, This Journal, **66**, 1901 (1944).

(5) Oldham and Rutherford, *ibid.*, **54**, 366 (1932).

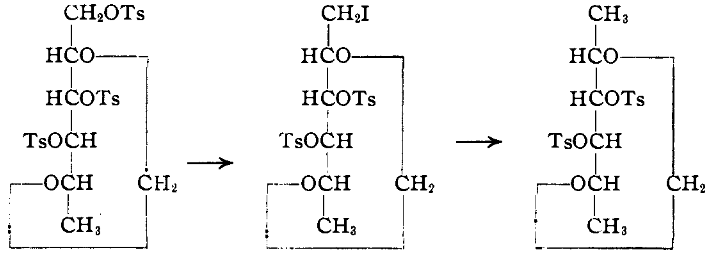
(6) Murray and Purves, *ibid.*, **62**, 3195 (1940).



(IX) 1,3,4,6-Tetratosyl-2,5-methylene-D-mannitol

(X) 1,6-Didesoxy-1,6-diiodo-3,4-ditosyl-2,5-methylene-D-mannitol

(XI) 1,6-Didesoxy-3,4-ditosyl-2,5-methylene-D-mannitol

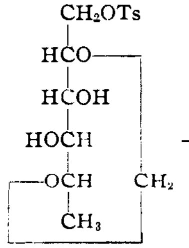


(XII) 1,3,4-Tritosyl-2,5-methylene-L-rhamnitol

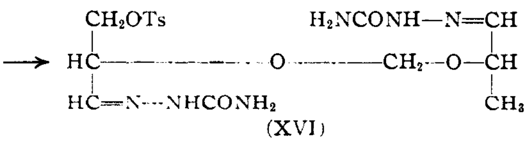
(XIII) 1-Desoxy-1-iodo-3,4-ditosyl-2,5-methylene-L-rhamnitol

(XIV) 1-Desoxy-3,4-ditosyl-2,5-methylene-L-rhamnitol

absence of formaldehyde proves that the glycol grouping is composed of two secondary hydroxyl groups and the absence of formic acid shows that the hydroxyl groups which are attached to the carbon atoms adjacent to this α-glycol grouping are concerned in the acetal linkage. All attempts to isolate the oxidation product or any of its derivatives were unsuccessful, but it was possible to convert 2,5-methylene-L-rhamnitol to a crystalline 1-tosyl-2,5-methylene-L-rhamnitol (XV) which upon oxidation in acetic acid by lead



(XV) 1-Tosyl-2,5-methylene-L-rhamnitol



(XVI) Di-semicarbazone of the formaldehyde mixed acetal of 3-tosyl-L-glyceraldehyde and L-lactaldehyde

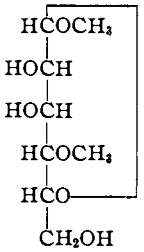
tetraacetate produced the expected formaldehyde mixed acetal of 3-tosyl-L-glyceraldehyde and L-lactaldehyde. The oxidation product could not be obtained in crystalline condition, but it was isolated in a yield of 46% as the crystalline disemicarbazone (XVI).

The position of the methylene group which is attached to the pair of secondary hydroxyls in the L-rhamnitol mono- and di-methylene acetals having been established as 2,5, it remained to locate the position of the second methylene group in the diacetal. Evidence supporting the prior deduction (from the action of the acid acetolyzing solution on the diacetal) that position 1 is one point of attachment of this second cyclic acetal group was obtained from the crystalline monotosyl derivative of dimethylene-L-rhamnitol by testing its reaction with sodium iodide in acetone solution at 100° for two hours. Under these standard conditions, the tosyloxy group which is attached to a primary carbon atom is usually replaced by iodine, while that attached to a secondary carbon atom is normally unaffected. The tosyl derivative in the present case was recovered unchanged in quantitative yield; this result is thus in agreement with the conclusion that the hydroxyl group which is tosylated in the tosyl-dimethylene-L-rhamnitol and free in the dimethylene-L-rhamnitol is a secondary one.

The only possible structures of dimethylene-L-rhamnitol which can conform to the limitations of having a 2,5 cyclic acetal ring and a free secondary hydroxyl group are 1,3:2,5- and 1,4:2,5-dimethylene-L-rhamnitol. A decision between these two structures was made by a comparison of the methylation product of the dimethylene-L-rhamnitol with the dimethylene acetal of authentic 4-methyl-D-rhamnitol (XXI). The dimethylene-L-rhamnitol, upon methylation with methyl iodide and silver oxide, formed a crystalline monomethyl dimethylene-L-rhamnitol which melted at 143–144° and showed a specific rotation $[\alpha]^{20}\mathrm{D}$ +50.0° in chloroform. Authentic 4-methyl-D-rhamnitol was made in the following way. Methyl 4-methyl-α-D-mannopyranoside (XVII), the structure of which has been established,[7] was converted to crystalline methyl 2,3-diacetyl-4-methyl-6-tosyl-α-D-mannopyranoside (XVIII). The 6-tosyloxy group of the latter compound was replaced by iodine by the method of Oldham and Rutherford[5] and the sirupy reaction product, presumably methyl 2,3-diacetyl-4-methyl-6-desoxy-6-iodo-α-D-mannopyranoside, was deacetylated to yield crystalline methyl 4-methyl-6-desoxy-6-iodo-α-D-mannopyranoside (XIX). This sub-

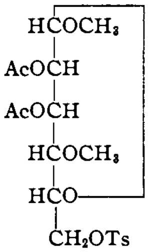
(7) Haskins, Hann and Hudson, This Journal, 65, 70 (1943).

stance was reduced with hydrogen in the presence of Raney nickel in methyl alcoholic solution containing barium methylate and it yielded sirupy methyl 4-methyl-α-D-rhamnopyranoside (XX). The glycoside was hydrolyzed with 0.1 *N* hydrochloric acid to 4-methyl-D-rhamnose, and an aqueous solution of the sirupy sugar was reduced at 100° for six hours with Raney nickel and hydrogen under a pressure of 67 atmospheres, to 4-methyl-D-rhamnitol (XXI). The alcohol, which could not be crystallized, was condensed with 37% aqueous formaldehyde in the presence of hydrochloric acid to give a crystalline dimethylene-4-methyl-D-rhamnitol (XXII) melting at 143–144° and rotating $[\alpha]^{20}D$ −49.6° in chloroform, which is thus the enantiomorph of the previously described substance that is obtained by the methylation of dimethylene-L-rhamnitol. Examination of the crystalline compounds from the two sources under the petrographic microscope showed that they possessed identical optical crystallographic properties. The enantiomorphs form a crystalline racemate which melts at 123–124°, exhibits no rotation in chloroform solution and differs in optical crystallographic properties from the components. The establishment of the enantiomorphous character of these compounds limits the position of the free hydroxyl in dimethylene-L-rhamnitol to carbon atom four; the prior proof that monomethylene-L-rhamnitol is 2,5-methylene-L-rhamnitol leaves only the one and three positions available for the second methylene group, and hence dimethylene-L-rhamnitol is 1,3:2,5-dimethylene-L-rhamnitol (I).



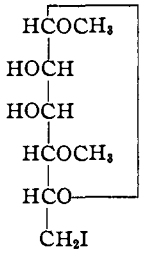
(XVII)

Methyl 4-methyl-α-D-mannopyranoside



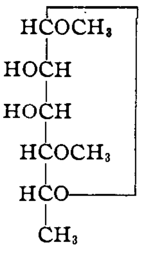
(XVIII)

Methyl 2,3-diacetyl-4-methyl-6-tosyl-α-D-mannopyranoside



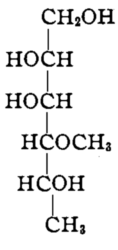
(XIX)

Methyl 4-methyl-6-desoxy-6-iodo-α-D-mannopyranoside



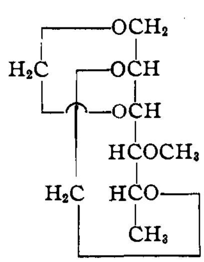
(XX)

Methyl 4-methyl-α-D-rhamnopyranoside



(XXI)

4-Methyl-D-rhamnitol



(XXII)

1,3:2,5-Dimethylene-4-methyl-D-rhamnitol

We are indebted to Mr. Joseph J. Fahey of the Geological Survey of the U. S. Department of the Interior for the determination of the optical crystallographic properties of the racemates and their component D- and L-forms and to Dr. A. T. Ness for performing the microchemical analyses.

Experimental

1,3:2,5-Dimethylene-L-rhamnitol (I).—A solution of 50 g. of L-rhamnitol in a mixture of 50 cc. of concentrated hydrochloric acid and 50 cc. of 37% aqueous formaldehyde solution was concentrated under vacuum at room temperature (23°) in a desiccator containing calcium chloride, sodium hydroxide pellets and several small beakers of concentrated sulfuric acid. After a few days the diacetal crystallized spontaneously from the solution and after a further fourteen days the magma was thinned with 25 cc. of water, cooled to 5° for several hours, and the nearly pure crystalline product (30 g.; m. p. 135–137°) was separated by filtration. A second fraction of 13.4 g. (m. p. 130–133°) was obtained by concentrating the mother liquor again in the desiccator. The yield of relatively pure product was therefore 43.4 g. (76%). The compound was recrystallized from four parts of water; under the microscope the crystals appear as elongated lath-like plates; the pure substance melted at 136–137° and rotated $[\alpha]^{20}D$ +93.0° in water (*c*, 0.83).[8] Weber and Tollens[3] recorded the melting point of their dimethylene-L-rhamnitol as 138–139° and the rotation $[\alpha]D$ as +8.86° and +9.12° in aqueous solution; however, there is an error in the decimal points because their data really lead to the values +88.6° and +91.2°. The dimethylene rhamnitol which we have prepared is undoubtedly the same acetal that Weber and Tollens discovered. The compound is very soluble in alcohol, glacial acetic acid, chloroform, acetone, pyridine and hot water and moderately soluble in ether, water at 25° and boiling hexane; it is nearly insoluble in benzene and cold hexane.

Anal. Calcd. for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.41; H, 7.55.

4-Acetyl-1,3:2,5-dimethylene-L-rhamnitol was obtained in 2.2 g. yield (92%) by the acetylation of 2.0 g. of 1,3:2,5-dimethylene-L-rhamnitol with 0.5 g. of fused sodium acetate and 8.0 cc. of acetic anhydride at 100° for one hour. It was recrystallized from 7 parts of alcohol in the form of elongated prisms which melted at 140–141° and showed a specific rotation $[\alpha]^{20}D$ +44.4° in chloroform (*c*, 0.93). The compound is soluble in pyridine, acetone and ether and insoluble in water and petroleum ether.

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94; CH_3CO, 18.5. Found: C, 51.84; H, 7.12; CH_3CO, 18.3.

4-Benzoyl-1,3:2,5-dimethylene-L-rhamnitol was obtained in quantitative yield (3.1 g.) by the benzoylation of 2.0 g. of 1,3:2,5-dimethylene-L-rhamnitol in cold pyridine solution with 2.0 cc. of benzoyl chloride. It crystallized from its solution in 10 parts of alcohol as clusters of elongated plates which melted at 135–136° and rotated $[\alpha]^{20}D$ +37.4° in chloroform (*c*, 0.89). Weber and Tollens[3] recorded a melting point of 136–137° for their monobenzoate, but they did not measure its rotation. The substance is soluble in acetone, ether and ethyl acetate and nearly insoluble in water and petroleum ether.

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17; C_6H_5CO, 35.7. Found: C, 61.18; H, 6.20; C_6H_5CO, 35.4.

1,4-Diacetyl-3-acetoxymethyl-2,5-methylene-L-rhamnitol (II).—To an ice-cold suspension of 10 g. of 1,3:2,5-dimethylene-L-rhamnitol (I) in a mixture of 17.5 cc. of acetic anhydride and 7.5 cc. of glacial acetic acid 25 cc. of an ice-cold acetolyzing solution (prepared by adding 1.0

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[8] All the crystalline compounds that are described 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. The melting points were determined with the stem of the thermometer immersed in the heated bath.

cc. of concentrated sulfuric acid dropwise to an ice-cold mixture of 35 cc. of acetic anhydride and 15 cc. of glacial acetic acid) was added. The diacetal dissolved at once and in one or two minutes a precipitate of 4-acetyl-1,3:2,5-dimethylene-L-rhamnitol was deposited. The reaction mixture was removed from the ice-bath and stirred until the acetate dissolved (ten minutes) and then returned to the bath and allowed to stand for an additional sixty minutes. The solution was poured into 500 cc. of ice-cold water and the precipitate which formed was separated by filtration and washed with dilute sodium bicarbonate solution and water. The yield was 11.7 g. (62%). The compound was recrystallized by solution in 5 parts of warm alcohol and the addition of 5 parts of warm water; it formed elongated prisms which melted at 87–88° and showed a specific rotation $[\alpha]^{20}\mathrm{D}$ $-10.4°$ in chloroform (*c*, 0.83). It is soluble in acetone, ether, alcohol and pyridine and insoluble in water and petroleum ether.

Anal. Calcd. for $C_{14}H_{22}O_9$: C, 50.29; H, 6.63; CH_3CO, 38.6. Found: C, 50.36; H, 6.49; CH_3CO, 38.9.

2,5-Methylene-L-rhamnitol (III).—A suspension of 13.0 g. of 1,4-diacetyl-3-acetoxymethyl-2,5-methylene-L-rhamnitol (II) in 100 cc. of methyl alcohol was agitated gently with 5.0 cc. of 1.68 *N* barium methylate solution. The crystals dissolved in a few minutes and the solution was allowed to stand at 25° for eighteen hours. The barium was precipitated as sulfate by the addition of 8.4 cc. of 1 *N* sulfuric acid and, following the separation of the barium sulfate by filtration, the filtrate was concentrated *in vacuo* to dryness. The crystalline residue was recrystallized by solution in 10 cc. of warm acetone and the addition of 10 cc. of ether; the crystals (4.8 g.) were separated by filtration and a further 1.5 g. of the same product (total yield, 91%) was obtained by concentrating the mother liquor. One further recrystallization from 10 parts of acetone gave prisms melting at 124–125° and rotating $[\alpha]^{20}\mathrm{D}$ $+62.1°$ in water (*c*, 0.81) and these constants were not changed upon further recrystallization. An optical crystallographic examination by Mr. Joseph J. Fahey of the Geological Survey showed the values of the refractive indices n_α and n_γ to be 1.494 and 1.538, respectively; the birefringence is therefore 0.044, all values ±0.002. The compound is very soluble in water and pyridine, moderately soluble in methyl and ethyl alcohol, and insoluble in ether, petroleum ether and chloroform.

Anal. Calcd. for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 47.27; H, 7.95.

1,3,4-Triacetyl-2,5-methylene-L-rhamnitol.—A mixture of 0.9 g. of 2,5-methylene-L-rhamnitol (III), 0.25 g. of fused sodium acetate and 4.0 cc. of acetic anhydride was heated on the steam-bath for one hour, cooled, and poured upon 50 g. of crushed ice; the precipitated triacetate (1.2 g., 80%) was recrystallized by solution in 3 parts of warm alcohol and the addition of 10 parts of warm water. It formed elongated prisms which melted at 78–79° and showed a specific rotation $[\alpha]^{20}\mathrm{D}$ $-12.8°$ in chloroform (*c*, 0.82). The substance is readily soluble in chloroform, ether, acetone and pyridine, moderately soluble in alcohol and nearly insoluble in water and petroleum ether.

Anal. Calcd. for $C_{13}H_{20}O_8$: C, 51.31; H, 6.62; CH_3CO, 42.4. Found: C, 51.32; H, 6.71; CH_3CO, 42.5.

6-(*syn.*-1)-Tosyl-2,5-methylene-D-mannitol (IV).—To a vigorously stirred ice-cold solution of 10.0 g. of 2,5-methylene-D-mannitol in 100 cc. of pyridine, a cold solution of 10.0 g. (1 molecular equivalent) of *p*-toluenesulfonyl chloride in 25 cc. of pyridine was added. The reaction mixture was allowed to stand at 25° for eighteen hours and the pyridine was removed by concentration *in vacuo*; the residual sirup was suspended in 350 cc. of water and the crystalline mixture of reaction products (11.2 g.; m. p. 122–126°) which formed was separated by filtration. The precipitate was dissolved in 15 parts of ethylene dichloride and upon allowing the solution to stand at 20° for eighteen hours clusters of lath-like crystals of nearly pure 6-tosyl-2,5-methylene-D-mannitol (6.7 g.; m. p. 124–125°; 37%) were deposited. This fraction was separated by filtration and recrystallized from 30 parts of ethylene dichloride. The pure 6-tosyl-2,5-methylene-D-mannitol melted at 124–125° and rotated $[\alpha]^{20}\mathrm{D}$ $-32.6°$ in acetone (*c*, 0.81); further recrystallization did not change these properties. The compound is readily soluble in pyridine, glacial acetic acid, hot alcohol and hot ethyl acetate and nearly insoluble in water, chloroform, ether and petroleum ether.

Anal. Calcd. for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; S, 9.20. Found: C, 48.19; H, 5.70; S, 9.12.

1,6-Ditosyl-2,5-methylene-D-mannitol.—The ethylene dichloride mother liquor from the 6.7 g. of the 6-tosyl-2,5-methylene-D-mannitol (IV) was concentrated to 50 cc. and allowed to stand at 20° for eighteen hours. The precipitate which deposited was recrystallized twice from 10 parts of alcohol and gave 2.3 g. (8.9%) of rod-like prisms which melted at 148–149° and rotated $[\alpha]^{20}\mathrm{D}$ $-22.6°$ in acetone (*c*, 0.84). These values are in good agreement with those of 1,6-ditosyl-2,5-methylene-D-mannitol (m. p. 148–149°; $[\alpha]^{20}\mathrm{D}$ $-22.7°$ in acetone, *c*, 1.0).[9] A mixed melting point determination with the authentic sample of the latter compound showed no depression.

Anal. Calcd. for $C_{21}H_{26}O_{10}S_2$: C, 50.19; H, 5.22; S, 12.76. Found: C, 50.04; H, 5.28; S, 12.58.

1,3,4-Triacetyl-6-tosyl-2,5-methylene-D-mannitol (V).—A solution of 4.6 g. of 6-tosyl-2,5-methylene-D-mannitol (IV) in a mixture of 5 cc. of pyridine and 5 cc. of acetic anhydride was allowed to stand at 25° for eighteen hours. The major portion of the solvent was removed by evaporation on the steam-bath with an air current and 100 cc. of water was added to the sirupy residue. The crystalline precipitate which formed (6.2 g.; 98%) was separated by filtration and recrystallized from 5 parts of alcohol, forming rectangular plates which melted at 105–106° and showed a specific rotation $[\alpha]^{20}\mathrm{D}$ $+20.7°$ in chloroform (*c*, 0.83). The substance is soluble in ether, pyridine and warm alcohol and nearly insoluble in water, petroleum ether and cold alcohol.

Anal. Calcd. for $C_{20}H_{26}O_{11}S$: C, 50.62; H, 5.52; S, 6.76. Found: C, 50.76; H, 5.58; S, 6.63.

1,3,4-Triacetyl-6-desoxy-6-iodo-2,5-methylene-D-mannitol (VI).—A solution of 3.0 g. of 1,3,4-triacetyl-6-tosyl-2,5-methylene-D-mannitol (V) and 3.0 g. of sodium iodide (3.16 molecular equivalents) in 50 cc. of acetone was heated at 100° for two hours in a pressure bottle. The precipitated sodium tosylate (1.2 g., quantitative) was separated by filtration and the filtrate was evaporated by an air current to dryness; the crystalline residue was extracted with cold water to remove the excess sodium iodide and the insoluble product (2.7 g.; quantitative) was recrystallized as prismatic needles which melted at 117–118° and rotated $[\alpha]^{20}\mathrm{D}$ $-11.0°$ in chloroform (*c*, 0.86). It is soluble in ether, acetone and warm alcohol and almost insoluble in water and petroleum ether.

Anal. Calcd. for $C_{13}H_{19}O_8I$: C, 36.29; H, 4.45; I, 29.50. Found: C, 36.31; H, 4.44; I, 29.69.

6-Desoxy-6-iodo-2,5-methylene-D-mannitol (VII).—To an ice-cold solution of 6.5 g. of 1,3,4-triacetyl-6-desoxy-6-iodo-2,5-methylene-D-mannitol (VI) in 150 cc. of methyl alcohol 2.0 cc. of 1.625 *N* barium methylate solution was added and the reaction mixture was allowed to stand at 5° for eighteen hours. The precipitate (2.7 g.) of 6-desoxy-6-iodo-2,5-methylene-D-mannitol (VII) was separated by filtration; the barium in the filtrate was precipitated as sulfate by the addition of 3.2 cc. of *N* sulfuric acid and, following the removal of the barium sulfate, the resulting solution was concentrated to recover a further 0.75 g. of reaction product. The total yield was therefore 3.45 g. (75%). The compound was recrystallized from 25 parts of methyl alcohol and it formed prismatic needles which melted with decomposition at 146–147° and rotated $[\alpha]^{20}\mathrm{D}$ $-25.8°$ in pyridine (*c*, 0.94). It is readily soluble in hot methyl and ethyl alcohols and hot water, moderately soluble in hot acetone and nearly insoluble in chloroform, cold water and cold methyl and ethyl alcohols.

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(9) Unpublished data determined by Dr. A. T. Ness of this Laboratory.

Anal. Calcd. for $C_7H_{13}O_5I$: C 27.65; H, 4.31; I, 41.74. Found: C, 27.79; H, 4 .27; I, 42.00.

6-Desoxy-2,5-methylene-D-mannitol (*syn.*-**2,5-Methylene-D-rhamnitol**) **(VIII)**.—To a suspension of 5.0 g. of 6-desoxy-6-iodo-2,5-methylene-D-mannitol (VII) in 200 cc. of methyl alcohol, 15 cc. (1.53 molecular equivalents) of 1.675 *N* barium methylate solution and 0.6 g. of Raney nickel were added, and the mixture was agitated with hydrogen at 25° under a slight positive pressure. Solution of the iodo compound was complete in a few minutes and after forty minutes the absorption of hydrogen ceased. The volume of hydrogen taken up was approximately 70% of the calculated amount, presumably because of the formation of a minor amount of an anhydro compound. The catalyst was removed by filtration and the filtrate was neutralized with carbon dioxide. Following the addition of 10 g. of silver carbonate, the solution was stirred until a filtered sample gave no test for barium or iodide and the solids were removed by filtration on a mat of decolorizing carbon. The filtrate was concentrated *in vacuo* to dryness and the residual sirup was dissolved in 20 cc. of boiling acetone and filtered to remove a slight turbidity; the filtrate upon concentration to one-half volume deposited 1.4 g. (50%) of prismatic crystals. After recrystallization from 10 parts of acetone the compound melted at 124–125° and rotated $[\alpha]^{20}D$ −61.9° in water (*c*, 0.90) and these values were not changed upon further recrystallization. An optical crystallographic examination of the compound showed the values of its refractive indices (n_α and n_γ 1.494 and 1.538, respectively) to be the same as those of the enantiomorphous 2,5-methylene-L-rhamnitol.

Anal. Calcd. for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 47.09; H, 7.91.

2,5-Methylene-D,L-rhamnitol.—A solution of 0.20 g. of 2,5-methylene-D-rhamnitol (VIII) and 0.20 g. of 2,5-methylene-L-rhamnitol (III) in 4 cc. of boiling acetone on cooling deposited clusters of elongated lath-like prisms which melted at 123–124° and showed no rotation in aqueous solution (*c*, 0.85). Upon admixture with a small amount of either the D or L component, the melting point of the D,L-compound was depressed to 111–115° indicating that a true racemic crystal is formed. Confirmation of this fact was obtained by Mr. Joseph J. Fahey through an optical crystallographic examination of the compound. Its refractive indices n_α, 1.508, and n_γ, 1.545, are different from those of its components and the crystals, which are probably monoclinic, show extinction angles varying from 0 to 11°.

Anal. Calcd. for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 47.07; H, 7.94.

1,6-Didesoxy-1,6-diiodo-3,4-ditosyl-2,5-methylene-D-mannitol (X).—A suspension of 10.0 g. of 1,3,4,6-tetratosyl-2,5-methylene-D-mannitol (IX)[2] and 10 g. of sodium iodide (5.4 molecular equivalents) in 50 cc. of acetonylacetone was heated at 80° for six hours; the solution of the solids was complete in one hour and shortly thereafter sodium tosylate precipitated from the solution. The cooled reaction mixture was filtered to remove the insoluble material (5.4 g.; calculated 4.8 g.) and the filtrate was poured into 200 cc. of water. The gummy precipitate which formed soon crystallized and it was separated by filtration, washed with water and recrystallized from 30 parts of methyl alcohol. The fine needles (5.0 g.; 56%) were again recrystallized from 50 parts of methyl alcohol and they then melted at 134–135° and rotated $[\alpha]^{20}D$ −12.8° in chloroform (*c*, 0.84); these values were not changed by further recrystallization. The compound is soluble in chloroform, acetone, hot methyl and ethyl alcohols and nearly insoluble in water and petroleum ether.

Anal. Calcd. for $C_{21}H_{24}O_8S_2I_2$: C, 34.91; H, 3.35; I, 35.14; S, 8.88. Found: C, 35.03; H, 3.35; I, 35.23; S, 9.05.

1,6-Didesoxy-3,4-ditosyl-2,5-methylene-D-mannitol (XI).—To a suspension of 2.0 g. of 1,6-didesoxy-1,6-diiodo-3,4-ditosyl-2,5-methylene-D-mannitol (X) in 150 cc. of methyl alcohol 1.2 cc. (4 molecular equivalents) of diethylamine and 0.6 g. of Raney nickel was added and the mixture was agitated at 27° with hydrogen under slight positive pressure. The absorption of the theoretical amount of hydrogen (136 cc. at 27° and 759.5 mm.) was completed in twenty minutes and no further absorption was noted in a further thirty minutes. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to a sirup which crystallized readily upon the addition of 50 cc. of water. The yield was 1.2 g. (92%). The compound was recrystallized from 10 parts of methyl alcohol as long fine needles which melted at 119–120° and rotated $[\alpha]^{20}D$ +15.7° in chloroform (*c*, 0.85). An optical crystallographic examination of the substance by Mr. Joseph J. Fahey showed that in parallel polarized light (crossed nicols) the extinction is parallel and the sign of elongation is positive. The refractive indices n_α and n_γ are 1.536 and 1.606, respectively. It is soluble in ether, chloroform, acetone and warm methyl and ethyl alcohols and insoluble in water and petroleum ether.

Anal. Calcd. for $C_{21}H_{26}O_8S_2$: C, 53.60; H, 5.57; S 13.63. Found: C, 53.65; H, 5.56; S, 13.70.

1,3,4-Tritosyl-2,5-methylene-L-rhamnitol (XII).—A solution of 10.0 g. of 2,5-methylene-L-rhamnitol (III) in 50 cc. of pyridine was cooled in an ice-bath and 33.0 g. (3.1 molecular equivalents) of *p*-toluenesulfonyl chloride was added; the chloride dissolved and the solution was removed from the bath and allowed to stand at 20° for forty-eight hours. The mixture, which now contained a considerable amount of crystalline pyridine hydrochloride, was poured into 500 cc. of ice-cold water and upon standing at 5° the precipitated gum gradually crystallized. The crude product was recrystallized from 300 cc. of methyl alcohol; the yield of product melting at 118–120° was 17.1 g. (48%). Further recrystallization from 15 parts of ethyl alcohol gave the pure compound as fine needles which melted at 119–120° and rotated $[\alpha]^{20}D$ −10.6° in chloroform (*c*, 0.84). The tritosylate is readily soluble in acetone, chloroform and pyridine and almost insoluble in ether, petroleum ether and water.

Anal. Calcd. for $C_{28}H_{32}O_{11}S_3$: C, 52.48; H, 5.03; S 15.01. Found: C, 52.32; H, 5.01; S, 15.20.

1-Desoxy-1-iodo-3,4-ditosyl-2,5-methylene-L-rhamnitol (XIII).—A solution of 10.0 g. of 1,3,4-tritosyl-2,5-methylene-L-rhamnitol (XII) and 10.0 g. of sodium iodide in 50 cc. of acetonylacetone was heated at 80° for six hours. The cooled reaction mixture was filtered to remove the precipitated sodium tosylate (3.7 g.; theory for 1 molecular equivalent, 3.0 g.) and the reddish-orange filtrate was poured into 200 cc. of water in which a few crystals of sodium thiosulfate had been dissolved. The thick gum which precipitated gradually crystallized; the crude product weighed 9.0 g. and melted at 110–120°, but upon recrystallization from 200 cc. of methyl alcohol it was obtained in the form of fine needles which melted at 126–128°. Further recrystallization from 20 parts of methyl alcohol gave the pure compound melting at 127–128° and rotating $[\alpha]^{20}D$ +3.2° in chloroform (*c*, 1.0). The yield was 7.1 g. (76%). It is soluble in ether, acetone and pyridine and nearly insoluble in water and petroleum ether.

Anal. Calcd. for $C_{21}H_{25}O_8S_2I_2$: C, 42.28; H, 4.22; S, 10.75; I, 21.28. Found: C, 42.34; H. 4.10; S, 10.65; I, 21.19.

1-Desoxy-3,4-ditosyl-2,5-methylene-L-rhamnitol (XIV).—A suspension of 7.1 g. of 1-desoxy-1-iodo-3,4-ditosyl-2,5-methylene-L-rhamnitol (XIII) and 0.6 g. of Raney nickel in a mixture of 200 cc. of methyl alcohol and 2.5 cc. (2 molecular equivalents) of diethylamine was agitated with hydrogen under slight positive pressure. Solution of the iodo compound took place rapidly and at the expiration of thirty minutes 311 cc. of hydrogen, measured at 28° and 758 mm., had been taken up and no further absorption was noted in a further thirty minutes (theory, 295 cc. at 28° and 758 mm.). The catalyst was separated by filtration and the filtrate was concentrated *in vacuo* to dryness.

The crystalline residue was stirred with 25 cc. of water to dissolve soluble salts and the insoluble portion was recovered by filtration and recrystallized from 10 parts of methyl alcohol as clusters of long fine needles identical in appearance with 1,6-didesoxy-3,4-ditosyl-2,5-methylene-D-mannitol (XI). The yield was 5.4 g. (96%). The compound agreed in melting point, namely 119–120°, with the latter substance and examination under the petrographic microscope showed that it also possessed identical optical crystallographic properties. Its specific rotation, $[\alpha]^{20}D$ −15.3° in chloroform (*c*, 0.96), was of the same magnitude, but opposite in sign to that of +15.7° exhibited by the enantiomorphous 1,6-didesoxy-3,4-ditosyl-2,5-methylene-D-mannitol. It is soluble in chloroform, acetone, ether and warm methyl and ethyl alcohols and insoluble in water and petroleum ether.

Anal. Calcd. for $C_{21}H_{26}O_8S_2$: C, 53.60; H, 5.57; S, 13.63. Found: C, 53.70; H, 5.49; S, 13.75.

1-Desoxy-3,4-ditosyl-2,5-methylene-D,L-rhamnitol.—A mixture of 0.50 g. of 1,6-didesoxy-3,4-ditosyl-2,5-methylene-D-mannitol (XI) and 0.50 g. of 1-desoxy-3,4-ditosyl-2,5-methylene-L-rhamnitol (XIV) was dissolved in 25 cc. of boiling methyl alcohol. As the solution cooled the D,L-compound crystallized in the form of prismatic needles; the substance melted at 138–139° and its solution in chloroform (*c*, 2.1) gave zero rotation. Upon admixture with a small amount of the L-component the melting point was depressed to 124–134°, indicating that the substance is a true racemic compound. Confirmation of this fact was obtained by Mr. Joseph J. Fahey through optical crystallographic examination; it was found that the D,L-compound differed optically from the D- and L-components, as would be expected in case it is a true racemic compound. In parallel polarized light (crossed nicols) the extinction is parallel and the sign of elongation is positive. The refractive indices n_α and n_γ are 1.540 and 1.601, respectively, the birefringence being 0.061. The racemic compound is much less soluble in hot methyl alcohol than the D- and L-form, requiring 25 parts for solution as compared with 10 parts for the optically active components.

Anal. Calcd. for $C_{21}H_{26}O_8S_2$: C, 53.60; H, 5.57; S 13.63. Found: C, 53.56; H, 5.61; S, 13.50.

1-Tosyl-2,5-methylene-L-rhamnitol (XV).—To an ice-cold solution of 4.0 g. of 2,5-methylene-L-rhamnitol (III) in 40 cc. of pyridine a cold solution of 4.7 g. (1.1 molecular equivalents) of *p*-toluenesulfonyl chloride was added and the mixture was allowed to stand at 20° for four hours. The precipitate (5.0 g.; 67%) which formed upon pouring the solution into 500 cc. of ice-cold water was separated by filtration and recrystallized from 7 parts of alcohol. The compound crystallized as elongated plates which melted at 135–136° and rotated $[\alpha]^{20}D$ +36.5° in acetone (*c*, 0.71); it is soluble in pyridine and hot alcohol and nearly insoluble in ether, petroleum ether, chloroform and water.

Anal. Calcd. for $C_{14}H_{20}O_7S$: C, 50.59; H, 6.06; S, 9.65. Found: C, 50.71; H, 6.24; S, 9.51.

Lead Tetraacetate Oxidation of 1-Tosyl-2,5-methylene-L-rhamnitol (XV). (a).—To a solution of 0.1052 g. of 1-tosyl-2,5-methylene-L-rhamnitol in 10 cc. of glacial acetic acid, 10 cc. (1.775 molecular equivalents) of a 0.05617 *M* solution of lead tetraacetate in glacial acetic acid was added, and the volume was adjusted to 25 cc. with glacial acetic acid. Analyses of samples at the end of one, six, twenty-three, forty-seven and seventy-one hours showed that 0.15, 0.51, 0.87, 1.05 and 1.09 molecular equivalents, respectively, of the oxidant had been consumed. The analytical results indicate that 1-tosyl-2,5-methylene-L-rhamnitol contains one glycol grouping as a part of its structure.

(b) A solution of 1.0 g. of 1-tosyl-2,5-methylene-L-rhamnitol (XV) in 45 cc. (1.14 molecular equivalents of 0.0765 *M* solution of lead tetraacetate in glacial acetic acid was allowed to stand for forty-eight hours at 25°. At the expiration of this time a solution of 1.5 g. of semicarbazide hydrochloride and 3.0 g. of sodium acetate in 10 cc. of water was added and the mixture was allowed to stand an additional twenty-four hours. The precipitated lead chloride was separated by filtration and the filtrate was concentrated *in vacuo* to dryness. The residue was reconcentrated successively with two 10-cc. portions of water and two 10-cc. portions of absolute alcohol and finally extracted with one 10-cc. portion and two 5-cc. portions of boiling absolute alcohol. The filtered alcoholic extract was concentrated to 5 cc. and diluted with 10 cc. of water; the precipitated di-semicarbazone of the formaldehyde mixed acetal of 3-tosyl-L-glyceraldehyde and L-lactaldehyde (XVI), which weighed 0.6 g. (46%), was separated by filtration and recrystallized from 20 parts of absolute alcohol as clusters of needles. The compound decomposed at 143–144° and showed a specific rotation $[\alpha]^{20}D$ −81.8° in glacial acetic acid. It is very soluble in pyridine, moderately soluble in dioxane and nearly insoluble in benzene, ether and petroleum ether.

Anal. Calcd. for $C_{16}H_{24}O_7N_6S$: C, 43.23; H, 5.44; N, 18.91; S, 7.21. Found: C, 43.25; H, 5.55; N, 18.70; S, 7.15.

4-Tosyl-1,3:2,5-dimethylene-L-rhamnitol.—A solution of 1.0 g. of 1,3:2,5-dimethylene-L-rhamnitol (I) and 1.1 g. of *p*-toluenesulfonyl chloride in 10 cc. of pyridine was allowed to stand at 25° for forty-eight hours. The precipitate (1.2 g.; 67%) which separated upon pouring the mixture into 100 cc. of ice-cold water was recovered by filtration and recrystallized from 6 parts of alcohol as clusters of prisms in dendritic form. The compound melted at 127–128° and rotated $[\alpha]^{20}D$ +49.7° in chloroform (*c*, 0.85); it is soluble in pyridine, ether and acetone and insoluble in water and petroleum ether. A solution of 0.9 g. of this tosyl derivative and 1.0 g. of sodium iodide in 25 cc. of acetone was heated in a pressure bottle at 100° for two hours. No precipitation of sodium tosylate was observed and upon evaporation of the acetone and extraction of the crystalline residue with water 0.9 g. (quantitative) of unchanged 4-tosyl-1,3:2,5-dimethylene-L-rhamnitol (m. p. 127–128°; $[\alpha]^{20}D$ +49.6° in chloroform) was recovered. These data show that the tosyl derivative did not react with sodium iodide under the experimental conditions, which indicates that the tosyl group is not attached to carbon atom 1.

Anal. Calcd. for $C_{15}H_{20}O_7S$: C, 52.31; H, 5.85; S, 9.31. Found: C, 52.22; H, 5.71; S, 9.44.

1,3:2,5-Dimethylene-4-methyl-L-rhamnitol.—To a solution of 5.0 g. of 1,3:2,5-dimethylene-L-rhamnitol (I) in 100 cc. of boiling methyl iodide 12.5 g. of "Drierite" and 25 g. of silver oxide were added and the mixture was refluxed for twenty-four hours. The solids were removed by filtration and washed with three 10-cc. portions of methyl iodide; the filtrate was again refluxed for twenty-four hours with 12.5 g. of "Drierite" and 25 g. of silver oxide. A previous test of the methylation of 1.0 g. of the compound had indicated that one treatment of twenty-four hours was insufficient to produce complete methylation, as was shown by the separation of two types of crystals (stout elongated prisms and long fine needles) from the solution in hexane of the partially methylated product. After a second methylation only long stiff needles were observed. The reaction mixture was filtered, concentrated *in vacuo* to dryness and the crystalline residue was dissolved in 325 cc. of boiling hexane. Upon cooling to 20°, the solution deposited clusters of long brittle needles (3.6 g.; m. p. 143–144°). Concentration of the mother liquor to 100 cc. gave a second crop (1.4 g., m. p. 140–142°) of slightly less pure material. The total yield was 5.0 g. (92%). The compound was recrystallized from 75 parts of hexane and when pure it melted at 143–144° and rotated $[\alpha]^{20}D$ +50.0° in chloroform (*c*, 0.85). Optical crystallographic examination by Mr. Joseph J. Fahey showed the refractive indices n_α and n_γ were 1.488 and 1.537 and that the crystals exhibited parallel extinction and negative elongation. It is very soluble in chloroform and acetone, moderately soluble in alcohol, ether and hot water and nearly insoluble in cold water and cold hexane.

Anal. Calcd. for $C_9H_{16}O_5$: C, 52.93; H, 7.90; OCH_3, 15.20. Found: C, 52.89; H, 7.83; OCH_3, 15.17.

Methyl 2,3-Diacetyl-4-methyl-6-tosyl-α-D-mannopyranoside (XVIII).—To an ice-cold solution of 10.0 g. of methyl 4-methyl-α-D-mannopyranoside (XVII)[7] in 100 cc. of pyridine an ice-cold solution of 9.5 g. (one molecular equivalent) of *p*-toluenesulfonyl chloride in 25 cc. of pyridine was added; after the mixture had stood for six hours at 20°, 20 cc. of acetic anhydride was added, and it was allowed to remain at 20° for an additional sixteen hours. The major part of the pyridine was removed by concentration *in vacuo* and the crystalline reaction product (20 g.; m. p. 105–110°), which precipitated upon the addition of 200 cc. of water to the residual sirup, was recrystallized from 3 parts of alcohol; the nearly pure compound (14.1 g.; 66%; m. p. 133–135°) was again recrystallized from 5 parts of alcohol and it formed short prisms which melted at 134–135° and rotated $[\alpha]^{20}D$ +41.0° in chloroform (*c*, 0.90). It is soluble in acetone, ether, ethyl acetate and warm alcohol and nearly insoluble in water and petroleum ether.

Anal. Calcd. for $C_{19}H_{26}O_{10}S$: C, 51.11; H, 5.87; S, 7.18; OCH_3, 13.90. Found: C, 51.16; H, 5.99; S, 7.27; OCH_3, 13.93.

Methyl 4-Methyl-6-desoxy-6-iodo-α-D-mannopyranoside (XIX).—A solution of 10.0 g. of methyl 2,3-diacetyl-4-methyl-6-tosyl-α-D-mannopyranoside (XVIII) and 10.0 g. (three molecular equivalents) of sodium iodide in 100 cc. of acetone was heated at 100° for two hours in a pressure bottle. The cold reaction mixture was filtered to remove the precipitated sodium tosylate (4.5 g.; calculated 4.4 g.) and the filtrate was concentrated *in vacuo* to dryness; the residue was treated with 50 cc. of water and extracted with three 25-cc. portions of ethylene dichloride and the washed and dried extract was concentrated *in vacuo* to a sirup. Attempts to induce crystallization of the product, which was presumably methyl 2,3-diacetyl-4-methyl-6-desoxy-6-iodo-α-D-mannopyranoside, were unsuccessful. The sirup was dissolved in 100 cc. of methyl alcohol, the solution was cooled to 0°, and 2.0 cc. of 1.625 *N* barium methylate was added; after standing at 5° for sixteen hours, the barium was precipitated from the solution as the sulfate by addition of an equivalent amount of 1 *N* sulfuric acid and the filtered solution was concentrated *in vacuo* to a crystalline residue. Traces of water were removed by reconcentration with 15 cc. of absolute alcohol and the crystals were dissolved in 15 cc. of chloroform; upon the addition of 30 cc. of hexane the product crystallized as clusters of long fine needles (4.5 g.) and a second crop (1.2 g.) was obtained by concentrating the mother liquor to a thin sirup and adding hexane; the total yield was therefore 5.7 g. (80%). The material was recrystallized by solution in 5 parts of warm chloroform and the addition of 5 parts of hexane; when pure it melted at 100–101° and rotated $[\alpha]^{20}D$ +75.5° in water (*c*, 0.87). It is very soluble in methyl and ethyl alcohols and water, moderately soluble in chloroform and ether and nearly insoluble in hexane and petroleum ether.

Anal. Calcd. for $C_8H_{15}O_5I$: C, 30.20; H, 4.75; I, 39.90; OCH_3, 19.51. Found: C, 30.03; H, 4.68; I, 39.81; OCH_3, 19.48.

1,3:2,5-Dimethylene-4-methyl-D-rhamnitol (XXII).—To a solution of 5.6 g. of methyl 4-methyl-6-desoxy-6-iodo-α-D-mannopyranoside (XIX) in 200 cc. of methyl alcohol, 11.0 cc. of 1.675 *N* barium methylate (1.05 molecular equivalents) and 1.2 g. of Raney nickel were added and the mixture was agitated in a glass bottle with hydrogen under a slight positive pressure. In one hour 445 cc. of hydrogen (theory 426 cc. at 24° and 766 mm.) was taken up and no further absorption occurred in an additional thirty minutes. The catalyst was removed by filtration and the filtrate was neutralized with carbon dioxide and then agitated with 10 g. of silver carbonate until a filtered sample gave no test for iodine or barium ions; the solids were separated by filtration and the filtrate was concentrated *in vacuo* to a dry sirup. Attempts to crystallize this sirup, which presumably consisted of methyl 4-methyl-α-D-rhamnopyranoside (XX) were unsuccessful. It was combined with the sirup resulting from a similar catalytic reduction of another batch (4.0 g.) of XIX and the material was refluxed with 250 cc. of 0.1 *N* hydrochloric acid; the course of the hydrolysis was followed polarimetrically and after ten hours, when the rotation had reached a constant value, the solution, which was strongly reducing to Fehling solution, was neutralized with 5 g. of silver carbonate, filtered, and the silver ions in the filtrate were removed as sulfide. The filtrate was concentrated *in vacuo* to a thick sirup (4.8 g.). This sirupy 4-methyl-D-rhamnose was dissolved in 50 cc. of water, 0.6 g. of Raney nickel was added and the mixture was reduced at 100° for six hours with hydrogen under a pressure of 67 atmospheres. The catalyst was removed by filtration and the filtrate, which was non-reducing to Fehling solution, was concentrated *in vacuo* to a thick sirup. The 4-methyl-D-rhamnitol (XXI) could not be crystallized. The sirup was dissolved in a mixture of 7.5 cc. of concentrated hydrochloric acid and 7.5 cc. of 37% aqueous formaldehyde and the solution was evaporated *in vacuo* at 25° in a desiccator containing small beakers of concentrated sulfuric acid and sodium hydroxide pellets. After three hours long fine needles were observed forming in the solution and after four days the dry solid mass of crystals was stirred with 5 cc. of ice-cold water, filtered and washed free of acid with cold water. The yield was 3.7 g. (60%) of practically pure material melting at 143–144° and rotating $[\alpha]^{20}D$ −49.6° in chloroform (*c*, 0.82). The compound was recrystallized twice from 75 parts of hexane from which it deposited in clusters of long brittle needles of the same appearance and solubility as the crystals of its previously described enantiomorph, 1,3:2,5-dimethylene-4-methyl-L-rhamnitol. The melting point and specific rotation $[\alpha]^{20}D$ remained unchanged from the values recorded above for the original material obtained from the reaction mixture. The indices of refraction of the substance were the same as those found for 1,3:2,5-dimethylene-4-methyl-L-rhamnitol.

Anal. Calcd. for $C_9H_{16}O_5$: C, 52.93; H, 7.90; OCH_3, 15.20. Found: C, 53.00; H, 7.78; OCH_3, 15.24.

1,3:2,5-Dimethylene-4-methyl-D,L-rhamnitol.—A solution of 0.5 g. of 1,3:2,5-dimethylene-4-methyl-D-rhamnitol and 0.5 g. of 1,3:2,5-dimethylene-4-methyl-L-rhamnitol in 10 cc. of boiling absolute alcohol upon cooling deposited a cluster of long fine needles differing in appearance from either component. The D,L-compound melted at 123–124° and its chloroform solution (*c*, 0.90) showed no rotation. Upon admixture with a small amount of the L-component only a slight depression of the melting point (121–124°) was observed. An optical crystallographic examination by Mr. Joseph J. Fahey showed that the refractive indices n_α and n_γ were 1.496 and 1.538, respectively; the extinction is parallel and the sign of elongation is negative. These properties are distinctly different from those of the components and the crystals are therefore to be regarded as a true racemate.

Anal. Calcd. for $C_9H_{16}O_5$: C, 52.93; H, 7.90; OCH_3, 15.20. Found: C, 52.98; H, 7.84; OCH_3, 15.18.

Summary

The action of an acid acetolyzing solution on the dimethylene-L-rhamnitol of Weber and Tollens yields 1,4-diacetyl-3-acetoxymethyl-2,5-methylene-L-rhamnitol which upon saponification forms 2,5-methylene-L-rhamnitol. Proof of the structure of the latter acetal was obtained (1) through synthesis of its enantiomorph, 2,5-methylene-D-rhamnitol from authentic 2,5-methylene-D-mannitol, (2) through its conversion to 1-desoxy-3,4-ditosyl-2,5-methylene-L-rhamnitol which proves to be the enantiomorph of 1,6-didesoxy-3,4-ditosyl-2,5-methylene-D-mannitol, and (3) through the oxidation of its 1-tosyl derivative by lead tetraacetate to produce the formaldehyde mixed acetal of 3-tosyl-L-glyceraldehyde and L-lactaldehyde.

The acetal grouping of the dimethylene-L-rhamnitol which is attacked by the acetolyzing solution is shown to be attached to the 1,3-positions of the L-rhamnitol moiety by proof (1) of the absence of a primary hydroxyl group in the dimethylene-L-rhamnitol molecule and (2) by the preparation from it of 1,3:2,5-dimethylene-4-methyl-L-rhamnitol which proves to be the enantiomorph of 1,3:2,5-dimethylene-4-methyl-D-rhamnitol prepared by the condensation of formaldehyde with 4-methyl-D-rhamnitol that is obtained by a series of standard reactions from authentic methyl 4-methyl-α-D-mannopyranoside.

The application to L-rhamnitol of the generalizations relating the structures and configurations of the methylene and benzylidene acetals of polyhydric alcohols indicates that in the case of rhamnitol a 1,3:2,5 acetal structure is to be expected; the experimental results bear out this prediction.

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[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY, ALBANY, CALIFORNIA[1]]

1,4-Anhydro-D,L-xylitol

BY J. F. CARSON AND W. D. MACLAY

In a study of the reactions of xylitol, its dehydration with acid catalysts has been investigated. Although the preparation of anhydro derivatives of the hexitols, sorbitol, mannitol and dulcitol has been studied by a number of investigators, the corresponding reaction with the pentitols has received very little attention.[2]

By dehydrating xylitol with sulfuric acid or benzenesulfonic acid, a pure optically inactive anhydroxylitol has been isolated in crystalline form and its structure determined. The results of periodate oxidation have shown that the new product obtained by the removal of one molecule of water from xylitol must contain a 1,4 oxygen bridge. Because of the meso configuration of xylitol, anhydroxylitol must exist as a racemic mixture and is accordingly named 1,4-anhydro-D,L-xylitol.

Xylitol on heating with 1% sulfuric or benzenesulfonic acid at 145–160° for forty to fifty minutes yielded a mixture of dehydration products from which anhydroxylitol could be separated by evaporative distillation *in vacuo* in a short-path still in yields of 65%. Anhydroxylitol has been characterized by the preparation of three crystalline derivatives, the tribenzoate, the monotrityl diacetate and the tricarbanilate. Refluxing the tricarbanilate with barium methylate in methanol regenerated the original anhydroxylitol. This procedure has been found useful for isolating the pure compound from mixtures. Anhydroxylitol, first obtained as a viscous sirup, crystallized very slowly under anhydrous conditions and was recrystallized from mixtures of isoamyl alcohol and diethyl ether. The crystals were very hygroscopic and became sirupy after a few minutes of exposure to the atmosphere.

When an aqueous solution of anhydroxylitol (I)[3] was oxidized with sodium metaperiodate, one molecular equivalent of oxidant was consumed and no formic acid or formaldehyde was produced. Reaction with periodic acid likewise consumed one equivalent of oxidant. The persumed dialdehyde (II) on further oxidation with bromine water in the presence of strontium carbonate yielded the strontium salt (III). Analyses of this salt showed it to be one of a dicarboxylic acid of five carbon atoms. The salt named in accordance with established terminology[4] is strontium D,L-hydroxymethyldiglycolate.

The consumption of one equivalent of periodic acid requires that two of the three hydroxyl groups must be adjacent and the absence of formaldehyde shows that both glycol hydroxyl groups must be secondary. The only structures satisfying these conditions would be a 1,4- or a 2,5-anhydroxylitol which constitute an enantiomorphic pair. Anhydroxylitol and its derivatives were found to be optically inactive. The assigned structure is conclusively proved by the isolation of the strontium salt (III) from the oxidation product of anhydroxylitol. The preparation of a monotrityl diacetyl derivative furnishes supporting evidence for a structure containing one primary hydroxyl group. The designation of the new compound as an anhydroxylitol is dependent on the reasonable assumption that no inversion of configuration occurs during dehydration. A Walden inversion occurring at the point of attachment of the oxygen ring would lead to a racemate of 1,4-anhydro-D- and -L-arabitols. It has been shown that in the analogous dehydration of sorbitol[5] no Walden inversion takes place. The formation of 1,4 oxygen rings has been observed in the dehydration of hexitols as sorbitol which on heat-

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[1] Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

[2] The Alien Property Custodian has made public the patent application A. P. C. No. 367,300 of Felix Grandel, describing the dehydration of xylitol with acids and salts to yield mixtures of mono- and dianhydroxylitol.

[3] In the formulas only the D members of the D,L pairs are shown.

[4] Jackson and Hudson, THIS JOURNAL, 59, 994 (1937).

[5] Hockett, Abstract of Paper, 105th meeting, American Chemical Society, Detroit, Michigan, April, 1943.