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## The Preparation of D-Rhamnose from Methyl $\alpha$ -D-Mannopyranoside

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D-Rhamnose, the enantiomorph of the naturally occurring L-rhamnose, was prepared in small quantity nineteen years ago by Votoček and Valentin<sup>1</sup> from natural D-epirhamnose ("isorhodoose," from the acid hydrolysis of convolvulin) through the reactions D-epirhamnose  $\rightarrow$  D-epirhammonic acid  $\rightarrow$  D-rhammonic acid (lactone)  $\rightarrow$  D-rhamnose. The subsequent discovery of methods for the easy desoxydation of  $-\text{CH}_2\text{OH}$  to  $-\text{CH}_3$  at carbon atom 6 in hexopyranosides has led us to investigate the possibility of using the readily available methyl  $\alpha$ -D-mannopyranoside<sup>2</sup> to replace the costly convolvulin as a source for the preparation of D-rhamnose. It is found that methyl 2,3,4-tribenzoyl-6-tosyl- $\alpha$ -D-mannopyranoside (II) may be prepared in 38% yield from methyl  $\alpha$ -D-mannopyranoside (I) in pyridine solution by monotosylation followed by benzylation. This pure derivative can be converted to crystalline D-rhamnose through the following customary reactions

Methyl 2,3,4-tribenzoyl-6-tosyl- $\alpha$ -D-mannopyranoside (II)

(Sodium iodide in acetone;  
yield, quantitative)

Methyl 2,3,4-tribenzoyl-6-desoxy-6-iodo- $\alpha$ -D-mannopyranoside (III)

(Reduction with hydrogen;  
yield, 95%)

Methyl 2,3,4-tribenzoyl- $\alpha$ -D-rhamnopyranoside (IV)

(Debenzylation;  
yield, 94%)

Methyl  $\alpha$ -D-rhamnopyranoside (V)

(Acid hydrolysis;  
yield, 85%)

D-Rhamnose (VI)

The over-all yield of crystalline D-rhamnose from methyl  $\alpha$ -D-mannopyranoside is 28%, and fortunately it is only in the initial preparation of the methyl 2,3,4-tribenzoyl-6-tosyl- $\alpha$ -D-mannopyranoside that the yield is not very high. The reaction in this first step yields some crystalline tetrabenzoyl- $\alpha$ -D-mannopyranoside, but the desired derivative is readily separable from it. The only derivative in this D-rhamnose series which did not crystallize is the methyl  $\alpha$ -D-rhamnopyranoside.

A similar monotosylation of methyl  $\alpha$ -D-mannopyranoside, followed by acetylation, results in a 29% yield of crystalline methyl 2,3,4-triacetyl-6-tosyl- $\alpha$ -D-mannopyranoside; the corresponding

tribenzoate is more readily crystallized and is preferred for the syntheses that are described. When methyl 2,3,4-tribenzoyl-6-tosyl- $\alpha$ -D-mannopyranoside is treated with sodium hydroxide solution, the known methyl 3,6-anhydro- $\alpha$ -D-mannopyranoside (VII)<sup>3</sup> is obtained in 85% yield.

The step of reducing the iodo-derivative (III) with hydrogen and a catalyst deserves comment. We find that this reaction proceeds readily in methyl alcohol solution at room temperature, using hydrogen at atmospheric pressure with Raney nickel as catalyst, provided a moderate excess of diethylamine is present. The yield of methyl  $\alpha$ -D-rhamnopyranoside tribenzoate is nearly quantitative, which shows that the benzoyl groups are essentially resistant to deacylation under the conditions employed. In such reactions we recommend the use of diethylamine and of the benzoates rather than acetates because of the greater stability of the benzoates.

Votoček, Valentin and Rác<sup>4</sup> found that the acicular crystals of D,L-rhamnose are anhydrous whereas the components crystallize in large prisms as a monohydrate, facts which show that the D,L-form is not a mechanical mixture of enantiomorphous crystals but is a true racemate having its own crystal lattice. We have confirmed their observations and have also studied the behavior of some other racemic mixtures. Three other D,L-substances of the rhamnose series prove to be true racemic crystals, as shown by the data in Table I. The fact that the melting point of methyl  $\alpha$ -D,L-rhamnopyranoside is much higher than that of the L-component proves the true racemic character and this conclusion is verified by optical measurements. In the case of methyl 2,3,4-tribenzoyl- $\alpha$ -D,L-rhamnopyranoside, the melting point is much lower than that of its components and accordingly no decision can be made from the comparison of these values; however, the optical data show conclusively that the crystals of the D,L-form are entirely different from those of its components, a fact which establishes the true racemic character of the D,L-crystals. Analogous comparisons of optical data prove that the crystals of D,L-rhamnitol are also a true racemate. In the case of crystalline rhamnose hydrate, it is known from rotatory relations that the separate D- and L-forms have the  $\alpha$ -pyranose structure; there exists no evidence at present which shows either the ring type or the  $\alpha,\beta$ -classification of the substance that is the crystalline racemate of D,L-rhamnose.<sup>5</sup>

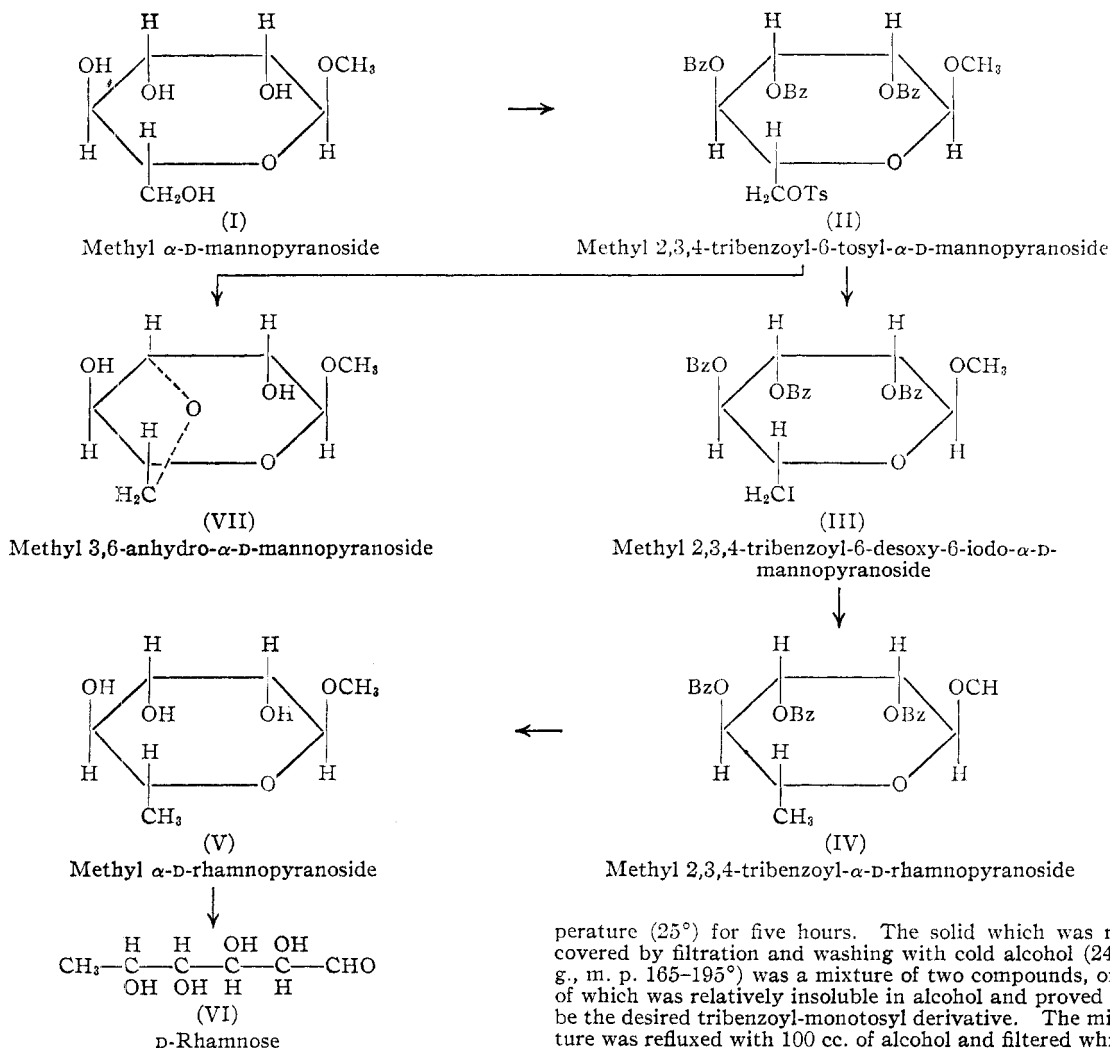
(1) Votoček and Valentin, *Compt. rend.*, **183**, 62 (1926).

(2) Hudson in "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, New York, N. Y., 1941, p. 371.

(3) Valentin, *Collection Czechoslov. Chem. Commun.*, **6**, 354 (1934).

(4) Votoček, Valentin and Rác, *ibid.*, **2**, 402 (1930).

(5) In this connection, compare Hudson, *THIS JOURNAL*, **65**, 1239 (1943).



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

### Experimental

**Methyl 2,3,4-Tribenzoyl-6-tosyl- $\alpha$ -D-mannopyranoside.**—A solution of 10.0 g. of methyl  $\alpha$ -D-mannopyranoside in 150 cc. of hot pyridine was cooled in an ice-bath and a cold solution of 11.0 g. (1.1 molecular equivalents) of *p*-toluenesulfonyl ("tosyl") chloride in 20 cc. of pyridine was added. After standing six hours at 20° the mixture was again cooled in an ice-bath and 20 cc. (3.3 molecular equivalents) of benzoyl chloride was added. After an additional eighteen hours at 20° the reaction mixture was poured into 2 liters of ice water, which resulted in the precipitation of a solid granular mass. The aqueous solution was decanted and the solid residue triturated with 200 cc. of 2% sodium bicarbonate solution, filtered and washed with water. The crude product weighed 32.4 g., melted from 120 to 160° and contained some gummy material. This non-crystalline portion was removed by refluxing the crude material with 50 cc. of alcohol for five minutes and allowing the resulting pasty mass to stand at room tem-

perature (25°) for five hours. The solid which was recovered by filtration and washing with cold alcohol (24.5 g., m. p. 165–195°) was a mixture of two compounds, one of which was relatively insoluble in alcohol and proved to be the desired tribenzoyl-monotosyl derivative. The mixture was refluxed with 100 cc. of alcohol and filtered while hot, and the extraction was repeated with 50 cc. of boiling alcohol. The remaining insoluble portion weighed 12.8 g. (38%) and melted from 190–193°. It was recrystallized from 10 parts of acetone to give pure methyl 2,3,4-tribenzoyl-6-tosyl- $\alpha$ -D-mannopyranoside melting at 197–199° and rotating  $[\alpha]_D^{20}$   $-102.4^\circ$  in chloroform solution (*c*, 0.90). It is soluble in chloroform, pyridine and boiling acetone, moderately soluble in benzene and ether and nearly insoluble in water, petroleum ether and cold alcohol; approximately 200 parts of boiling absolute alcohol is required to dissolve it and it crystallizes on cooling as large thin plates. The large negative rotation of this derivative was verified.

*Anal.* Calcd. for  $C_{35}H_{42}O_{11}S$ : C, 63.62; H, 4.88; S, 4.85. Found: C, 63.47; H, 5.01; S, 4.95.

The hot alcoholic extracts of the crude product upon cooling deposited 8.5 g. of elongated prisms which melted from 130–134°; an additional 1.2 g. of the same substance was obtained by concentration of the mother liquor, making the total yield 9.7 g. (31%). After several recrystallizations from 10 parts of alcohol pure methyl 2,3,4,6-tetra-benzoyl- $\alpha$ -D-mannopyranoside melting at 134–135°, and showing no depression of this value when mixed with an authentic sample of methyl 2,3,4,6-tetra-benzoyl- $\alpha$ -D-mannopyranoside, was obtained; its specific rotation  $[\alpha]_D^{20}$  was  $-66.3^\circ$  in chloroform solution (*c*, 0.84), and this levorotation was verified.

**Methyl 2,3,4,6-Tetra-benzoyl- $\alpha$ -D-mannopyranoside.**—A solution of 1.0 g. of methyl  $\alpha$ -D-mannopyranoside in 15 cc.

TABLE I  
 DATA CONCERNING SOME SUBSTANCES OF THE RHAMNOSE SERIES<sup>a</sup>

Substance	M. p., °C.	$[\alpha]^{20}_D$	Solvent	$n_\alpha$	$n_\beta$	$n_\gamma$	Optic sign	Optic angle (2V)
Methyl 2,3,4-tribenzoyl- $\alpha$ -D-rhamnopyranoside	132-133	-175.8	CHCl <sub>3</sub>	1.538	1.552	1.632	+	50°
Methyl 2,3,4-tribenzoyl- $\alpha$ -L-rhamnopyranoside	132-133	+175.8	CHCl <sub>3</sub>	1.538	1.552	1.632	+	50
Methyl 2,3,4-tribenzoyl- $\alpha$ -D,L-rhamnopyranoside	108-109	0	CHCl <sub>3</sub>	1.528	1.629	1.645	-	40
Methyl $\alpha$ -D-rhamnopyranoside	Amorphous	+ 61	H <sub>2</sub> O					
Methyl $\alpha$ -L-rhamnopyranoside	108-109	- 62.3	H <sub>2</sub> O	1.538	1.542	1.543	-	40
Methyl $\alpha$ -D,L-rhamnopyranoside	160-161	0	H <sub>2</sub> O	1.530	1.532	1.533	-	60
D-Rhamnitol	123-124	- 12.0	H <sub>2</sub> O	1.528	1.540	1.544	-	60
L-Rhamnitol	123-123.5	+ 12.0	H <sub>2</sub> O	1.528	1.540	1.544	-	60
D,L-Rhamnitol	112-113	0	H <sub>2</sub> O	1.519	1.524	1.531	+	85
$\alpha$ -D-Rhamnopyranose monohydrate	90-91	- 8.2	H <sub>2</sub> O	1.522	1.534	1.537	-	55
$\alpha$ -L-Rhamnopyranose monohydrate	90-91	+ 8.2	H <sub>2</sub> O	1.522	1.534	1.537	-	55
D,L-Rhamnose (anhydrous)	151-153	0	H <sub>2</sub> O	1.536	1.547	1.558	-	85

<sup>a</sup> The optical properties of the crystals were determined by Mr. Joseph J. Fahey of the Geological Survey, U. S. Department of the Interior; the measurements were made in ordinary light at 25° and the limit of error is  $\pm 0.002$ .

of warm pyridine was cooled in an ice-bath and 3.0 cc. (5 molecular equivalents) of benzoyl chloride was added. After standing at 20° for eighteen hours, 100 cc. of ice water was added and the thick gum which precipitated soon crystallized. It was recovered by filtration and washed with dilute bicarbonate solution and water (3.1 g.; quantitative). The crude product was recrystallized from 10 parts of alcohol, separating as elongated prisms melting at 134-135° and rotating  $[\alpha]^{20}_D -66.2^\circ$  in chloroform solution (*c*, 0.85). It is very soluble in chloroform, pyridine, acetone, ether and warm alcohol and nearly insoluble in water and petroleum ether.

*Anal.* Calcd. for C<sub>35</sub>H<sub>30</sub>O<sub>10</sub>: C, 68.84; H, 4.95; C<sub>6</sub>H<sub>5</sub>-CO, 68.9; CH<sub>3</sub>O, 5.08. Found: C, 68.80; H, 4.96; C<sub>6</sub>H<sub>5</sub>CO, 68.7; CH<sub>3</sub>O, 5.08.

**Methyl 2,3,4-Triacetyl-6-tosyl- $\alpha$ -D-mannopyranoside.**—A solution of 5.0 g. of methyl  $\alpha$ -D-mannopyranoside in 75 cc. of warm pyridine was cooled in an ice-bath and a solution of 5.5 g. of tosyl chloride (1.1 molecular equivalents) in 10 cc. of pyridine was added. After standing at 20° for six hours the solution was again cooled in an ice-bath, 10 cc. (4 molecular equivalents) of acetic anhydride was added and the solution allowed to stand for an additional eighteen hours at 20°. The reaction mixture was concentrated *in vacuo* to a thin sirup and poured into 200 cc. of ice water; the resulting sirupy precipitate was washed several times with water by decantation, dissolved in 35 cc. of methyl alcohol, filtered through a carbon mat and 10 cc. of water added to the filtrate. Upon standing in the refrigerator for two days the material gradually crystallized and was recovered by filtration and washed with methyl alcohol (3.5 g.; 29%). The product was recrystallized from 2 parts of methyl alcohol, forming prisms which melted at 89-90° and rotated  $[\alpha]^{20}_D +57.2^\circ$  in chloroform solution (*c*, 0.82). It is very soluble in pyridine, chloroform and warm alcohol, moderately soluble in alcohol and ether and nearly insoluble in water and petroleum ether.

*Anal.* Calcd. for C<sub>20</sub>H<sub>26</sub>O<sub>11</sub>S: C, 50.62; H, 5.52; S, 6.76. Found: C, 50.76; H, 5.62; S, 6.68.

**Methyl 2,3,4-Tribenzoyl-6-desoxy-6-iodo- $\alpha$ -D-mannopyranoside.**—A solution of 5.0 g. of methyl 2,3,4-tribenzoyl-6-tosyl- $\alpha$ -D-mannopyranoside and 5.0 g. of sodium iodide in 100 cc. of warm acetone was heated at 100° for two hours in a pressure flask. The cooled reaction mixture was filtered to remove the precipitated sodium tosylate (1.5 g., quantitative) and evaporated to a dry crystalline residue. The crystals were shaken with 25 cc. of water and the insoluble portion recovered by filtration

(4.7 g., quantitative). The compound was recrystallized from 70 parts of absolute alcohol, forming granular prisms melting at 202-203° and rotating  $[\alpha]^{20}_D -101.6^\circ$  in chloroform solution (*c*, 0.84). It is soluble in benzene, chloroform and warm acetone and nearly insoluble in water, hexane, cold alcohol and cold acetone.

*Anal.* Calcd. for C<sub>28</sub>H<sub>26</sub>IO<sub>8</sub>: C, 54.56; H, 4.09; I, 20.59. Found: C, 54.50; H, 4.22; I, 20.60.

**Methyl 2,3,4-Tribenzoyl- $\alpha$ -D-rhamnopyranoside.**—A suspension of 5.0 g. of finely ground methyl 2,3,4-tribenzoyl-6-desoxy-6-iodo- $\alpha$ -D-mannopyranoside and 0.6 g. of Raney nickel in 200 cc. of methyl alcohol containing 1.67 cc. (2 molecular equivalents) of diethylamine was agitated with hydrogen gas under slight pressure. After ninety minutes the absorption of gas was complete and the iodo compound had passed into solution (206 cc. of hydrogen was taken up; the calculated value for one molecular equivalent of hydrogen at 27° and 753 mm. pressure is 202 cc.). The catalyst was removed by filtration and the solution concentrated *in vacuo* to a dry crystalline mass. The crystals were stirred with 25 cc. of water, filtered and washed thoroughly with water. The yield was 3.8 g. (95%) of nearly pure product. The compound was recrystallized from 10 parts of methyl alcohol, forming elongated prisms melting at 132-133° and rotating  $[\alpha]^{20}_D -175.8^\circ$  in chloroform solution (*c*, 0.81). It is soluble in chloroform, acetone, benzene and warm alcohol and nearly insoluble in water and petroleum ether. The optical properties of the substance are recorded in Table I.

*Anal.* Calcd. for C<sub>28</sub>H<sub>26</sub>O<sub>8</sub>: C, 68.56; H, 5.34; C<sub>6</sub>H<sub>5</sub>-CO, 64.3; CH<sub>3</sub>O, 6.33. Found: C, 68.41; H, 5.60; C<sub>6</sub>H<sub>5</sub>CO, 64.0; CH<sub>3</sub>O, 6.35.

**Methyl  $\alpha$ -D-Rhamnopyranoside.**—A suspension of 5.0 g. of finely ground 2,3,4-tribenzoyl- $\alpha$ -D-rhamnopyranoside in 25 cc. of methyl alcohol containing 0.25 cc. of 1.75 *N* barium methylate solution was shaken for thirty minutes, at which time solution was complete. After standing for twenty-four hours at 25°, the solution was neutralized with carbon dioxide, filtered through a carbon mat and concentrated *in vacuo* to a sirup. The sirup was diluted with 20 cc. of water and extracted with three 5-cc. portions of chloroform to remove the methyl benzoate. The aqueous solution was concentrated to a dry sirup (1.7 g.; 94%) which resisted all attempts to crystallize it. The specific rotation  $[\alpha]^{20}_D$  of the sirup was +61.0° in aqueous solution (*c*, 1.0) as compared to -62.48° reported by Minsaa<sup>6</sup> for methyl  $\alpha$ -L-rhamnopyranoside.

(6) Minsaa, *Kgl. Norske Videnskab. Selskabs Forh.*, **6**, 177 (1933).

**$\alpha$ -D-Rhamnopyranose Monohydrate from Methyl 2,3,4-Tribenzoyl- $\alpha$ -D-rhamnopyranoside.**—Twenty grams of 2,3,4-tribenzoyl- $\alpha$ -D-rhamnopyranoside was debenzoylated as previously described and the sirupy methyl  $\alpha$ -D-rhamnopyranoside was hydrolyzed with 200 cc. of 0.1 *N* hydrochloric acid by refluxing eleven hours to constant rotation, which was  $[\alpha]_D -6.1^\circ$  calculated as D-rhamnose monohydrate. The acid was removed from the solution by shaking with 4 g. of silver oxide and filtering; the excess silver was precipitated as the sulfide and the colorless filtrate from the sulfide precipitation was concentrated *in vacuo* to a thick sirup which was dried by two successive concentrations with 25 cc. of absolute alcohol. The solution of the residual sirup in 25 cc. of warm absolute alcohol was filtered through a carbon mat to remove turbidity and the filtrate again evaporated to a thick sirup, which was dissolved in 4 cc. of water and seeded with D-rhamnose hydrate. Crystallization was rapid and after standing overnight at 5°, 5.0 g. of the sugar was obtained; concentration of the mother liquor gave an additional 1.3 g., making the total yield 6.3 g. (85%). The sugar was recrystallized from 0.66 parts of water, forming granular prisms which melted at 90–91° and mutarotated  $[\alpha]^{20}_D +3.76^\circ$  (four minutes) to  $-8.2^\circ$  (three hours, constant value). Votoček and Valentin<sup>1</sup> recorded the rotation of their D-rhamnose hydrate as  $[\alpha]^{16}_D -8.25^\circ$ .

*Anal.* Calcd. for  $C_6H_{12}O_5 \cdot H_2O$ : C, 39.56; H, 7.75;  $H_2O$ , 9.89. Found: C, 39.53; H, 7.81;  $H_2O$ , 10.02.

The over-all yield of  $\alpha$ -D-rhamnopyranose monohydrate from methyl  $\alpha$ -D-mannopyranoside was 28%.

**Methyl 3,6-Anhydro- $\alpha$ -D-mannopyranoside.**—To a hot solution of 20.0 g. of methyl 2,3,4-tribenzoyl-6-tosyl- $\alpha$ -D-mannopyranoside in 300 cc. of methyl cellosolve was added 133 cc. (4.4 molecular equivalents) of 1.0 *N* sodium hydroxide solution and the mixture was heated on the steam-bath for one hour. After neutralizing the excess alkali with carbon dioxide the solution was concentrated *in vacuo* to dryness and the solid residue was reconstituted with a 100-cc. portion of ethyl acetate. The product was separated from the mixture of sodium benzoate and sodium tosylate by extraction with three 100-cc. portions of boiling ethyl acetate. The filtered extract was concentrated to a thin sirup which crystallized readily to yield 4.5 g. (85%) of material; upon recrystallization from 20 parts of ethyl acetate it formed prisms melting at 129–131° and rotating  $[\alpha]^{20}_D +96.6^\circ$  in aqueous solution (*c*, 0.82), in agreement with the values given by Valentin<sup>3</sup> for methyl 3,6-anhydro- $\alpha$ -D-mannopyranoside (m. p. 130–132°,  $[\alpha]_D +97.1^\circ$ ).

**Methyl  $\alpha$ -L-Rhamnopyranoside.**—A solution of 10 g. of L-rhamnose hydrate in 200 cc. of methyl alcohol containing 1% of hydrogen chloride gas was refluxed for three hours. The reaction was followed polarimetrically and no further change in rotation occurred after the second hour. The acid was removed by shaking the reaction mixture with 10 g. of silver oxide followed by filtration through a carbon mat; the filtrate, which was free of excess silver, was concentrated *in vacuo* to a thick sirup, dissolved in 25 cc. of ethyl acetate and reconstituted to remove the residual methyl alcohol. The sirup resisted all attempts to crystallize it, but upon dissolving it in 25 cc. of ethyl acetate and seeding with methyl  $\alpha$ -L-rhamnopyranoside, kindly furnished by Dr. J. Minsaa, it crystallized rapidly to yield 6.5 g. of the glycoside and an additional 1.1 g. was obtained by concentration of the mother liquor; total yield 7.6 g. (78%). It was recrystallized from 4 parts of ethyl acetate, forming large prisms which melted at 108–109° and rotated  $[\alpha]^{20}_D -62.3^\circ$  in aqueous solution (*c*, 0.86) in agreement with the values reported by Minsaa<sup>5</sup> [m. p. 109–110°,  $[\alpha]^{20}_D -62.48^\circ$  (*c*, 10.0)].

The optical properties of the compound are recorded in Table I.

**Methyl 2,3,4-Tribenzoyl- $\alpha$ -L-rhamnopyranoside.**—The sirupy methyl  $\alpha$ -L-rhamnopyranoside resulting from the methylation of 10 g. of L-rhamnose hydrate with methyl alcohol containing 1% of hydrogen chloride was dissolved in 50 cc. of pyridine, cooled in an ice-bath and 30 cc. of

benzoyl chloride was added. After standing at 20° for eighteen hours the mixture was poured into one liter of ice water. The precipitated gum was washed several times with water by decantation and, upon seeding with crystals obtained by rubbing a small portion of the gum with methyl alcohol, it crystallized. The crude product, which is somewhat sticky, was recrystallized from 50 cc. of methyl alcohol to yield 21.5 g. (80%) of nearly pure product melting at 130–132°; further recrystallization from 10 parts of methyl alcohol gave the pure material in the form of elongated prisms of the same general appearance as the D-form, melting at 132–133° and rotating  $[\alpha]^{20}_D +175.8^\circ$  in chloroform solution (*c*, 0.88). Its solubilities and optical properties were the same as those of the D-form previously described.

*Anal.* Calcd. for  $C_{22}H_{26}O_8$ : C, 68.56; H, 5.34;  $C_6H_5$ -CO, 64.3;  $CH_3O$ , 6.33. Found: C, 68.56; H, 5.44;  $C_6H_5$ -CO, 64.4;  $CH_3O$ , 6.34.

**Methyl 2,3,4-Tribenzoyl- $\alpha$ -D,L-rhamnopyranoside.**—A solution of 0.50 g. of methyl 2,3,4-tribenzoyl- $\alpha$ -L-rhamnopyranoside and 0.50 g. of methyl 2,3,4-tribenzoyl- $\alpha$ -D-rhamnopyranoside in 10 cc. of boiling methyl alcohol upon cooling deposited the racemate as elongated prisms considerably smaller but of the same general appearance as those of its component enantiomorphs. The crystals (0.95 g.) melted at 108–109° and showed no rotation in chloroform solution (*c*, 0.83).

The optical data (see Table I) show that the compound is a true racemate.

**Methyl  $\alpha$ -D,L-Rhamnopyranoside.**—A mixture of 1.0 g. of sirupy methyl  $\alpha$ -D-rhamnopyranoside and 1.0 g. of crystalline methyl  $\alpha$ -L-rhamnopyranoside, upon the addition of 5 cc. of ethyl acetate, set to a nearly solid crystalline magma which required 100 cc. of boiling ethyl acetate to dissolve it. Upon cooling, the racemate crystallized as glistening thin plates of entirely different appearance from the large prisms of the L-form. The yield was 1.7 g. and it melted at 160–161° and showed no rotation in aqueous solution. It may also be recrystallized from 6 parts of alcohol, forming the same type of thin plates.

Optical examination (see Table I) also showed it to possess different properties from the L-form. These data show that the crystals are those of a true racemate.

*Anal.* Calcd. for  $C_7H_{14}O_6$ : C, 47.18; H, 7.92;  $CH_3O$ , 17.42. Found: C, 47.25; H, 7.92;  $CH_3O$ , 17.44.

**$\alpha$ -D,L-Rhamnose.**—A solution of 0.50 g. of D-rhamnose hydrate and 0.50 g. of L-rhamnose hydrate in 5 cc. of hot alcohol was evaporated on the steam-bath to a thick sirup which crystallized spontaneously as rosettes of prismatic needles (0.95 g.). After recrystallization from 5 parts of alcohol, the compound melted at 151–153° and exhibited no rotation in aqueous solution (*c*, 0.96). Votoček, Valentin and Rác<sup>4</sup> record the same melting point and they have shown that the crystals are those of a true racemate, containing no water of crystallization. As would be expected, the optical properties of the compound (see Table I) are entirely different from those of its components.

*Anal.* Calcd. for  $C_6H_{12}O_5$ : C, 43.90; H, 7.37. Found: C, 44.09; H, 7.36.

**D-Rhamnitol.**—A solution of 3.0 g. of D-rhamnose hydrate in 50 cc. of water was reduced with hydrogen at 100 atmospheres pressure at 100° for five hours, using 0.6 g. Raney nickel catalyst. The reaction mixture, which did not reduce Fehling solution, was filtered and concentrated *in vacuo* to a dry crystalline mass, which was dissolved in 10 cc. of hot absolute alcohol; upon cooling, the solution deposited 2.5 g. of prisms and a further 0.2 g. of the same material was obtained by concentration of the mother liquor; total yield 2.7 g. (100%). The product was recrystallized from 4 parts of 95% alcohol; it formed prisms melting at 123–124° and rotating  $[\alpha]^{20}_D -12.0^\circ$  in aqueous solution (*c*, 1.0). Votoček, Valentin and Rác<sup>4</sup> found m. p. 123° and  $[\alpha]_D -12.4^\circ$  for their D-rhamnitol, and W. D. Maclay observed in this laboratory several years ago m. p. 123–123.5° and  $[\alpha]^{20}_D +12.0^\circ$  for L-rhamnitol.

**D,L-Rhamnitol.**—A solution of 0.50 g. of D-rhamnitol and 0.50 g. of L-rhamnitol in 5 cc. of hot alcohol upon cooling deposited 0.9 g. of prisms of much the same appearance as those of its components. The substance may be recrystallized from 4 parts of alcohol the same as the D- or L-forms; it melts at 112–113° and exhibits no rotation in aqueous solution. Valentin<sup>7</sup> reported m. p. 117° and describes the substance as crystallizing from aqueous solution in the form of anhydrous microscopic needles.

Proof that it is a true racemate was obtained through optical measurements (see Table I). The D,L-rhamnitol shows indices of refraction which are different from those of its components; it also differs from the components in that its optic sign is positive and the axial angle  $2V$  is 85°.

### Summary

The very accessible methyl  $\alpha$ -D-mannopyranoside, which can be produced from vegetable ivory, methyl alcohol and sulfuric acid in over 40% yield, proves to be an excellent source for the preparation of D-rhamnose, the enantiomorph of the naturally occurring L-rhamnose. The intermediates are methyl 2,3,4-tribenzoyl-6-tosyl- $\alpha$ -

(7) Valentin, *Collection Czechoslov. Chem. Commun.*, **2**, 691 (1930).

D-mannopyranoside, methyl 2,3,4-tribenzoyl-6-desoxy-6-iodo- $\alpha$ -D-mannopyranoside, methyl 2,3,4-tribenzoyl- $\alpha$ -D-rhamnopyranoside and methyl  $\alpha$ -D-rhamnopyranoside, the last of which is hydrolyzed by acid to D-rhamnose. The over-all yield is about 28%. The reactions conclusively correlate the  $\alpha$ -D-forms of methyl mannopyranoside and methyl rhamnopyranoside and thereby verify the previously inferred correlation of these glycosides through rotatory relations. Methyl 2,3,4-tribenzoyl-6-tosyl- $\alpha$ -D-mannopyranoside is readily converted to methyl 3,6-anhydro- $\alpha$ -D-mannopyranoside. The crystallization of several D,L-substances in the rhamnose series is described, and all of them prove to be true racemates. The use of a moderate excess of diethylamine as acceptor for hydriodic acid proves advantageous in the reduction of methyl tribenzoyl-6-desoxy-6-iodo- $\alpha$ -D-mannopyranoside to methyl tribenzoyl- $\alpha$ -D-rhamnopyranoside by hydrogen and Raney nickel.

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## Studies on the Willgerodt Reaction. II. The Mechanism of the Reaction

BY JOHN A. KING AND FREEMAN H. McMILLAN

The first paper of this series<sup>1,2</sup> showed that the scope of the Willgerodt reaction was considerably broader than had previously been supposed. The present paper indicates the probable course of the reaction and offers a mechanism which satisfactorily explains all experimental data so far obtained.

In 1888 Willgerodt<sup>3</sup> made three significant observations relevant to the mechanism of this reaction: aldehydes are converted to the corresponding acids and amides under the conditions of the reaction; the ketone is not reduced to an alkylbenzene as an intermediate at any stage of the reaction because the latter are unchanged under the conditions of the reaction; and, because amides are almost unchanged under the conditions of the reaction, they are formed either concurrently with or, more probably, from the acids. In his later papers Willgerodt<sup>4</sup> found that the yield of amide decreased inversely with the chain length of the alkyl group of the ketone; this was confirmed, much later, by Bachmann and Carmack<sup>5</sup> and by Cavalieri and co-workers.<sup>2</sup> He<sup>4</sup> also observed that when too much sulfur was

used in the reaction the ketones underwent cleavage and when too little sulfur was used alkylbenzenes and diarylthiophenes often constituted the major reaction products. He further found that sodium polysulfide could be used to convert acetophenone to phenylacetic acid. Kindler<sup>6</sup> was the first to use anhydrous amines and free sulfur in the reaction and obtained as products the thioamides analogous to the carboxylic amides that were formed from the same carbonyl compounds and ammonium polysulfide.

Before attempting to discover the course of the reaction it was essential to determine whether the reaction always proceeded without any rearrangement in the alkyl group. This was assumed by Willgerodt,<sup>4</sup> while Fieser and Kilmer<sup>7</sup> implied that they doubted if isovalerophenone yielded  $\alpha$ -methyl- $\gamma$ -phenylbutyramide and Bachmann and Carmack and Hartmann and co-workers<sup>8</sup> were non-committal. Willgerodt's assumption was shown to be correct. When the reaction was carried out on isobutyrophenone and isovalerophenone, under the same conditions as were used by Willgerodt and Merk, the products were, respectively, the  $\alpha$ -methyl amides of  $\beta$ -phenylpropionic and  $\gamma$ -phenylbutyric acids, identified by mixed melting point determinations with authentic samples of the amides.

(1) King and McMILLAN, *THIS JOURNAL*, **68**, 525 (1946).

(2) This is also confirmed by the work of Cavalieri, Pattison and Carmack, *THIS JOURNAL*, **67**, 1783 (1945), who applied the reaction to purely aliphatic and to alicyclic-aliphatic ketones.

(3) Willgerodt, *Ber.*, **21**, 534 (1888).

(4) (a) Willgerodt, *J. prakt. Chem.*, [2] **80**, 183 (1909); (b) Willgerodt and Merk, *ibid.*, [2] **80**, 192 (1909); (c) Willgerodt and Hambrecht, *ibid.*, [2] **81**, 74 (1910); (d) Willgerodt and Scholtz, *ibid.*, [2] **81**, 382 (1910).

(5) Bachmann and Carmack, *THIS JOURNAL*, **63**, 2494 (1941).

(6) Kindler, *Ann.*, **431**, 187 (1923).

(7) Fieser and Kilmer, *THIS JOURNAL*, **62**, 1354 (1940).

(8) Hartmann, Miescher, Kaegi and Bosshard, Canadian Patent 414,941.