known 1,6-didesoxy-2,3,4,5-dimethylene-D-mannitol and 1,6-didesoxy-D-mannitol; the latter substance yields the expected quantity of acetaldehyde on oxidation with per-iodic acid, a result which confirms the 1,6-didesoxy structure.

A second dimethylene-D-mannitol, so named provisionally, has been found in the mother liquor of the trimethylene-D-mannitol that results from the condensation of D-mannitol with formaldehyde under strongly acidic conditions. Evidence is presented which indicates that this isomer is either 1,3:4,6- or 1,3:5,6-dimethylene-D-mannitol.

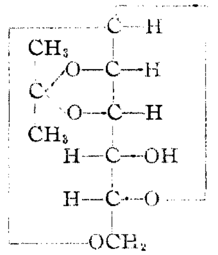
BETHESDA, MD. RECEIVED OCTOBER 23, 1942

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

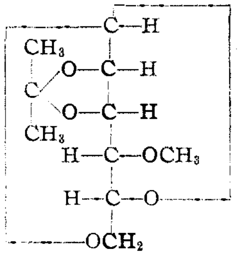
Crystalline 4-Methyl-D-mannose and Some of its Derivatives

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

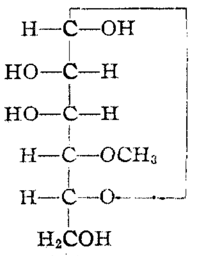
Pacsu and Trister[1] have recently prepared crystalline 2-methyl-D-mannose. This substance, in amorphous form, was first obtained by Pacsu and Kary[2] and thought to be 4-methyl-D-mannose, but subsequent studies,[3] which have now resulted in its crystallization as mentioned, show it to be the 2-methyl derivative. It was recently stated[4] that 4-methyl-D-mannose (III) has been prepared in this Laboratory through the complete acid hydrolysis of the methylation product (II) of 2,3-isopropylidene-D-mannosan<1,5>β<1,6> (I). The present paper describes the new sugar and some of its derivatives. Crystalline 4-methyl-D-mannose is an alpha form, since its aqueous solution at 20° shows a change in specific rotation from an initial value of +34° to an equilibrium value of +22.6°; the mutarotation constant, calculated for a unimolecular reaction, is 0.020 at 20°, which corresponds closely to that of D-mannose, for which the values 0.019[5] and 0.017[6] have been reported. A solution of the sugar in 1 N hydrochloric acid at 20° attained an equilibrium rotation $[\alpha]^{20}\text{D}$ + 22.4° within five minutes, but on heating the acid solution for one hour at 98° the rotation decreased to +18.5°, and this value was not changed on further heating; this rotation is close to that of +17.7° observed when 2,3-isopropylidene-4-methyl-D-mannosan <1,5>β<1,6> is hydrolyzed by 1 N hydrochloric acid at 98° and is also in agreement with the final value, namely, +18.7°, obtained when 4-methyl-α-methyl-D-mannopyranoside is completely hydrolyzed by 0.05 N hydrochloric acid at 98°; these agreeing results suggest that solutions of the sugar are converted by the action of the hydrochloric acid into an equilibrium mixture of the sugar and a substance of more negative rotation, possibly the sugar anhydride. The sugar yields a crystalline methylglycoside, which is doubtless a pyranoside of alpha configuration because its specific rotation (+83.9° in water) is more positive than the initial or the equilibrium rotation of the sugar, and furanose forms are not possible for this sugar. The difference in the molecular rotations of the glycoside ($[M]^{20}\text{D}$ +17,470) and the alpha form of the sugar ($[M]^{20}\text{D}$ +6600) is +10,870, which conforms with the fairly agreeing ($a_{\text{me}} - a_{\text{OH}}$) values that are known for many sugars and



2,3-Isopropylidene-D-mannosan<1,5>β<1,6>
(I)



2,3-Isopropylidene-4-methyl-D-mannosan<1,5>β<1,6>
(II)



4-Methyl-α-D-mannose
(III)

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(1) Pacsu and Trister, THIS JOURNAL, **63**, 925 (1941).

(2) Pacsu and Kary, *Ber.*, **62**, 2811 (1929).

(3) Levene, Meyer and Raymond, *J. Biol. Chem.*, **91**, 498 (1931); Pacsu, *Ber.*, **65**, 51 (1932).

(4) Knauf, Hann and Hudson, THIS JOURNAL, **63**, 1449 (1941).

(5) Hudson and Sawyer, *ibid.*, **39**, 475 (1917).

(6) Isbell and Pigman, *J. Research Natl. Bur. Standards*, **18**, 180 (1937).

their methylglycosides.[7] Other derivatives of the new sugar which possess a pyranose ring also resemble the corresponding ones of D-mannose in rotation, except in the case of the second tetraacetate (Table I); its unusual rotation suggests that it is not the true β-acetate, and it is therefore designated provisionally as shown. It may possibly be a molecular compound of the alpha and the true beta tetraacetate, or an ortho-acetate, or an acetate of the *aldehydo* form. The phenylhydrazone of 4-methyl-D-mannose is precipitated at once and in high yield when a weak acetic acid solution of the sugar is treated with phenylhydrazine; its low solubility agrees with that property of mannose phenylhydrazone.

TABLE I

COMPARISON OF SPECIFIC ROTATIONS ($[\alpha]^{20}$D) OF SUBSTANCES IN THE 4-METHYL-D-MANNOSE AND D-MANNOSE SERIES

	4-Methyl-D-mannose series	D-Mannose series
Sugar (initial) (α)	+34.0°	+29.3°[a]
Sugar (final)	+22.6	+14.2 [a]
Sugar acetate (α)	+59.2	+54.9 [b]
Sugar acetate (II)	+20.2	...
Sugar acetate (β)	...	−25.3 [b]
Methylglycoside (α)	+83.9	+78.6 [c]
Aldonic acid amide	+11.9	−17.3 [d]
Aldonic acid phenylhydrazide	+10.6	−10.5 [e]
Aldonic acid-δ-lactone	+163.8	+114.8 [f]
Sugar alcohol	+16.7	− 0.5 [g]
Sugar alcohol acetate	+35.4	+25.0 [h]

[a] Isbell and Pigman, *J. Research Natl. Bur. Standards*, **18**, 141 (1937). [b] Hudson and Dale, THIS JOURNAL, **37**, 1280 (1915). [c] Fischer and Beensch, *Ber.*, **29**, 2927 (1896). [d] Hudson and Komatsu, THIS JOURNAL, **41**, 1141 (1919). [e] Levene and Meyer, *J. Biol. Chem.*, **31**, 625 (1917). The temperature was 85°; Hudson, THIS JOURNAL, **39**, 462 (1917), records −8.1° at a temperature of 80°. [f] Isbell and Frush, *J. Research Natl. Bur. Standards*, **11**, 659 (1933). [g] Maclay, Hann and Hudson, forthcoming publication. [h] Pacsu and Rich, THIS JOURNAL, **55**, 3023 (1933).

The δ-lactone, aldonic acid amide and alcohol derived from 4-methyl-D-mannose are likewise similar to the corresponding derivatives of D-mannose in ease of crystallization and low solubility. A γ-lactone is not possible for 4-methyl-D-mannonic acid and its lactone is presumably the delta one. It is worthy of note that the presence of the methyl group on carbon atom four causes a large change in the rotation of the sugar alcohol, aldonic acid amide and phenylhydrazide; the quantitative evaluation of such effects in their relationship to the amide and phenylhydrazide rules of rotation must await the compilation of more data on methylated derivatives.

Appreciation is expressed to Dr. A. T. Ness for performing the microchemical analyses.

Experimental

4-Methyl-α-D-mannose from 2,3-Isopropylidene-4-methyl-D-mannosan<1,5>β<1,6>.—A solution of 5 g. of 2,3-isopropylidene-4-methyl-D-mannosan<1,5>β<1,6> ($[\alpha]^{20}$D −33.4°)[4] in 50 cc. of normal hydrochloric acid was heated on the steam-bath for five hours, during which period its specific rotation[8] (calculated as 4-methyl-D-mannose) reached a constant value of +17.7°. The hydrochloric acid was removed by silver carbonate and the solution was concentrated *in vacuo* to a dry sirup. Crystalline 4-methyl-D-mannose deposited in a yield of 3.5 g. (78%) upon cooling a solution of the sirup in 10 cc. of warm dioxane. The sugar was purified by recrystallization from 5 parts of dioxane or absolute alcohol, and it separated in the form of prisms which melted at 127–128° (cor.) and showed an equilibrium $[\alpha]^{20}$D value of +22.6° in water (*c*, 0.8; *l*, 4). The course of its mutarotation (Table II) was unimolecular and extrapolation indicates a value of +34° as the initial rotation of the compound; it is therefore to be classified as an α-form.

TABLE II

MUTAROTATION OF 4-METHYL-α-D-MANNOSE IN WATER

Concentration, 0.5214 g. in 25 cc. of solution; tube length, 4 dm.; $T = 20 \pm 0.5°$.

Time, minutes	$[\alpha]^{20}$D	$k_1 + k_2$
5	31.8°	...
10	29.9	0.020
15	28.4	.020
20	27.0	.021
25	25.9	.022
30	25.3	.021
35	24.7	.021
40	24.3	.021
50	23.7	.021
60	23.2	.022
90	22.8	.020
135	22.6	...
24 hr.	22.6	...

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.29; H, 7.27; OCH_3, 15.98. Found: C, 43.35; H, 7.37; OCH_3, 15.94.

4-Methyl-D-mannose Phenylhydrazone.—To a cold solution of 1.0 g. of 4-methyl-D-mannose in 2 cc. of water, a drop of acetic acid and 0.5 cc. of phenylhydrazine were added. The phenylhydrazone crystallized immediately, and it was obtained in a yield of 1.4 g. (quantitative). The product was recrystallized from 7 parts of alcohol and formed pale yellow, elongated prisms which melted at 158–159° (cor.). A mixed melting point with 4-methyl-D-mannose phenylosazone (m. p. 157–158°) gave a melting

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[7] Hudson, THIS JOURNAL, **47**, 271 (1925); Montgomery and Hudson, *ibid.*, **56**, 2074 (1934).

[8] All of the crystalline compounds described in the experimental part 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.

point of 143–145°. The hydrazone exhibited mutarotation in pyridine solution at 20° from an initial specific rotation of +46.2° to an equilibrium value of +17.8° in six days.

Anal. Calcd. for $C_{13}H_{20}O_5N_2$: N, 9.85; OCH_3, 10.92. Found: N, 9.78; OCH_3, 11.11.

4-Methyl-D-mannose Phenylosazone.—A solution of 0.5 g. of the hydrazone in a mixture of 5 cc. of water, 0.1 cc. of glacial acetic acid and 1 cc. of phenylhydrazine was heated for one hour on the steam-bath; the oily sirup that had deposited was separated by decantation and crystallized by treatment with alcohol. The recrystallized osazone formed yellow needles which melted at 157–158° (cor.) and showed mutarotation in pyridine solution at 20° from an initial $[\alpha]^{20}\mathrm{D}$ of −36° to an equilibrium value of −14.4° in twenty-four hours. Schinle[9] records a melting point of 159° and an equilibrium rotation of −13° in pyridine for the same osazone prepared from 4-methyl-D-glucose.

Anal. Calcd. for $C_{19}H_{24}O_4N_4$: C, 61.27; H, 6.50; OCH_3, 8.33. Found: C, 61.19; H, 6.63; OCH_3, 8.21.

4-Methyl-α-methyl-D-mannopyranoside.—A solution of 20 g. of 2,3-isopropylidene-4-methyl-D-mannosan<1,5>β-<1,6> in 100 cc. of methyl alcohol containing 3% of dry hydrochloric acid was refluxed for eight hours. Following the removal of the acid in the usual manner by silver carbonate, the solution was concentrated to a dry sirup, which was dissolved in 10 cc. of warm methyl ethyl ketone. The glycoside deposited from the cooled solution in a yield of 10.7 g. (55%) and after recrystallization from two parts of methyl ethyl ketone it was obtained in colorless prisms, melting at 101–102° (cor.) and showing $[\alpha]^{20}\mathrm{D}$ +83.9° in water (*c*, 0.8). Its rate of hydrolysis in 0.05 *N* hydrochloric acid at 98° was 0.00084 (expressed in minutes and decimal logarithms) proving that it is a glycoside of the stable type; as previously mentioned, the final constant specific rotation (ninety-two hours), calculated as 4-methyl-D-mannose, was +18.7° in agreement with the value of +18.5° obtained by heating 4-methyl-α-D-mannose in 1 *N* hydrochloric acid. Phelps and Hudson[10] and Isbell and Frush[11] have recorded values of 0.00089 and 0.00069, respectively, for the hydrolysis constant of α-methyl-D-mannopyranoside with 0.05 *N* hydrochloric acid at 98°.

Anal. Calcd. for $C_8H_{16}O_6$: C, 46.15; H, 7.75; OCH_3, 29.81. Found: C, 46.16; H, 7.61; OCH_3, 29.68.

1,2,3,6-Tetraacetyl-4-methyl-α-D-mannose.—A solution of 6.8 g. of 4-methyl-D-mannose in a mixture of 25 cc. of pyridine and 25 cc. of acetic anhydride was allowed to stand at 25° for sixteen hours and then poured into 200 cc. of ice-water. The precipitated solid was separated by filtration and upon recrystallization from dilute alcohol it yielded stubby prisms which melted at 75–76° (cor.) and showed $[\alpha]^{20}\mathrm{D}$ +59.2° in chloroform (*c*, 0.8). The yield was 6.3 g. (50%).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; CH_3CO, 47.5. Found: C, 49.61; H, 6.09; CH_3CO, 47.7.

A Second Tetraacetyl-4-methyl-D-mannose.—The aqueous mother liquor remaining after the separation of the α-acetate, as described in the preceding paragraph, was extracted with chloroform and the dried extract concentrated to a sirup. Crystallization was difficult to attain, but after standing for thirteen months in an evacuated desiccator the sirup crystallized almost completely as quadrilateral plates in a yield of 5.8 g. (46%). The compound, following recrystallization from 4 parts of 40% alcohol, melted at 63–64° and showed $[\alpha]^{20}\mathrm{D}$ +20.2° in chloroform (*c*, 0.8), and these constants were not changed by further recrystallization.

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; CH_3CO, 47.5. Found: C, 49.91; H, 6.06; CH_3CO, 47.7.

4-Methyl-D-mannonic-δ-lactone.—To a solution of 6.8 g. of 4-methyl-D-mannose in 100 cc. of water, 50 g. of barium carbonate and 5 cc. of bromine were added, and the mixture was shaken for one hour and then allowed to stand overnight at room temperature. The inorganic reagents were removed in the usual manner and the resulting solution of the organic acid was concentrated *in vacuo* at 50°. The lactone crystallized in a yield of 4.4 g. (66%). The substance was recrystallized from 13 parts of alcohol; it formed elongated prisms which melted at 165–166° (cor.). An aqueous solution of the lactone exhibited mutarotation, changing from $[\alpha]^{20}\mathrm{D}$ +163.8° to the constant value +94.2° in the course of six days at a rate which indicates that the reaction is unimolecular (Table III).

Anal. Calcd. for $C_7H_{12}O_6$: C, 43.75; H, 6.29; OCH_3, 16.15, neut. equiv., 192. Found: C, 43.96; H, 6.35; OCH_3, 16.32, neut. equiv., 193.

TABLE III

MUTAROTATION OF 4-METHYL-D-MANNONIC-δ-LACTONE

Concentration, 0.2021 g. in 25 cc. of aqueous solution; tube length, 4 dm.; $T = 20 \pm 0.5°$

Time	$[\alpha]^{20}\mathrm{D}$	$k_1 + k_2$
3 min.	+163.8°	..
1 hr.	161.1	0.0003
2 hr.	158.9	.0003
4 hr.	155.2	.0002
6 hr.	150.4	.0003
27 hr.	115.1	.0003
51 hr.	100.1	.0004
95 hr.	95.3	.0003
6 days	94.2	...
27 days	94.2	...

4-Methyl-D-mannonic Phenylhydrazide.—A mixture of 1.0 g. of 4-methyl-D-mannonic-δ-lactone, 1 cc. of phenylhydrazine, 0.2 cc. of glacial acetic acid and 30 cc. of water was heated for three hours on the steam-bath. The solvent was removed by concentration *in vacuo* and an alcoholic solution of the residual sirup gradually deposited the phenylhydrazide. The compound was recrystallized from 4 parts of alcohol as fine needles which melted at 146–147° (cor.) and showed $[\alpha]^{20}\mathrm{D}$ +10.6° in water (*c*, 0.8). The yield was 1.2 g. (77%).

Anal. Calcd. for $C_{13}H_{20}O_6N_2$: C, 51.99; H, 6.71; OCH_3, 10.33. Found: C, 51.92; H, 6.82; OCH_3, 10.35.

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(9) Schinle, *Ber.*, **65**, 317 (1932).

(10) Phelps and Hudson, THIS JOURNAL, **48**, 506 (1926).

(11) Isbell and Frush, *J. Research Natl. Bur. Standards*, **24**, 131 (1940).

4-Methyl-D-mannonic Amide.—A solution of 5 g. of 4-methyl-D-mannonic-δ-lactone in 15 cc. of liquid ammonia was allowed to evaporate to dryness at room temperature and the residue (5.4 g., quantitative) was recrystallized from 12 parts of 50% alcohol. The pure amide crystallized in the form of prisms, melting at 171–172° (cor.) and showing $[\alpha]^{20}\text{D}$ +11.9° in aqueous solution (*c*, 0.8).

Anal. Calcd. for $C_7H_{15}O_6N$: C, 40.19; H, 7.23; OCH_3, 14.83; N, 6.70. Found: C, 40.16; H, 7.18; OCH_3, 14.95; N, 6.80.

1,2,3,5,6-Pentaacetyl-4-methyl-D-mannonic Amide.—One gram of finely powdered 4-methyl-D-mannonic-amide was added to an ice-cold solution of 10 cc. of acetic anhydride containing 2.0 g. of fused zinc chloride. The suspension was allowed to stand at 0° for two hours and then overnight at 20°, at which time solution was complete. The reaction mixture was poured upon crushed ice and the homogeneous solution was extracted with chloroform. The washed chloroform extract upon concentration gave a sirup which crystallized after standing in an evacuated desiccator for two weeks. The compound, recrystallized from 2 parts of water, separated in plates melting at 98–99° (cor.) and showing $[\alpha]^{20}\text{D}$ +11.4° in chloroform (*c*, 0.9). The yield was 1.2 g. (60%).

Anal. Calcd. for $C_{17}H_{25}O_{11}N$: C, 48.68; H, 6.01; CH_3CO, 51.3. Found: C, 48.67; H, 5.95; CH_3CO, 51.4.

4-Methyl-D-mannitol.—A solution of 10 g. of 4-methyl-D-mannose in 125 cc. of water was reduced for four hours at 100° under a pressure of 167 atm. of hydrogen in the presence of Raney nickel. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to a thick sirup; a solution of the sirup in 50 cc. of warm alcohol deposited 10.0 g. (91%) of fine needles, which, judging from their specific rotation of +15.4° in water and behavior on melting, were probably 4-methyl-D-mannitol monohydrate, as will now be explained. They melted with foaming at 86–87° (cor.), then resolidified and remelted at 133–134° (cor.). Upon standing for a few hours the hydrated compound apparently changed into anhydrous 4-methyl-D-mannitol and it could not again be obtained in hydrated condition even by recrystallization of the anhydrous form from water. The anhydrous substance also crystallized as needles, but it melted at 133–134° (cor.) and its rotation in aqueous solution (*c*, 2.0) was $[\alpha]^{20}\text{D}$ +16.7°.

Anal. Calcd. for $C_7H_{16}O_6$: C, 42.85; H, 8.22; OCH_3, 15.81. Found: C, 42.77; H, 8.24; OCH_3, 16.01.

1,2,3,5,6-Pentaacetyl-4-methyl-D-mannitol.—This compound was obtained by acetylation of the alcohol with acetic anhydride and pyridine in the usual manner. It crystallized from 9 parts of 25% alcohol as quadrilateral prisms melting at 85–86° (cor.) and showing $[\alpha]^{20}\text{D}$ +35.4° in chloroform (*c*, 0.8).

Anal. Calcd. for $C_{17}H_{26}O_{11}$: C, 50.24; H, 6.45; CH_3CO, 53.0. Found: C, 50.32; H, 6.63; CH_3CO, 53.4.

Di-isopropylidene-4-methyl-D-mannitol.—A solution of 2.0 g. of 4-methyl-D-mannitol in a mixture of 20 cc. of acetone and 0.2 cc. of concentrated sulfuric acid was allowed to stand at room temperature for forty-eight hours; the sulfuric acid was neutralized by agitating the reaction mixture with solid potassium carbonate, and the excess reagents and solid reaction products were removed by filtration. The sirup which resulted from the concentration of the filtrate was distilled in a micro distillation apparatus at a bath temperature of 155° and a pressure of 4 mm., and it yielded a distillate and a still residue of unchanged 4-methyl-D-mannitol. After standing for several days, the distillate solidified to a mass of fine needles, which, after recrystallization from 3 parts of isopentane, melted at 57–58° (cor.) and showed $[\alpha]^{20}\text{D}$ +9.0° in alcohol (*c*, 0.9). The yield was 1.0 g. (36%).

Anal. Calcd. for $C_{13}H_{24}O_6$: C, 56.50; H, 8.76. Found: C, 56.60; H, 8.68.

Summary

Crystalline 4-methyl-D-mannose has been obtained by the complete acid hydrolysis of 2,3-isopropylidene-4-methyl-D-mannosan$<1,5>\beta<1,6>$. The new sugar crystallizes as an alpha form and resembles α-D-mannose in magnitude and sign of initial and equilibrium rotations and mutarotation rate; the specific rotation of its alpha methylglycoside and alpha acetate are also similar to those of the corresponding derivatives of D-mannose. Several other derivatives are described.

BETHESDA, MD. RECEIVED OCTOBER 30, 1942