

PREPARATION OF THE METHYL D-GALACTOPYRANOSIDES*

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Directions are given for a simple, reproducible preparation of methyl α - and methyl β -D-galactopyranoside by the Fischer method.¹ The initial separation affords the two compounds, 97–98% pure, in yields of 41 and 15% respectively, raised to about 58 and 21% by re-equilibration of the residual syrup that contains methyl galactofuranosides.

The preparation of the methyl galactopyranosides has been described many times. The yields obtained by the Fischer method and the details of the separation of the pure isomers vary widely, and at least some of the published procedures have proved to be capricious and unreliable in this and other laboratories. For example, Dale and Hudson² reported a clean separation of α and β isomers when the crude, syrupy mixture of methyl galactosides was dissolved in isopropyl alcohol, the α isomer separating first, as the monohydrate. In other hands,³ this caused the two pyranosides to crystallize as a mixture, and when the method was tried in this laboratory the β isomer separated first, but both isomers were very impure.

The conflicting results were probably caused by different amounts of water in solvents, although it is possible that both isomers may exist in more than one crystalline form. The α isomer seems to crystallize only as a monohydrate. It showed no tendency to crystallize in anhydrous form from anhydrous solvents, and no unequivocal statement that this has been achieved could be found in the literature. The monohydrate could usually be crystallized from organic solvents containing water, but the results were sometimes unpredictable. The hydrated α form did crystallize excellently from concentrated solutions in water alone,^{1,4} and showed a remarkable power to exclude isomers and coloured impurities. The β isomer, which does not form a hydrate, showed the opposite behaviour—it was very soluble in water, but crystallized readily from anhydrous ethanol. The use of water and then ethanol as solvent provided reproducible conditions under which the two pyranosides could be isolated from the crude mixture of methyl galactosides obtained by the Fischer method. The β form could be isolated first,⁵ by using ethanol before water. The yield of β form was then lower, but the method is more convenient than the four-stage preparation⁶ of the β form through tetra-*O*-acetyl- α -D-galactopyranosyl

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¹ Fischer, E., and Beensch, L., *Ber. dt. chem. Ges.*, 1894, **27**, 2478; Fischer, E., *Ber. dt. chem. Ges.*, 1895, **28**, 1145.

² Dale, J. K., and Hudson, C. S., *J. Am. Chem. Soc.*, 1930, **52**, 2534.

³ Sorkin, E., and Reichstein, T., *Helv. Chim. Acta*, 1945, **28**, 1.

⁴ Voss, W., *Liebigs Ann.*, 1931, **485**, 283.

⁵ Reber, F., and Reichstein, T., *Helv. Chim. Acta*, 1945, **28**, 1164.

⁶ Khare, M. P., Schindler, O., and Reichstein, T., *Helv. Chim. Acta*, 1962, **45**, 1547.

bromide. The syrupy residue from the separation of the pyranosides should be a source of the methyl galactofuranosides, which can be separated on strong-base, ion-exchange resins.⁷

Both isomers were easily recrystallized to constant optical rotation and were probably obtained quite pure. The reported rotation and melting point for the α isomer each covers a fair range, and sometimes insufficient details are given of the history and probable purity of the specimen. Only one crystalline form of it could be obtained in the present work, a monohydrate that was quite stable at room temperature and had $[\alpha]_D^{25} +178.1^\circ$ in water (0.1M), corresponding to $[\alpha]_D^{25} +194.6^\circ$ for the anhydrous form, which agrees well with several published figures.^{1,2,4,8-10} The specific rotation is apparently slightly higher in more concentrated solutions.^{1,4,8} The melting point of the hydrate varied with the method used for determining it (see Experimental) and was lower if partial dehydration could occur in the process. The highest melting point observed by us for anhydrous α isomer, obtained by careful dehydration of the hydrate, was $116-116.5^\circ$, but Bell and Greville¹⁰ have reported $123-125^\circ$. The specific rotation of the β isomer in water was practically zero in agreement with published statements.^{1-3,8} Its melting point was reproducible but not sharp, $177-180^\circ$, and it formed an unusually viscous melt. A melting point of $184-185^\circ$ has been reported,⁶ and it is possible that the β isomer also exists in more than one crystalline form.

Experimental

Evaporation of solutions was conducted in a rotary vacuum still in a bath at $70-75^\circ$. A stout-walled flask with a fairly shallow layer of solution should be used for recrystallization of methyl α -D-galactopyranoside, which forms very hard crusts of massive crystals. Optical rotations were measured for 0.1M aqueous solutions in 2-dm tubes. All results were confirmed in repeated experiments.

Separation of Methyl D-Galactopyranosides: α Isomer First

Reagent-grade, anhydrous D-galactose (50 g) was boiled vigorously under reflux with a solution of hydrogen chloride in pure methanol (2% w/v, 400 ml) until it dissolved (20-30 min), then gently for 7 hr (boiling for 12 hr gave the same result). The cooled solution was shaken with powdered, precipitated lead carbonate (50 g) for 3 hr, and was then neutral to moist litmus paper. Lead salts were removed with the aid of Celite and washed with methanol (70 ml), and the total filtrate was evaporated to an amber syrup (60 g). The warm syrup was mixed with water (15 ml) and rapidly deposited coarse crystals of methyl α -D-galactopyranoside monohydrate. Crystallization was completed during 20 hr at room temperature and 24 hr at 5° . The syrupy mother liquor was removed from the crystals by suction without difficulty (cooled 7-cm sintered-glass funnel) and the solid was washed by carefully stirring it, under gentle suction, with small portions of 80% ethanol (chilled to 5° ; total, 25 ml), followed by pure ethanol (2×8 ml). The air-dried solid (24.6 g) was only faintly yellow; $[\alpha]_D^{25} +174^\circ$. If the solution had been stirred during crystallization it gave fine crystals, more difficult to wash.

The mother liquor and washings were evaporated to a syrup and two portions of anhydrous ethanol (each 50 ml) were mixed with and evaporated from it. The dehydrated syrup (37 g) was

⁷ Austin, P. W., Hardy, F. E., Buchanan, J. G., and Baddiley, J., *J. Chem. Soc.*, 1963, 5350.

⁸ Riiber, C. N., Minsas, J., and Lyche, R. T., *J. Chem. Soc.*, 1929, 2173.

⁹ Ault, R. G., Haworth, W. N., and Hirst, E. L., *J. Chem. Soc.*, 1935, 1012.

¹⁰ Bell, D. J., and Greville, G. D., *J. Chem. Soc.*, 1955, 1136.

dissolved in hot ethanol (150 ml) and the warm solution was seeded with methyl β -D-galactopyranoside. Crystallization occurred in crusts of small, pale brown grains during 4 hr at room temperature and 4 days at 5°. The product (8.6 g) had m.p. 170–174°, $[\alpha]_D^{23} + 3.7^\circ$.

The final mother liquors from two preparations were combined and evaporated to a syrup, from which methanol was repeatedly distilled (total 100 ml). The syrup (48 g) was boiled under reflux for 7 hr with methanol containing hydrogen chloride (2% w/v, 350 ml) and the solution was worked up as before. The syrupy mixture of methyl galactosides was deep reddish brown, but the methyl α -D-galactopyranoside hydrate (18.7 g, $[\alpha]_D^{23} + 177^\circ$) and methyl β -D-galactopyranoside (6.1 g, $[\alpha]_D^{23} + 3.0^\circ$) separated from it showed little colour.

Separation of Methyl D-Galactopyranosides: β Isomer First

The mixture of methyl galactosides obtained from D-galactose (50 g) as above was dissolved in hot, anhydrous ethanol (250 ml) and the warm solution was seeded with the β isomer. After storage at room temperature for 3 hr and at 5° for 4 days, it afforded practically colourless grains of methyl β -D-galactopyranoside (6.1 g), $[\alpha]_D^{23} + 6.0^\circ$. The syrup obtained by evaporation of the mother liquor was mixed with water (14 ml) and afforded methyl α -D-galactopyranoside monohydrate (24.9 g) with $[\alpha]_D^{23} + 176^\circ$. The syrupy residues isolated from the final mother liquors of two such separations were combined and, after several portions of methanol had been evaporated from them, re-equilibrated in methanol containing hydrogen chloride. Additional crops of β isomer (5.2 g) and hydrated α isomer (21.4 g) were obtained, of the same quality as before.

Pure Methyl α -D-Galactopyranoside

Crude monohydrate (100 g) was dissolved in water (50 ml) at the boiling point and the pale yellow solution was filtered if necessary (by suction), cooled to about 50°, seeded, and allowed to crystallize, with occasional gentle swirling, during 1 day at room temperature and 1 day at 5°. The large, colourless, rhombic crystals were collected as in the first experiment, washed with chilled 85% ethanol (50 ml) and with pure ethanol (40 ml), and dried in air. The pure monohydrate recovered (73.5 g) showed $[\alpha]_D^{23} + 178.1^\circ$, not altered by further recrystallization. The mother liquors and washings were evaporated to a semi-solid residue that was recrystallized from water at the same concentration, affording a second crop of faintly yellow solid (18.0 g) with $[\alpha]_D^{23} + 176.3^\circ$.

The melting point of the pure monohydrate was determined on a large sample in a sealed capillary tube, on a small sample in an open capillary tube, and on the Fisher-Johns hotplate. The various stages of melting for the respective treatments were: initial change at 99, 84, 75°; partial liquefaction by 105, 90, 92°; main melting over range 107–113, 102–103, 96–99°. When finely powdered, pure monohydrate was dehydrated at 83° at 2 mm pressure over phosphoric oxide, it showed the theoretical loss (8.5%) in 8 hr. Partial fusion occurred during dehydration, and the anhydrous residue had m.p. 107–112°. If dehydration was conducted at 61° instead of 83°, it required about 36 hr (5% loss in 10 hr), no fusion occurred, and the anhydrous residue had m.p. 116–116.5°. The residue gained weight corresponding to re-formation of the monohydrate when exposed to the air for 1 week, but the rehydrated material still had m.p. 116–116.5° (Fisher-Johns hotplate).

Pure Methyl β -D-Galactopyranoside

Crude β isomer was dissolved in boiling absolute ethanol (30 ml/g) and the solution was decolorized (Darco G-60), seeded, and allowed to crystallize at room temperature for 5 hr and at 5° for 1 day. The purified material (79% recovered) was obtained as coarsely granular or acicular crystals, with m.p. 177–180° and $[\alpha]_D^{23} - 0.3$ to -0.5° .