

# Synthesis of Methyl- $\alpha$ -maltoside

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Anomerization of methyl-hepta-*O*-acetyl- $\beta$ -maltoside with titanium tetrachloride followed by deacetylation gave methyl- $\alpha$ -maltoside and methyl- $\beta$ -maltoside in the ratio 7 : 1. Reaction of maltose with methanol under catalytic action of ion-exchanger Amberlite IR-120 led to the formation of methyl- $\alpha$ , $\beta$ -D-glucoside as the main product, and small amounts of methyl- $\beta$ -maltoside and methyl- $\alpha$ -maltoside in the ratio 3 : 1. Methyl- $\alpha$ -maltoside was separated from the  $\beta$ -anomer by ion-exchange chromatography on Dowex 1.

Methyl-hepta-*O*-acetyl- $\beta$ -maltoside was prepared on treatment of per-*O*-acetyl-maltosylbromide with methanol [1, 2]. Using in this reaction per-*O*-acetylmaltosylchloride, *Freudenberg et al.* [3] obtained a methyl-per-*O*-acetylmaltoside having rotatory power different from that of methyl-per-*O*-acetyl- $\beta$ -maltoside. Methyl- $\alpha$ -maltoside was found to be formed on reaction of maltose with methanol in the presence of hydrogen chloride (yield unspecified) [4] and was also isolated from the products of reaction of maltodextrine and methyl- $\alpha$ , $\beta$ -D-glucoside catalyzed enzymically [5, 6]. *Inoue* and co-workers [7] prepared methyl-per-*O*-acetyl- $\alpha$ -maltoside by anomerization of the  $\beta$ -anomer catalyzed with antimony pentachloride but not with titanium tetrachloride or selenium tetrachloride. However, the anomerization of methyl-per-*O*-acetyl- $\beta$ -cellobioside catalyzed with titanium tetrachloride, described by *Pascu* [8], afforded 25% of the  $\alpha$ -anomer and 50% of an unidentified by-product, which was reported to be the only product of the same reaction catalyzed with antimony pentachloride or selenium tetrachloride elsewhere [9].

The present work deals with anomerization of methyl-per-*O*-acetyl- $\beta$ -maltoside and methyl-per-*O*-acetyl- $\beta$ -cellobioside with titanium tetrachloride as catalyst. We have found that this reaction is suitable for preparation of larger quantities of the corresponding  $\alpha$ -anomers.

## Experimental

Specific rotations were measured with a Bendix—Ericson polarimeter, type 143 A. Melting points were determined on a Kofler apparatus. The sugars were identified by paper chromatography on Whatman No. 1 paper in *n*-butanol—ethanol—water (5:1:4, v/v) and detected with periodate—benzidine reagent [10], or by gas—liquid chromatography as the per(trimethylsilyl) derivatives [11] with a Chrom III gas chromatograph (Labo-

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ratorní přístroje, n. p., Czechoslovakia) with a hydrogen microflame ionization detector. A column (150 × 0.3 cm) packed with 5% XE-60 on Chromosorb W (AWSi, 80/100 mesh) was used at the temperature 208°C and the nitrogen flow rate 65 ml/min. A satisfactory separation of methyl- $\alpha$ - and methyl- $\beta$ -maltoside on paper was achieved only after 10 day continuous flow of the elution system. Fractionation of reaction mixtures was carried out either by column chromatography on cellulose (Whatman CF 12, 75 × 4 cm) using the same elution system as on paper chromatography, or by ion-exchange chromatography on Dowex 1X8 (OH-form, 100–200 mesh) column (80 × 3.8 cm) eluted with water.

### *Methyl- $\alpha$ -maltoside*

#### A. Methylglycosidation of maltose catalyzed with hydrogen chloride

A solution of 5 g of dry maltose in 100 ml of anhydrous methanol containing 0.1% of hydrogen chloride was allowed to stand at 50°C for 42 hours. The examination of the reaction mixture by paper chromatography showed that the portion of methylmaltosides in whole amount of sugars (maltose, methyl- $\alpha$ ,D-glucoside, glucose) represented less than 10%.

#### B. Methylglycosidation of maltose in the presence of ion-exchanger IR-120 as catalyst

A mixture of 20 g of dry maltose, 20 g of Amberlite IR-120 (H<sup>+</sup>-form) in 500 ml of anhydrous methanol was boiled for 16 hours. Paper chromatography of the reaction mixture revealed the presence of maltose ( $R_{\text{Glc}}$  0.2–0.25), methyl- $\alpha$ -maltoside ( $R_{\text{Glc}}$  0.68), methyl- $\beta$ -maltoside ( $R_{\text{Glc}}$  0.84), glucose, methyl- $\alpha$ ,D-glucoside ( $R_{\text{Glc}}$  2.65) and 1,6-anhydro-glucose ( $R_{\text{Glc}}$  3.5). After removing the ion-exchanger the solution was evaporated to dryness and dissolved in water (300 ml). This solution was treated for 3 days with 2 g of baker's yeast to remove glucose and unreacted maltose. After filtration and treatment with charcoal the solution was evaporated to dry residue (19 g). This was fractionated on cellulose column to give 12.6 g of methyl- $\alpha$ ,D-glucoside and 1.8 g of the mixture of methyl- $\beta$ - and methyl- $\alpha$ -maltoside in the ratio 3 : 1,  $[\alpha]_{\text{D}}^{24} + 103^\circ$  (c 2.5, water). The methylmaltoside anomers were separated on Dowex 1 column as described in the following section (procedure C).

#### C. Anomerization of methyl-per-O-acetyl- $\beta$ -maltoside with titanium tetrachloride

7 g of methyl-per-O-acetyl- $\beta$ -maltoside [7], m.p. 128–130°C,  $[\alpha]_{\text{D}}^{24} + 55.1^\circ$  (c 2, chloroform), was dissolved in anhydrous chloroform (100 ml) and 40 ml of chloroform containing 1.3 ml of titanium tetrachloride were added. After boiling the mixture under a reflux condenser for 6 hours, the solution was poured into ice-water mixture, the chloroform layer was washed with water, separated, dried with sodium sulfate and evaporated. The dry amorphous powdery residue (6.7 g),  $[\alpha]_{\text{D}}^{24} + 128^\circ$  (c 1.5, chloroform) was dissolved in methanol (60 ml) and after adding 6 ml of 0.2 M sodium methanolate the solution was left to stand at room temperature for 5 hours. The solution was then neutralized with solid carbon dioxide, treated with charcoal and evaporated to dryness. The dry residue (3.6 g) was dissolved in 30 ml of anhydrous ethanol and crystallized at room temperature

to give a crystalline mixture of methyl- $\alpha$ - and methyl- $\beta$ -maltoside,  $[\alpha]_D^{24} + 148^\circ$  (*c* 1.5, water), having  $R_{G1c}$  0.85 and 0.68 on paper chromatography and retention times 4.7 and 5.2 minutes of the per(trimethylsilyl) derivatives on gas chromatography. The ratio of  $\alpha$ - to  $\beta$ -anomer was found to be 7 : 1. This value did not change after recrystallization from ethanol or isopropanol.

The deacetylated product (11 g) was fractionated on a Dowex 1 column eluted with water at the rate 30 ml/hour. Evaporation of the fraction eluted between 1.9 and 3.5 l of the eluant gave chromatographically homogeneous methyl- $\alpha$ -maltoside,  $[\alpha]_D^{24} + 176^\circ$  (*c* 1.2, water). Evaporation of the fraction eluted between 3.5 and 5.0 l of the eluant afforded 1.5 g of the mixture of methyl- $\alpha$ - and methyl- $\beta$ -maltoside in the ratio 1 : 1. The same operation with the eluant between 5.0 and 7.5 l gave 1.1 g of methyl- $\beta$ -maltoside,  $[\alpha]_D^{24} + 80^\circ$  (*c* 1.2, water). These data were obtained for a sample of methyl- $\alpha$ -maltoside dried over  $P_2O_5$  in vacuum (0.01 Torr) at 25°C for 24 hours:  $[\alpha]_D^{24} + 179.6 \pm 0.5^\circ$  (*c* 1, water),  $CH_3O$  content 8.86% (calculated 8.71%).

On crystallization from anhydrous ethanol and isopropanol, methyl- $\alpha$ -maltoside forms crystalline alcoholates with m.p. 60–80°C. Amorphous methanolate, having  $[\alpha]_D^{24} + 175^\circ$  (*c* 1, water), was isolated evaporating the methanolic solution of methyl- $\alpha$ -maltoside.

For  $C_{13}H_{24}O_{11} \cdot 1/2CH_3OH$  (372.34) calculated: 43.53% C, 7.04% H, 12.51%  $CH_3O$ ; found: 43.40% C, 7.53% H, 12.55%  $CH_3O$ .

The yield of the chromatographically homogeneous methyl- $\alpha$ -maltoside calculated for methyl-per-*O*-acetyl- $\beta$ -maltoside represents 75%. Literature data for methyl- $\alpha$ -maltoside: [4] m.p. 201–202°C,  $[\alpha]_D^{16} + 183^\circ$  (*c* 1, water); [5]  $[\alpha]_D + 180^\circ$  (water); [6]  $[\alpha]_D + 184^\circ$  (water).

#### *Methyl-hepta-O-acetyl- $\alpha$ -maltoside*

A solution of methyl- $\alpha$ -maltoside (2 g) in the mixture of 10 ml of acetanhydride and 14 ml of pyridine was kept at room temperature for 3 days and then poured into ice-water mixture and extracted with chloroform. The chloroform solution was washed with water, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated to dryness to give 2.9 g of amorphous methyl-hepta-*O*-acetyl- $\alpha$ -maltoside, m.p. 66–69°C,  $[\alpha]_D^{24} + 134.0^\circ$  (*c* 2, chloroform); lit. [9] m.p. 68°C,  $[\alpha]_D^{20} + 130.6^\circ$  (chloroform).

The product was homogeneous as shown by chromatography and did not crystallize from methanol, ethanol, ether—petroleum ether, and ethyl acetate—petroleum ether.

#### *Methyl-hepta-O-acetyl- $\alpha$ -cellobioside*

Methyl-hepta-*O*-acetyl- $\beta$ -cellobioside (7 g) was anomerized with titanium tetrachloride essentially in the same way as methyl-per-*O*-acetyl- $\beta$ -maltoside. After evaporating chloroform, the dry residue was crystallized from 96% ethanol to give 4.3 g of crystalline methyl-hepta-*O*-acetyl- $\alpha$ -cellobioside (60% yield). Recrystallization from ethanol gave a product with double melting point 165°C and 183–184°C,  $[\alpha]_D^{24} + 50.5^\circ$  (*c* 1.5, chloroform); lit. [8] m.p. 185°C,  $[\alpha]_D^{20} + 55.7^\circ$  (chloroform).

For  $C_{27}H_{38}O_{18}$  (650.57) calculated: 4.77%  $CH_3O$ ; found: 5.14%  $CH_3O$ .

Methyl- $\alpha$ -cellobioside was obtained by Zemplen's deacetylation of methyl-hepta-*O*-acetyl- $\alpha$ -cellobioside. The product was homogeneous as shown by paper chromatography ( $R_{G1c}$  0.77) and by gas—liquid chromatography (retention time for the per(trimethylsilyl) derivative 4.7 minutes). Those values for the  $\beta$ -anomer:  $R_{G1c}$  0.66, retention time 5.9 minutes.

## Results and Discussion

*Matsubara* [4] has described the preparation of methyl- $\alpha$ -maltoside by glycosidation under catalytic action of hydrogen chloride. He reported the product crystallized directly from the reaction mixture. Investigating this procedure we found that the reaction mixture contained less than 10% of methylmaltosides of overall sugars. Methylglycosidation with Amberlite IR-120 as catalyst afforded a mixture of methyl- $\beta$  and methyl- $\alpha$ -maltoside in the ratio 3 : 1 in about 10% yield only. The main product of this reaction was found to be methyl- $\alpha$ ,D-glucoside as a result of the splitting of the  $\alpha(1 \rightarrow 4)$  linkage of maltose. Small amounts of glucose, maltose and 1,6-anhydroglucose were also present in the final reaction mixture.

The treatment of methyl-per-*O*-acetyl- $\beta$ -maltoside with titanium tetrachloride gave an equilibratory mixture of methyl-per-*O*-acetyl- $\alpha$ -maltoside and the  $\beta$ -anomer in the ratio 7 : 1 having  $[\alpha]_D^{24} +128^\circ$  (chloroform); after deacetylation  $[\alpha]_D^{24} +148^\circ$  (water). Prolonging the anomerization time from 6 hours to 12 hours the ratio of the anomers did not change.

The fractionation of the deacetylated mixture of the anomers on a Dowex 1 column gave chromatographically homogeneous methyl- $\alpha$ -maltoside,  $[\alpha]_D^{24} +176^\circ$  (water), in 75% yield. Acetylation of this compound gave amorphous methyl-hepta-*O*-acetyl- $\alpha$ -maltoside, m.p. 66–69°C,  $[\alpha]_D^{24} +134.0^\circ$  (chloroform). This derivative prepared by anomerization of the  $\beta$ -anomer with antimony pentachloride but not with titanium tetrachloride or selenium tetrachloride had  $[\alpha]_D^{20} +130.6^\circ$  (chloroform) and m.p. 68°C [7].

Specific rotation of the equilibratory mixture of methyl-hepta-*O*-acetyl- $\alpha$ - and methyl-hepta-*O*-acetyl- $\beta$ -maltoside obtained by anomerization of the  $\beta$ -anomer with titanium tetrachloride was by 2.6° lower than that of the product obtained by treatment with antimony pentachloride [7]. However, acetylation of the chromatographically homogeneous methyl- $\alpha$ -maltoside gave a product having  $[\alpha]_D$  higher by 3.4°. It can be assumed therefore that the methyl-hepta-*O*-acetyl- $\alpha$ -maltoside obtained by anomerization with antimony pentachloride [7] also contained as an impurity the  $\beta$ -anomer. Based on these results it may be pointed out that the „new maltoside“,  $[\alpha]_{518} +117^\circ$  (water), prepared by *Freudenberg et al.* [3], is apparently a mixture of methyl- $\alpha$ - and methyl- $\beta$ -maltoside. The same fact is indicated by the rotatory power of the fully acetylated derivative,  $[\alpha]_{518} +101.6^\circ$  (ethylene tetrachloride) [3].

Contrary to the report [7] in which titanium tetrachloride was found as ineffective in the transformation of methyl-per-*O*-acetyl- $\beta$ -cellobioside, we have obtained methyl-hepta-*O*-acetyl- $\alpha$ -cellobioside using this catalyst in 60% yield by direct crystallization of the reaction mixture.

## References

1. Newth F. H., Nicholas S. D., Smith F., Wiggins L. F., *J. Chem. Soc.* **1949**, 2550.
2. Wolfrom M. L., Yen-Lung Hung, Chakravarty P., Yuen C. U., Horton D., *J. Org. Chem.* **31**, 2227 (1966).
3. Freudenberg K., Hochstetter H., Engels H., *Ber.* **58**, 666 (1925).
4. Matsubara S., *Bull. Chem. Soc. Japan* **34**, 718 (1961).
5. Peat S., Whelan W. J., Jones G., *J. Chem. Soc.* **1957**, 2490.
6. Pazur J. H., Marsh J. M., Ando T., *J. Amer. Chem. Soc.* **81**, 2170 (1959).

7. Inoue Y., Onodera K., Karasawa I., Nishisawa Y., *J. Agr. Chem. Soc. Japan* **26**, 631 (1952); *Chem. Abstr.* **49**, 872g (1955).
8. Pacsu E., *J. Amer. Chem. Soc.* **52**, 2570 (1930).
9. Inoue Y., Onodera K., Karasawa I., Nishisawa Y., *J. Agr. Chem. Soc. Japan* **26**, 537 (1952); *Chem. Abstr.* **49**, 872e (1955).
10. Cifonelli J. A., Smith F., *Anal. Chem.* **26**, 1132 (1954).
11. Sweeley C. C., Bentley R., Makita M., Wells W. W., *J. Amer. Chem. Soc.* **85**, 2497 (1963).

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