Synthesis of α-Maltosides. I

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Although a large number of glycoside derivatives[1,2] have been synthesized, many attempts to prepare various α-maltoside derivatives have not been promising[3]. At present, non-crystalline phenyl-α-maltoside and methyl-α-maltoside synthesized by Fischer and Bergmann[4], and also by Helferich and Peterson[5] have only been reported. After many trials, the author has succeeded in the synthesis of various α-maltosides.

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[1] G. Wagner, *Arch. Pharm.*, **290**, 625 (1957).
[2] G. Wagner, ibid., **291**, 278 (1958).
[3] G. Zemplén, *Ber.*, **60**, 1555 (1935).
[4] E. Fischer, M. Bergmann and A. Rabe, ibid., **53**, 2362 (1920).
[5] B. Helferich and S. R. Peterson, ibid., **68**, 790 (1935).

The purpose of this study is to obtain some fundamental information concerning the substrate specificity[6-8]; namely, it is to investigate the influence of substituents in the phenyl group on the enzymatic hydrolysis of phenyl-α-maltoside by taka-amylase A[9], and also the mode of interaction of the enzyme activity with structural changes in their substrates. From this point of view, the detailed descriptions of the synthesis are briefly described in this paper.

Experimental

Octaacetylmaltose[3]. — To a solution of 20 g. of anhydrous maltose dissolved in 100 cc. of acetic anhydride, 20 g. of fused sodium acetate was added and the mixture was gently heated. The color of the solution changed from yellow through brown to dark brown. When the violent initial reaction ceased, the solution was heated under stirring for two hours at 100°C in a water bath, poured onto crushed ice, and then diluted with water. The separated yellowish brown oil was allowed to stand overnight in a refrigerator. The crystals which separated out were collected by filtration, dissolved in chloroform, and washed well with water, and dried over anhydrous calcium chloride. The solvent was then evaporated under reduced pressure. The solid was dissolved in hot methanol, filtrated, and the crystalline residue which was obtained from the mother liquor was recrystallized from methanol, giving 14 g. of octaacetylmaltose in the form of colorless crystals, m. p. 158~159°C, $[\alpha]_D^{19}=+124°$ (c 1.0, in chloroform).

Heptaacetylphenyl-α-maltoside[4,5].—The mixture of 68 g. (1 mol.) of octaacetylmaltose, 57 g. (6 mol.) of phenol and 10 g. of fused zinc chloride was heated under violent stirring for two and a half hours at 100°C in a water bath. After cooling, the dark brown oily substance was diluted with water, to remove the zinc chloride. To the solution mixture, benzene was added and the benzene extract was well washed successively with water, with 1 N aqueous sodium hydroxide, with water until it became colorless, and finally dried over anhydrous calcium chloride. The solvent was then evaporated under reduced pressure, leaving a yellowish brown oil. The oily residue was crystallized from 100 cc. of ethanol to give colorless crystals. The crude crystals were combined and recrystallized from ethanol-dioxane mixture (contained 10% dioxane), m. p. 184~184.5°C, $[\alpha]_D^{20}=+170.2°$ (c 1.0, in chloroform).

Found: C, 53.92; H, 5.63. Calcd. for $C_{32}H_{40}O_{18}$: C, 53.91; H, 5.66%.

Phenyl-α-maltoside. — A solution of 10 g. of heptaacetylphenyl-α-maltoside dissolved in 100 cc. of a mixture of absolute methanol and chloroform (1 : 1, by volume) was saturated with ammonia gas under cooling. After being kept more than four hours at room temperature, the methanol and ammonia were removed under reduced pressure. The syrupy residue was dissolved in a small quantity of absolute ethanol, and the precipitate was obtained by adding ether. After removing the supernatant solvents, the residue was then successively treated in the same manner as described above to afford pure crystals. The precipitate obtained was combined and washed with ether. This crude crystalline phenyl-α-maltoside was crystallized from absolute ethanol. The yield was 4.75 g., m. p. 202~204°C, $[\alpha]_D^{14.5}=+211°$ (c 1.3, in water).

Found: C, 51.57; H, 6.25. Calcd. for $C_{18}H_{26}O_{11}$: C, 51.65; H, 6.27%.

The ultraviolet absorption of the product showed maxima at 266 mμ in water.

Heptaacetyl-*p*-nitrophenyl-α-maltoside. — To a mixture of 20 cc. of glacial acetic acid and 10 cc. of acetic anhydride, 5 g. of heptaacetylphenyl-α-maltoside was added. A mixture of 25 g. of concentrated sulfuric acid (95%) and 25 g. of glacial acetic acid was added under cooling and stirring. Then to this solution, a mixture of 5 g. of nitric acid (sp. gr. 1.38) and 10 cc. of glacial acetic acid was added dropwise, while stirring vigorously. The mixture was kept for four hours at room temperature, and poured into a large amount of ice and water. Within a few minutes a powdery white precipitate was separated, collected, washed completely with water, and dried over anhydrous calcium chloride. The yield of the crude substance was 4.83 g. The crude crystals were recrystallized from absolute ethanol, and the yield of heptaacetyl-*p*-nitrophenyl-α-maltoside was 4.75 g., m. p. 176~178°C, $[\alpha]_D^{14.5}=+223°$ (c 1.2, in chloroform).

Found: C, 50.71; H, 5.21; N, 1.83. Calcd. for $C_{32}H_{39}O_{20}N$: C, 50.74; H, 5.19; N, 1.85%.

***p*-Nitrophenyl-α-maltoside.** — The heptaacetyl-*p*-nitrophenyl-α-maltoside was deacetylated by dissolving in absolute methanol (200~300 cc. for 25 g.) and adding a freshly prepared solution of sodium methoxide (from sodium, 10~20 mg., and methanol, 10 cc.). The mixture was kept at room temperature overnight. The methanol was then removed under reduced pressure, and the oily substance was dissolved in 10 cc. of ethanol. The solid was obtained by adding ether, and was then successively treated in the same manner as described above to give pure maltoside crystals which were crystallized to constant melting point using, when possible, a mixture of ethanol-dioxane containing 10% of dioxane. The crude crystals were combined and recrystallized from absolute ethanol/petroleum ether, m. p. 145~146°C, $[\alpha]_D^{14.5}=+265°$ (c 1.0, in water).

Found: C, 46.72; H, 5.40; N, 3.04. Calcd. for $C_{18}H_{25}O_{13}N$: C, 46.63; H, 5.44; N, 3.02%.

The ultraviolet absorption of the product showed maxima at 310 mμ in water.

Other Substituted Heptaacetylphenyl-α-maltosides. — The corresponding phenols (0.3~0.4 mol.) and octaacetylmaltose (0.1 mol.) were heated with fused zinc chloride (0.5~2.0 g.) under violent stirring at 110~115°C for 1.5 to 2 hr. The cooled oily product was diluted with water and extracted with

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[6] R. L. Nath and H. N. Rydon, *Biochem. J.*, **57**, 1 (1954).

[7] S. Matsubara, *J. Biochem.*, **49**, 226 (1961).

[8] S. Matsubara, ibid., **49**, 232 (1961).

[9] S. Matsubara, T. Ikenaka and S. Akabori, ibid., **46**, 425 (1959).

benzene to remove zinc chloride. The benzene solution was washed with water, and then repeatedly with 5% aqueous sodium hydroxide until the washings were colorless. The solution was again washed with water and dried over anhydrous calcium chloride. The solvent was then evaporated under reduced pressure, leaving a dark yellowish brown oil. The oily residue was crystallized from suitable solvents to give colorless crystals. The crude crystals were recrystallized from one more suitable solvent.

Other Substituted Phenyl-α-maltosides. — The other substituted phenyl-α-maltoside was prepared by the same method as with phenyl-α-maltoside. The obtained crude product was recrystallized from suitable solvents.

***o*-Cresyl-α-maltoside.** — Recrystallized from ethanol/ether, m. p. 182∼183°C, $[\alpha]_D^{14.5}=+218°$ (*c* 1.0, in water).

Found: C, 52.50; H, 6.45. Calcd. for $C_{19}H_{28}O_{11}$: C, 52.75; H, 6.53%.

The heptaacetyl derivative recrystallized from ethanol, m. p. 175∼176°C $[\alpha]_D^{18}=+182°$ (*c* 1.5, in chloroform).

Found: C, 54.60; H, 5.89. Calcd. for $C_{33}H_{42}O_{18}$: C, 54.56; H, 5.83%.

***m*-Cresyl-α-maltoside.**—This was very hydroscopic and resisted all attempts at recrystallization; the product, dried at 100°C in vacuo over P_2O_5, had m. p. 93∼98°C, $[\alpha]_D^{17}=+235°$ (*c* 0.5, in water).

Found: C, 51.95; H, 6.42. Calcd. for $C_{19}H_{28}O_{11}$: C, 52.75; H, 6.53%.

The heptaacetyl derivative recrystallized from ethanol, m. p. 135∼140°C, $[\alpha]_D^{18}=+185°$ (*c* 1.5, in chloroform).

Found: C, 54.53; H, 5.84. Calcd. for $C_{33}H_{42}O_{18}$: C, 54.56; H, 5.83%.

***p*-Cresyl-α-maltoside.** — Recrystallized from ethanol/ether, m. p. 192∼194°C, $[\alpha]_D^{18}=+204°$ (*c* 0.5, in water).

Found: C, 53.02; H, 6.49. Calcd. for $C_{19}H_{28}O_{11}$: C, 52.75; H, 6.53%.

The heptaacetyl derivative recrystallized from ethanol, m. p. 180∼181°C, $[\alpha]_D^{18}=+201°$ (*c* 1.0, in chloroform).

Found: C, 54.55; H, 5.81. Calcd. for $C_{33}H_{42}O_{18}$: C, 54.56; H, 5.83%.

***o*-Isopropylphenyl-α-maltoside.** — Recrystallized from ethanol/petroleum ether, m. p. 163∼165°C, $[\alpha]_D^{18}=+222°$ (*c* 1.0, in water).

Found: C, 54.57; H, 7.10. Calcd. for $C_{21}H_{32}O_{11}$: C, 54.75; H, 7.01%.

The heptaacetyl derivative recrystallized from ethanol/petroleum ether, m. p. 110∼111°C, $[\alpha]_D^{18}=+205°$ (*c* 1.0, in chloroform).

Found: C, 55.67; H, 6.08. Calcd. for $C_{35}H_{46}O_{18}$: C, 55.71; H, 6.15%.

***p*-Isopropylphenyl-α-maltoside.** — Recrystallized from ethanol/petroleum ether, m. p. 175∼176°C, $[\alpha]_D^{14.5}=+216°$ (*c* 1.0, in water).

Found: C, 54.71; H, 6.98. Calcd. for $C_{21}H_{32}O_{11}$: C, 54.75; H, 7.01%.

The heptaacetyl derivative recrystallized from ethanol/petroleum ether, m. p. 145∼147°C, $[\alpha]_D^{14.5}=+192°$ (*c* 1.0, in chloroform).

Found: C, 55.61; H, 6.21. Calcd. for $C_{35}H_{46}O_{18}$: C, 55.71; H, 6.15%.

***o-tert*-Butylphenyl-α-maltoside.** — This was very hydroscopic and resisted all attempts at recrystallization; the product, dried at 100°C in vacuo over P_2O_5, had m. p. 60∼65°C, $[\alpha]_D^{18}=+232°$ (*c* 0.5, in water).

Found: C, 54.89; H, 7.18. Calcd. for $C_{22}H_{36}O_{11}$: C, 55.66; H, 7.23%.

The heptaacetyl derivative recrystallized from ethanol/petroleum ether, m. p. 212∼214°C, $[\alpha]_D^{18}=+202°$ (*c* 1.15, in chloroform).

Found: C, 56.26; H, 6.28. Calcd. for $C_{36}H_{48}O_{18}$: C, 56.22; H, 6.30%.

***p-tert*-Butylphenyl-α-maltoside.** — Recrystallized from ethanol, m. p. 170∼172°C, $[\alpha]_D^{18}=+228°$ (*c* 0.62, in water).

Found: C, 55.61; H, 7.20. Calcd. for $C_{22}H_{34}O_{11}$: C, 55.66; H, 7.23%.

The heptaacetyl derivative recrystallized from ethanol/petroleum ether, m. p. 78∼80°C, $[\alpha]_D^{18}=+211°$ (*c* 1.32, in chloroform).

Found: C, 56.21; H, 6.26. Calcd. for $C_{36}H_{48}O_{18}$: C, 56.22; H, 6.30%.

***p*-Isoamylphenyl-α-maltoside.** — Recrystallized from ethanol, m. p. 160∼163°C, $[\alpha]_D^{18}=+242°$ (*c* 0.65, in water).

Found: C, 56.48; H, 7.47. Calcd. for $C_{23}H_{36}O_{11}$: C, 56.52; H, 7.43%.

The heptaacetyl derivative recrystallized from ethanol/petroleum ether, m. p. 185∼187°C, $[\alpha]_D^{18}=+213°$ (*c* 1.2, in chloroform).

Found: C, 56.80; H, 6.44. Calcd. for $C_{37}H_{50}O_{18}$: C, 56.80: H, 6.44%.

***o*-Methoxyphenyl-α-maltoside.** — Recrystallized from ethanol, m. p. 165∼166°C, $[\alpha]_D^{14.5}=+184°$ (*c* 0.1, in water).

Found: C, 50.78; H, 6.27. Calcd. for $C_{19}H_{28}O_{12}$: C, 50.87; H, 6.30%.

The heptaacetyl derivative recrystallized from ethanol, m. p. 140∼141°C, $[\alpha]_D^{14.5}=+162°$ (*c* 0.1, in chloroform).

Found: C, 53.36; H, 5.65. Calcd. for $C_{33}H_{42}O_{19}$: C, 53.38; H, 5.70%.

***m*-Methoxyphenyl-α-maltoside.** — Recrystallized from ethanol, m. p. 172∼175°C, $[\alpha]_D^{14.5}=+193°$ (*c* 0.95, in water).

Found: C, 50.79; H, 6.26. Calcd. for $C_{19}H_{28}O_{12}$: C, 50.87; H, 6.30%.

The heptaacetyl derivative recrystallized from ethanol, m. p. 163∼165°C, $[\alpha]_D^{14.5}=+165°$ (*c* 0.95, in chloroform).

Found: C, 52.90; H, 5.59. Calcd. for $C_{33}H_{42}O_{19}$: C, 53.38; H, 5.70%.

***p*-Methoxyphenyl-α-maltoside.** — Recrystallized from ethanol, m. p. 187∼189°C, $[\alpha]_D^{14.5}=+201°$ (*c* 0.85, in water).

Found: C, 50.80; H, 6.28. Calcd. for $C_{19}H_{28}O_{12}$: C, 50.87; H, 6.30%.

The heptaacetyl derivative recrystallized from ethanol, m. p. 206∼208°C, $[\alpha]_D^{14.5}=+195°$ (*c* 3.1, in chloroform).

Found: C, 53.31; H, 5.78. Calcd. for $C_{33}H_{42}O_{19}$: C, 53.38; H, 5.70%.

***o*-Chlorophenyl-α-maltoside.**—Recrystallized from ethanol, m. p. 193∼196°C, $[\alpha]_D^{18}=+165°$ (*c* 0.5, in water).

Found: C, 47.68; H, 5.60; Cl, 7.84. Calcd. for $C_{18}H_{25}O_{11}Cl$: C, 47.72; H, 5.57; Cl, 7.83%.

The heptaacetyl derivative recrystallized from ethanol/petroleum ether, m. p. 195~197°C, $[\alpha]_D^{18}=+154°$ (*c* 2.3, in chloroform).

Found: C, 51.38; H, 5.23; Cl, 4.68. Calcd. for $C_{32}H_{39}O_{18}Cl$: C, 51.44; H, 5.27; Cl, 4.75%.

***p*-Chlorophenyl-*α*-maltoside.**—Recrystallized from ethanol, m. p. 205~206°C, $[\alpha]_D^{19}=+213°$ (*c* 1.13, in water).

Found: C, 47.70; H, 5.59; Cl, 7.81. Calcd. for $C_{18}H_{25}O_{11}Cl$: C, 47.72; H, 5.57; Cl, 7.83%.

The heptaacetyl derivative recrystallized from ethanol/petroleum ether, m. p. 197~199°C, $[\alpha]_D^{19}=+177°$ (*c* 1.5, in chloroform).

Found: C, 51.43; H, 5.25; Cl, 4.75. Calcd. for $C_{32}H_{39}O_{18}Cl$: C, 51.44; H, 5.27; Cl, 4.75%.

***o*-Nitrophenyl-*α*-maltoside.** — Recrystallized from ethanol/ether, m. p. 153~155°C, $[\alpha]_D^{14.5}=+245°$ (*c* 1.2, in water).

Found: C, 46.75; H, 5.48; N, 2.95. Calcd. for $C_{18}H_{25}O_{13}N$: C, 46.63; H, 5.44; N, 3.02%.

The heptaacetyl derivative recrystallized from ethanol, m. p. 185~187°C, $[\alpha]_D^{14.5}=+222°$ (*c* 1.5, in chloroform).

Found: C, 50.68; H, 5.15; N, 1.84. Calcd. for $C_{32}H_{39}O_{20}N$: C, 50.74; H, 5.19; N, 1.85%.

***m*-Nitrophenyl-*α*-maltoside.**—Recrystallized from ethanol/petroleum ether, m. p. 132~136°C, $[\alpha]_D^{14.5}=+261°$ (*c* 2.1, in water).

Found: C, 46.78; H, 5.39; N, 2.95. Calcd. for $C_{18}H_{25}O_{13}N$: C, 46.63; H, 5.44; N, 3.02%.

The heptaacetyl derivative recrystallized from ethanol, m. p. 170~171°C, $[\alpha]_D^{14.5}=+234°$ (*c* 1.8, in chloroform).

Found: C, 50.65; H, 5.11; N, 1.87. Calcd. for $C_{32}H_{39}O_{20}N$: C, 50.74; H, 5.19; N, 1.85%.

***α*-Naphthyl-, cyclohexyl- and *o*-, *m*-, *p*-Nitrophenyl-*α*-maltosides.** — The mixture of α-naphthol, cyclohexanol, *o*-, *m*-, or *p*-nitrophenol (0.3~0.4 mol.) and octaacetyl-β-maltose (0.1 mol.) were heated with fused zinc chloride (0.5~2.0 g.) and titanic chloride[10] (10 g.) under violent stirring at 110~115°C for 1.5 to 2 hr. by the same method as that described above.

***α*-Naphthyl - *α* - maltoside.** — Recrystallized from ethanol/ether, m. p. 156~158°C, $[\alpha]_D^{16}=+192°$ (*c* 1.5, in water).

Found: C, 56.41; H, 6.07. Calcd. for $C_{22}H_{28}O_{11}$: C, 56.39; H, 6.03%.

The heptaacetyl derivative recrystallized from ethanol/ether, m. p. 192~194°C, $[\alpha]_D^{16}=+185°$ (*c* 1.5, in chloroform).

Found: C, 56.71; H, 5.53. Calcd. for $C_{36}H_{42}O_{18}$: C, 56.67; H, 5.56%.

Cyclohexyl - *α* - maltoside. — Recrystallized from ethanol/ether, m. p. 112~115°C, $[\alpha]_D^{16}=+211°$ (*c* 1.5, in water).

Found: C, 50.85; H, 7.63. Calcd. for $C_{18}H_{32}O_{11}$: C, 50.91; H, 7.60%.

The heptaacetyl derivative recrystallized from ethanol, m. p. 152~155°C, $[\alpha]_D^{16}=+202°$ (*c* 1.5, in chloroform).

Found: C, 53.42; H, 6.50. Calcd. for $C_{32}H_{46}O_{18}$: C, 53.46; H, 6.46%.

Alkyl-*α*-maltosides.—Alkyl-α-maltosides could be prepared by warming maltose with an alcoholic solution of hydrochloric acid. Dry hydrogen chloride was passed into 200 g. of absolute alcohol, with ice cooling and exclusion of moisture, until the increase in weight amounted to 10 g. This solution 20 cc. was then diluted with 980 g. of alcohol, a 0.1% solution of hydrogen chloride being thus obtained. To this solution 50 g. of finely powdered anhydrous maltose was added, and the mixture was warmed at 50°C for forty-two hours, a clear solution being obtained after the first fifteen minutes' warming. It was well to attach a soda-lime tube to the upper end of the condenser, in order to exclude moisture. The clear pale yellow solution was cooled to 0°C, and crystallization was induced by scratching. After standing for two days at 0°C, the first crop was filtered by suction and was washed twice with 100 cc. portions of cold alcohol. The mother liquor and washings were returned to the flask and again warmed for forty-two hours under reflux at 50°C. The liquid was concentrated to 800 cc. and again chilled to 0°C, incubated and allowed to stand at 0°C for two days. The second crop of maltoside so obtained was filtered by suction and washed three times with each 100 cc. portion of cold alcohol. The mother liquor and washings were combined and concentrated to about 300 cc., chilled to 0°C, and again incubated and allowed to stand for two days. The resulting mush of crystals was dissolved in twice its weight of absolute ethanol, and, after standing for two days at 0°C, the third crop of maltoside was filtered. This was recrystallized from 2.5 parts of ethanol. The product was contaminated by slight traces of maltose and possessed a very faint reducing power towards Fehling's solution. For complete purification it was recrystallized (practically with neither loss nor change in melting point) from five parts of absolute ethanol with the use, if necessary, of decolorizing carbon.

Methyl-*α*-maltoside.—Recrystallized from ethanol, m. p. 201~202°C, $[\alpha]_D^{16}=+183°$ (*c* 1.0, in water).

Found: C, 43.77; H, 6.75. Calcd. for $C_{13}H_{24}O_{11}$: C, 43.80; H, 6.79%.

Isopropyl - *α* - maltoside. — Recrystallized from ethanol, m. p. 177~179°C, $[\alpha]_D^{16}=+166°$ (*c* 1.0, in water).

Found: C, 46.81; H, 7.32. Calcd. for $C_{15}H_{28}O_{11}$: C, 46.85; H, 7.35%.

***tert* - Butyl - *α* - maltoside.** — Recrystallized from ethanol, m. p. 188~190°C, $[\alpha]_D^{16}=+153°$ (*c* 1.0, in water).

Found: C, 48.18; H, 7.62. Calcd. for $C_{16}H_{30}O_{11}$: C, 48.21; H, 7.59%.

Isoamyl-*α*-maltoside. — Recrystallized from ethanol, m. p. 152~155°C, $[\alpha]_D^{16}=+143°$ (*c* 1.5, in water).

Found: C, 49.52; H, 7.80. Calcd. for $C_{17}H_{32}O_{11}$: C, 49.48; H, 7.82%.

Summary

Substituted phenyl-, α-naphthyl-, and cyclohexyl-α-maltosides were prepared from octaacetyl-β-maltose and the corresponding phenols. *p*-Nitrophenyl-α-maltoside was also prepared by

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[10] A. P. Jansen and P. G. A. B. Wydeveld, *Nature*, **182**, 525 (1958).

another method from the nitration of hepta-acetylphenyl-α-maltoside. Alkyl-α-maltosides were prepared from maltose and corresponding alcohol.

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