

Reactions of Methyl α -D-Mannoside with Aldehydes.

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The condensations of acetaldehyde, propaldehyde, and benzaldehyde with methyl α -D-mannoside give fully substituted compounds as the main products. However, a method is described for the preparation of methyl 4 : 6-*O*-ethylidene- α -D-mannoside.

In contrast with methyl α -D-glucoside and α -D-galactoside, which are readily converted into the 4 : 6-*O*-benzylidene compounds, the α -D-mannoside reacts with benzaldehyde at 150° to give a complex mixture from which Robertson (*J.*, 1934, 330) isolated one methyl 4 : 6-*O*-benzylidene- α -D-mannoside and two isomeric 2 : 3-4 : 6-di-*O*-benzylidene derivatives. By shaking the mannoside at room temperature with paraldehyde containing concentrated sulphuric acid, propaldehyde and concentrated hydrochloric acid, or benzaldehyde and zinc chloride, one isomer of each of the fully substituted di-*O*-ethylidene, di-*O*-propylidene, and di-*O*-benzylidene derivatives has now been prepared. Similar reactions of methyl α -D-glucoside with paraldehyde or propaldehyde give, by contrast, the methyl 4 : 6-*O*-alkylidene-2 : 3-oxydialkylidene- α -D-glucoside. The di-*O*-alkylidenemannosides contain no free hydroxyl groups, as they are recovered unchanged when their nitration by Honeyman and Morgan's general method (*Chem. and Ind.*, 1953, 1035) is attempted. By using a short reaction time it has been possible to prepare, reasonably, methyl 4 : 6-*O*-ethylidene- α -D-mannoside. This was difficult to purify to analytical standard because it separated from suitable solvents as a jelly, from which the last traces of solvent were difficult to remove. It was shown, nevertheless, to be a very pure single compound by its conversion in high yield into its crystalline diacetate, dinitrate, ditoluene-*p*-sulphonate, and dimethyl ether, and its regeneration in the same form from its diacetate. The specified structure was determined by methylation, hydrolysis, and benzoylation to methyl 2 : 3-di-*O*-methyl- α -D-

mannoside 4 : 6-dibenzoate, previously prepared by Robertson (*loc. cit.*). Methyl 2 : 3-4 : 6-di-*O*-ethylidene- α -D-mannoside was readily hydrolysed to methyl α -D-mannoside, but the mono-ethylidene derivative was not isolated in this reaction.

EXPERIMENTAL

Solvents were evaporated at reduced pressure.

Methyl α -D-Mannoside.—This was prepared from carob gum by Smith's method (*J.*, 1948, 1989). The average yield was lower than that obtained by Smith.

Methyl 4 : 6-O-Ethylidene- α -D-mannoside and Methyl 2 : 3-4 : 6-Di-O-ethylidene- α -D-mannoside.—Finely ground methyl α -D-mannoside (20 g.) was shaken at room temperature with paraldehyde (200 ml.), containing concentrated sulphuric acid, until all the solid had dissolved (about 30 min.). Acid was neutralised with anhydrous potassium carbonate, and the mixture then filtered. Evaporation of the filtrate gave a syrup which solidified when shaken with water (150 ml.). The solid was collected, dried (14 g., 55%), and recrystallised from aqueous alcohol or light petroleum, forming soft needles of *methyl 2 : 3-4 : 6-di-O-ethylidene- α -D-mannoside*, m. p. 72°, $[\alpha]_D^{20} + 14.2^\circ$ (*c.* 1.0 in CHCl_3) (Found: C, 53.8; H, 7.3; $\text{CH}_3 \cdot \text{CHO}$, 36.2. $\text{C}_{11}\text{H}_{18}\text{O}_6$ requires C, 53.6; H, 7.3; $\text{CH}_3 \cdot \text{CHO}$, 35.8%). The aqueous filtrate was evaporated to a white solid which, recrystallised from carbon tetrachloride, was *methyl 4 : 6-O-ethylidene- α -D-mannoside* (7.1 g., 31%), m. p. 117°, $[\alpha]_D^{20} + 77^\circ$ (*c.* 1.0 in CHCl_3) (Found: C, 50.0; H, 7.8. $\text{C}_9\text{H}_{16}\text{O}_6$ requires C, 49.1; H, 7.3%).

In a similar experiment, with a longer reaction time, only the di-*O*-ethylidene compound was obtained.

Estimation of Acetaldehyde.—The ethylidene content of the fully substituted mannoside was estimated by an adaptation of Ripper's method (see Wild, "Estimation of Organic Compounds," University Press, Cambridge, 1953, p. 151) for determining acetaldehyde. A suspension of the compound was gently distilled with 3% sulphuric acid into an ice-cooled flask. The acetaldehyde was estimated by adding aqueous sodium hydrogen sulphite and titrating the excess with iodine. As a control experiment the ethylidene content of methyl 4 : 6-*O*-ethylidene-2 : 3-*O*-oxydiethylidene- α -D-glucoside was determined (Found: $\text{CH}_3 \cdot \text{CHO}$, 44.6. $\text{C}_{13}\text{H}_{22}\text{O}_7$ requires $\text{CH}_3 \cdot \text{CHO}$, 45.5%).

Characterization of Methyl 4 : 6-O-Ethylidene- α -D-mannoside.—Silver oxide (10 g.) was added in 1-g. portions during 5—6 hr. to methyl 4 : 6-*O*-ethylidene- α -D-mannoside (3 g.) in boiling methyl iodide (20 ml.). After the suspension had boiled for 18 hr. more the silver residue was filtered off and washed with methanol, and the washings and filtrate combined and evaporated. Two such treatments were necessary for complete methylation. The crystalline product (2.94 g., 87%) was purified by chromatography in benzene solution through alumina, yielding large prisms of *methyl 4 : 6-O-ethylidene-2 : 3-di-O-methyl- α -D-mannoside*, m. p. 42—44°, $[\alpha]_D^{20} + 65.8^\circ$ (*c.* 0.48 in CHCl_3) (Found: C, 53.4; H, 8.1. $\text{C}_{11}\text{H}_{20}\text{O}_6$ requires C, 53.2; H, 8.1%).

This compound (1 g.), Amberlite ion-exchange resin IR 120 (H) (1 g.), and water (20 ml.) were heated on a steam-bath for 4½ hr. The resin was filtered off and the filtrate was concentrated to a syrup, a solution of which in pyridine (5 ml.) was mixed with benzoyl chloride (1.5 ml.) in pyridine (5 ml.) at 0°. After 90 min., water (1 ml.) was added dropwise, and 30 min. later the solution was poured into aqueous potassium carbonate at 0°. Dissolution of the resulting solid (1.23 g.) in a small amount of ether followed by cooling to 0° gave methyl 2 : 3-di-*O*-methyl- α -D-mannoside 4 : 6-dibenzoate (0.70 g., 40%), $[\alpha]_D^{20} + 50.2^\circ$ (*c.* 1.2 in CHCl_3). This compound when first obtained melted at 101—102°, resolidified, and melted again at 120—121°, but a mixture with an authentic specimen prepared by Robertson (*loc. cit.*), m. p. 120—121°, $[\alpha]_D + 52.9^\circ$, had m. p. 120—121°. Subsequent recrystallizations gave only the higher-melting form.

Acid Hydrolysis of Methyl 2 : 3-4 : 6-Di-O-ethylidene- α -D-mannoside.—Crude methyl 2 : 3-4 : 6-di-*O*-ethylidene- α -D-mannoside (40 g.) was boiled in water (100 ml.) with Amberlite ion-exchange resin IR 120 (H) (8 g.). When the compound had dissolved (4—5 hr.) the resin was filtered off and the filtrate concentrated. Extraction of the residue with carbon tetrachloride and concentration of the extract gave no methyl 4 : 6-*O*-ethylidene- α -D-mannoside. The residue, recrystallized from methanol, gave methyl α -D-mannoside (20.6 g., 65%), m. p. 188—189°.

Methyl 4 : 6-O-Ethylidene- α -D-mannoside 2 : 3-Diacetate.—Methyl 4 : 6-*O*-ethylidene- α -D-mannoside (5 g.), sodium acetate (1.5 g.), and acetic anhydride (15 g.) were heated on a steam-bath for 1 hr., and the mixture was then poured into ice-water (50 ml.). Recrystallization of the crude product from light petroleum gave slender needles (74%) of *methyl 4 : 6-O-ethylidene- α -D-*

mannoside 2:3-diacetate, m. p. 132°, $[\alpha]_D^{25} + 36.7^\circ$ (*c*, 1.0 in CHCl_3) (Found: C, 51.3; H, 6.2. $\text{C}_{13}\text{H}_{20}\text{O}_8$ requires C, 51.3; H, 6.6%).

Deacetylation of this compound (0.5 g.), in methanol (20 ml.) containing sodium (0.01 g.), gave a solid which recrystallized from carbon tetrachloride as jelly-like, very fine needles of methyl 4:6-O-ethylidene- α -D-mannoside (0.24 g., 69%), m. p. 114°, $[\alpha]_D^{18} + 74^\circ$ (*c*, 1.0 in CHCl_3).

Methyl 4:6-O-Ethylidene- α -D-mannoside 2:3-Ditoluene-p-sulphonate. Toluene-*p*-sulphonyl chloride (5.7 g.) in pyridine (20 ml.) was mixed with methyl 4:6-O-ethylidene- α -D-mannoside (2.2 g.) in pyridine (20 ml.) at 0°. The solution was kept at room temperature for 3 days and then poured into ice-water. After several changes of water, with constant stirring, the initial syrup solidified. The dried solid (3.2 g., 60%) was recrystallized from methanol, giving *methyl 4:6-O-ethylidene- α -D-mannoside 2:3-ditoluene-p-sulphonate*, m. p. 121—122°, $[\alpha]_D^{21} - 11.6^\circ$ (*c*, 1.2 in CHCl_3) (Found: C, 52.6; H, 5.2; S, 12.4. $\text{C}_{23}\text{H}_{28}\text{O}_{10}\text{S}_2$ requires C, 52.2; H, 5.3; S, 12.1%).

Methyl 4:6-O-Ethylidene- α -D-mannoside 2:3-Dinitrate.—Fuming nitric acid (4 ml.) in acetic anhydride (10 ml.) was added to an ice-cold suspension of methyl 4:6-O-ethylidene- α -D-mannoside (4 g.) in acetic anhydride (10 ml.), and after 15 min. at 0° the mixture was stirred into ice-water (200 ml.). After being washed and dried, the resulting solid (92%), m. p. 69—73°, was recrystallized from light petroleum, giving *methyl 4:6-O-ethylidene- α -D-mannoside 2:3-dinitrate*, m. p. 73—74°, $[\alpha]_D^{19} + 20.0^\circ$ (*c*, 1.3 in CHCl_3) (Found: C, 35.0; H, 4.7; N, 8.6. $\text{C}_9\text{H}_{14}\text{O}_{10}\text{N}_2$ requires C, 34.8; H, 4.5; N, 9.0%).

Condensation of Propaldehyde with Methyl α -D-Mannoside.—Methyl α -D-mannoside (8 g.), propaldehyde (10 g.), and concentrated hydrochloric acid (1 ml.) were shaken at room temperature for 5 min. After 15 min. more, water was added and the solid was collected. Recrystallization from methanol gave fine needles of *methyl 2:3-4:6-di-O-propylidene- α -D-mannoside*, m. p. 92—93°, $[\alpha]_D^{18} + 5.2^\circ$ (*c*, 1.0 in CHCl_3) (Found: C, 57.4; H, 8.1%; *M*, 277. $\text{C}_{19}\text{H}_{22}\text{O}_8$ requires C, 56.9; H, 8.0%; *M*, 274).

Attempted Nitration of Methyl 2:3-4:6-Di-O-ethylidene- and -Di-O-propylidene- α -D-mannoside.—The methyl di-*O*-alkylidene- α -D-mannoside (1 g.) in acetic anhydride (2.5 ml.) was mixed with fuming nitric acid (1 ml.) in acetic anhydride (2.5 ml.) at 0°. The solution was allowed to warm to room temperature during 15 min. and then poured into aqueous potassium carbonate. The crude solid which separated was recrystallized and, in each case, was identified as the unchanged di-*O*-alkylidene compound.

Condensation of Benzaldehyde with Methyl α -D-Mannoside.—Methyl α -D-mannoside (20 g.), zinc chloride (15 g.), and benzaldehyde (40 ml.) were shaken at room temperature for 21 hr. The syrup, which separated when the mixture was poured into ice-water, crystallized on trituration with aqueous sodium hydrogen sulphite (10%; 500 ml.). The solid was subsequently washed with aqueous sodium hydrogen carbonate and light petroleum; recrystallization from ethanol-acetone of the residue insoluble in water yielded needles (7 g.) of one of the known isomers of methyl 2:3-4:6-di-*O*-benzylidene- α -D-mannoside, m. p. 174—178°. A further crop (1.1 g.) of the same compound was obtained from the mother liquors. Robertson (*loc. cit.*) records m. p. 181—182° for this.

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