

SYNTHESIS OF MONOMERIC FORMS OF α -HYDROXY- β -METHOXYPROPIONALDEHYDE AND 1:3-DIMETHOXY-PROPANONE-2

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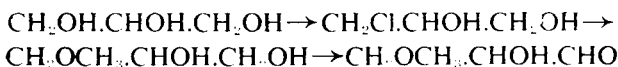
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THE compounds concerned in this communication are required for the synthesis of methylated hexoses which could not possess a pyranose structure.

α -Hydroxy- β -methoxypropionaldehyde had not been obtained in the monomeric form, although the dimeride was prepared by Fisher and Bear¹ and proved to be a crystalline substance melting at 120 to 121° C. which on heating with pyridine suffered rearrangement into the monomethyl ether of dihydroxyacetone. Alkaline condensation of this dimeride gave rise to sugars with branched chains.

The monomeric form was prepared by the following series of reactions:



The α -monomethylether of glycerol was obtained by the gradual addition of a methyl alcoholic solution of glycerol- α -monochlorohydrin to a solution of sodium methylate, the mixture being refluxed until separation of sodium chloride ceased: it was obtained as a syrup boiling at 135° to 136° C./40 mm. Hg. pressure. The oxidation was attempted *via* the Oppenauer² reaction using aluminium tertiary butoxide as this method was successful in the oxidation of cholesterol to cholestenone as applied by Adkins and Cox³. The conditions of Adkins and Cox were used, but a very poor yield was obtained.

Fenton and Jackson⁴ originated the hydrogen peroxide-ferrous sulphate oxidation of polyhydric alcohols. This reagent appears to be specific for the primary alcoholic groups, no instance of ketone formation being reported. It has been successfully used for the oxidation of ethylene glycol to glycol aldehydes, mannitol to mannose⁵ and glycerol to glyceraldehyde. After numerous trials satisfactory conditions were established for the oxidation of the α -monomethylether of glycerol, and the product on isolation gave a positive test with Schiff's reagent, reduced Fehling's and ammoniacal silver nitrate solutions, gave an immediate precipitate with 2:4-dinitrophenylhydrazine and a solid bisulphite compound. The product obtained with 2:4-dinitrophenylhydrazine, melted at 234° to 236° C. (with decomposition) and gave analytical figures in agreement with those of the osazone of α -hydroxy- β -methoxypropionaldehyde. The formation of the osazone proves the

monomeric character of the substance, and this is further supported by the fact that the hydrazone could not be isolated, the dimeric forms yielding hydrazones under similar conditions.

The compound could not be further purified by distillation under very low pressure as polymerisation then occurred. The syrup itself darkens slowly on exposure to air, and hence it was always used immediately after preparation. Reeve⁶ had previously observed that the monomeric form of glyceraldehyde was a syrup whilst the bimolecular was crystalline.

The synthesis of 1:3-dimethoxypropanone-2 was achieved as follows: glycerol \rightarrow 1:3-glycerol-dichlorohydrin \rightarrow 1:3-dimethoxypropanol-2 \rightarrow 1:3-dimethoxypropanone-2. Previous methods of preparation included the ketonic hydrolysis of α - γ -dialkoxyacetoacetic esters^{7,8,9} and the distillation of calcium salts of the alkoxyacetic acids. Methylation of symmetrical dichloroacetone with sodium methylate failed owing to the polymerisation of the product during the isolation.

Eventually the required compound was achieved by acid chromate oxidation, at 20° to 23°C., of 1:3-dimethoxypropanol-2 (b.pt. 58° to 60°C./12 mm. Hg. pressure), which was obtained from glycerol-1:3-dichlorohydrin (b.pt. 70° to 72°C./14 mm. Hg. pressure) by the gradual addition of its solution in methyl alcohol to a solution of sodium methoxide. The isolated product was finally fractionated, and the portion boiling at 42°C./22 mm. Hg. pressure answered all the requirements. It gave positive colour tests with sodium nitroprusside, *m*-dinitrobenzene and 3:5-dinitrobenzoic acid characteristic of ketones; it reduced Fehling's solution and ammoniacal silver nitrate solution and gave a 2:4-dinitrophenylhydrazone melting at 112° to 113°C., which gave correct analytical figures. The ketone itself gave the analytical figures required, and hence the structure was confirmed.

EXPERIMENTAL

α -Hydroxy- β -methoxypropionaldehyde $\text{CH}_2\text{OCH}_3\text{CHOH}\cdot\text{CHO}$.—The oxidation of glycerol- α -monomethylether boiling at 136°C./40 mm. Hg. pressure, obtained by treatment of glycerol-2-chlorohydrin (b.pt. 104° to 108°C./9 mm. Hg.) with sodium methoxide, was attempted (A) with aluminium tertiary butoxide. 100 g. of the monomethylether was placed in a dry 5-l. flask provided with a reflux condenser and a drying tube together with 750 ml. of pure dry acetone and 1 l. of pure benzene. To this mixture, maintained between 75° and 85°C., a solution of 80 g. of aluminium tertiarybutoxide in 500 ml. of dry benzene was added in one portion. The mixture turned milky and was refluxed for a total period of 8 hours. After cooling, 200 ml. of water, 500 ml. of 10 per cent. sulphuric acid and a further 1.5 l. of water were added successively and the whole allowed to separate. The separated aqueous layer was extracted with benzene, and the combined benzene solutions were dried over anhydrous sodium sulphate. The aqueous layer was neutralised with barium carbonate and fractionated, but the isolation of the desired

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product was not achieved. The higher boiling fraction, collected between 85° and 95°C., was saturated with salt and extracted many times with chloroform. On removal of the chloroform little residue was obtained. The aqueous solution saturated with salt was therefore extracted with ether, and from this ethereal solution 2 ml. of a brown syrup was isolated which gave a positive test with Schiff's reagent.

(B) As a result of the above failure the oxidation was attempted with Fenton's reagent. The α -monomethyl ether was diluted with an equal bulk of water and mixed with an aqueous solution of 2.5 g. of ferrous sulphate. Hydrogen peroxide (20 vol.) 112.5 ml. was gradually added during half an hour, or until the reaction ceased, the flask being cooled between the separate additions. After standing for 2 hours excess of finely powdered barium carbonate was added, the mixture filtered and the clear and colourless filtrate concentrated under reduced pressure at a temperature not higher than 30°C. The residue was extracted with absolute alcohol, ether being added to the filtered alcoholic solution until no more solid separated. The clear alcohol-ether solution was concentrated under reduced pressure at 20°C., the residue being a colourless syrupy liquid which responded to qualitative tests for aldehydes. In all 321 g. was prepared.

α -Hydroxy- β -methoxypropionaldehyde-2:4-dinitrophenylosazone. — A solution of the above syrup (2 g.) in 5 ml. of absolute alcohol was added to a solution of 2:4-dinitrophenylhydrazine (2 g.) and 1 ml. of concentrated sulphuric acid in 25 ml. of absolute alcohol. An immediate precipitation occurred and the mixture was warmed at 66° to 70°C. for 20 minutes. On cooling, the fine crystals which separated were collected, washed, dried and recrystallised twice from alcohol. They appeared as fine orange needles melting at 234° to 236°C. after drying *in vacuo*. Found: N, 24.8 per cent.; $C_{10}H_{14}O_9N_2$ requires N, 24.24 per cent.

1:3-Dimethoxypropanol (CH_3OCH_2)₂CHOH.—Glycerol-1:3-dichlorohydrin, 100 g. dissolved in 120 ml. of methyl alcohol, was slowly added with vigorous shaking to the solution obtained by the addition of 40 g. of sodium to 560 ml. of methyl alcohol. After standing for 3 hours the reaction was completed by refluxing for 6 hours. The product was isolated in the usual manner and purified by fractional distillation. The fraction boiling at 55° to 60°C./12 mm. Hg. pressure consisted mainly of the required substance and was redistilled collecting the fraction boiling at 58° to 60°C./12 mm. Hg. pressure.

1:3-Dimethoxypropanone-2 (CH_3OCH_2)₂C:O.—To a mixture of 50 g. of 1:3-dimethoxypropanol-2, 75 ml. of water and 42 g. of powdered sodium dichromate, 52 g. of sulphuric acid diluted with 29 ml. of water was added at intervals of 10 minutes during 5 hours whilst stirring vigorously and maintaining the temperature between 22° and 23°C. The stirring was continued for a further 3 hours when tests for hydrogen peroxide became negative. The mixture was extracted with ether, the

ethereal extracts being washed with sodium bicarbonate solution, with water, and then dried over anhydrous sodium sulphate. On removal of the ether 10 g. of a colourless syrup remained. After precipitation of chromium salts with sodium bicarbonate a further 15 g. of colourless syrup was obtained from the mother liquors by extraction with absolute alcohol. The combined syrups were then fractionated under reduced pressure when a main fraction boiling at 40° to 42°C./22 mm. Hg. pressure was obtained. On redistillation this fraction yielded 20 g. of 1:3-dimethoxypropanone-2. Yield, 40 per cent. Found: C, 49.76; H, 8.44 per cent.; $C_5H_{10}O_3$ requires C, 50.85; H, 8.47 per cent. The product gave positive qualitative reactions of a ketone.

1:3-Dimethoxypropanone-2-2':4'-dinitrophenylhydrazone.

$(CH_3O.CH_2)_2C:N.NH.C_6H_3(NO_2)_2$.—A solution of 2 g. of 1:3-dimethoxypropanone-2 in 5 ml. of absolute alcohol was mixed with a filtered solution of 2:4-dinitrophenylhydrazine (2 g. in 30 ml. of absolute alcohol plus 1 ml. of concentrated sulphuric acid). The mixture was warmed and, on cooling, yellow needle-shaped crystals separated. After two recrystallisations from boiling alcohol and drying *in vacuo* the melting point was found to be 112° to 113°C. Found: C, 44.66; H, 4.75; N, 18.8 per cent.; $C_{11}H_{14}O_6N_4$ requires C, 44.30; H, 4.70; N, 18.79 per cent.

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