

## Oxidation of Carbohydrate Derivatives with Silver Carbonate on Celite. VIII. Oxidation of Trioses and Some Related Compounds

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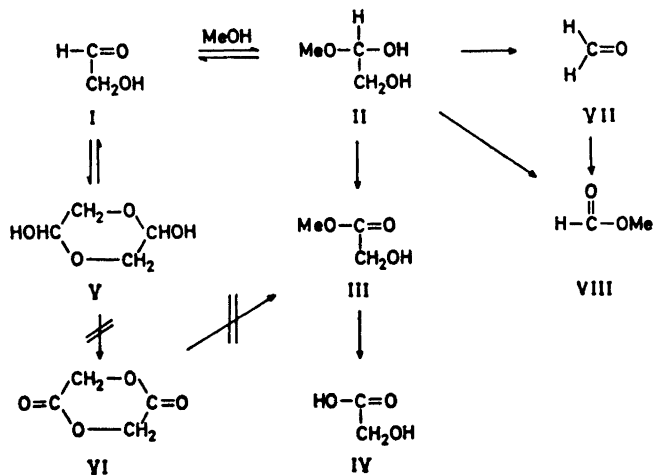
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Glycolaldehyde and D,L-glyceraldehyde are oxidized by silver carbonate on Celite in methanol to methyl esters of the corresponding acids. Methyl glycolate is also the product obtained on oxidation of dihydroxy acetone. Glyoxal gives methyl glyoxylate with the same oxidant, the second aldehyde group of this compound resisting oxidation. Formaldehyde is oxidized at a somewhat higher temperature than the other compounds.

Methyl esters of oxalic, glyoxylic, glyceric and presumably glycolic acid were found to be secondary products on oxidation of aldopentoses with silver carbonate on Celite in methanol.<sup>1</sup> Glyceraldehyde has been identified as one of the products after oxidation of the pentoses, and small amounts of compounds which were tentatively identified as glycolaldehyde and glyoxal, based on the chromatographic and electrophoretic behaviour, were also detected. To establish whether these compounds might be precursors of the methyl esters mentioned above, it seemed of interest to examine the effect of silver carbonate on Celite on these compounds in methanol. An investigation of the effect of the oxidant on  $\alpha$ -hydroxy aldehydes and ketones which are unable to form cyclic hemiacetals was further of general interest, since such compounds would be expected to form hemiacetals with the solvent in methanolic solution, and hence possibly undergo reactions analogous to those occurring with aldoses<sup>1</sup> and ketoses,<sup>2</sup> but in non-cyclic form. Aldoses have been found to give mixtures of aldonolactones and aldoses with a shorter carbon chain,<sup>1</sup> whereas 2-ketoses primarily are cleaved between C-2 and C-3 by this oxidant.<sup>2</sup>

### RESULTS AND DISCUSSIONS

Glycolaldehyde (I) was completely oxidized in methanol by the oxidant within 45 min at 35°C. Methyl glycolate (III) was the only product found after removal of the solvent. Hydrolysis of the ester gave glycolic acid (IV) in



about 55 % yield based on glycolaldehyde. The direct formation of the methyl ester (III) on oxidation of glycolaldehyde indicated that the reaction occurred *via* the hemiacetal (II). Glycolaldehyde crystallizes in the dimeric form (V), and an alternative way to the methyl ester (III) might be an oxidation of this dimer in two steps to the dimeric form (VI) of glycolic acid, and subsequent conversion to the methyl ester in the methanolic solution. This possibility has, however, been excluded by the fact that glycolic acid dimer (VI) is not converted to methyl glycolate (III) under the conditions employed.

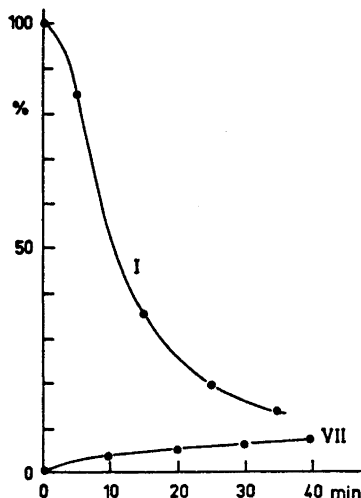


Fig. 1. Oxidation of glycolaldehyde. Per cent glycolaldehyde (I) and formaldehyde (VII) present as a function of time.

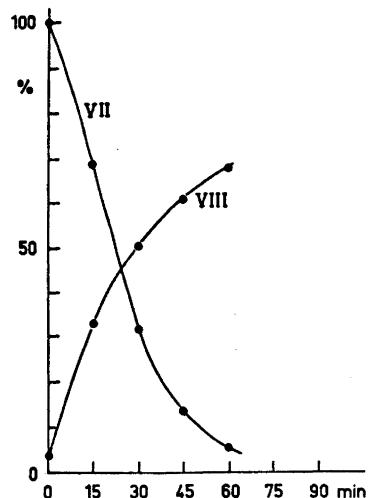
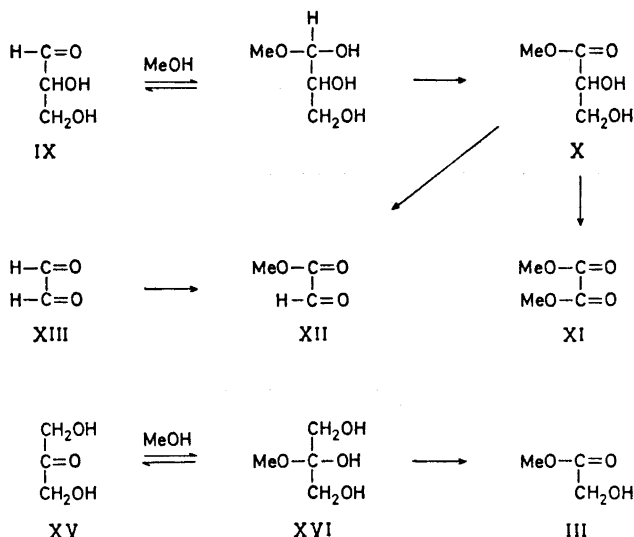


Fig. 2. Oxidation of formaldehyde. Per cent formaldehyde (VII) and methyl formate (VIII) present as a function of time.

Since the yield of glycolic acid (IV) from glycolaldehyde is about 55 %, the occurrence of glycol cleavage of the hemiacetal (II) in analogy to the degradation of aldopentoses,<sup>1</sup> is not excluded as a side reaction. The expected products after a glycol cleavage are formaldehyde (VII) and methyl formate (VIII). The presence of formaldehyde is indicated colorimetrically with the acetylacetone-ammonium acetate reagent.<sup>3</sup> Glycolaldehyde interferes slightly in this determination, and thus simultaneous colorimetric determinations of glycolaldehyde with  $\alpha$ -naphthol-sulphuric acid<sup>4</sup> and formaldehyde with acetyl acetone - ammonium acetate reagent have been performed. The result is shown in Fig. 1; the formaldehyde curve is corrected for the glycolaldehyde present. It is seen that formaldehyde may be present in about 8 % yield at the end of the reaction.

The question arose whether formaldehyde was further oxidized by the oxidant under the reaction conditions. The effect of silver carbonate on Celite in methanol on formaldehyde (VII) was thus investigated, and it was found that only a slight oxidation occurred at 35°C. At 50°C, however, formaldehyde was almost completely oxidized within 60 min (Fig. 2). Colorimetric determination of ester formed in the solution under the reaction with time, by use of the hydroxylamine - ferric perchlorate reagent<sup>5</sup> (Fig. 2), shows that a possible yield of about 70 % of methyl formate (VIII) is obtained, a slight loss of the low-boiling methyl formate is not excluded. The formation of a formic acid ester in the solution was further indicated by infrared spectroscopy after distillation of the product from the reaction mixture.

DL-Glyceraldehyde (IX) afforded in analogy to glycolaldehyde almost exclusively DL-glyceric acid methyl ester (X) at 35°C. Chromatography indicated the additional formation of traces of methyl glycolate (III), the product expected after degradation of DL-glyceraldehyde to glycolaldehyde (I) followed



by oxidation of this compound as described above. At 45°C glyceric acid methyl ester (X) undergoes a slow further oxidation, and the products were found to be dimethyl oxalate (XI) and methyl glyoxylate (XII) on chromatographic and spectroscopic evidence.

The presence in addition to methyl glyoxylate of a compound assumed to be glyoxal (XIII) after oxidation of aldopentoses,<sup>1</sup> suggests a possible relationship between these compounds in this oxidation. To establish whether such a relationship may exist, glyoxal (XIII) was also treated with silver carbonate on Celite in methanol. One of the aldehyde groups of the dialdehyde was smoothly oxidized to a carbomethoxy group, whereas the remaining aldehyde group was resistant to oxidation, methyl glyoxylate (XIII) could not be further oxidized at 45°C. The tendency of methyl glyoxylate (XII) to hemiacetal formation with methanol must be expected to be greatly reduced as compared to that of glyoxal (XIII) with an activating second aldehyde group. Since the hemiacetal form is the form in which all the investigated compounds obviously are oxidized, the lack of reactivity of methyl glyoxylate may easily be understood.

The initial attack on 2-ketoses with silver carbonate on Celite in methanol occurs between C-2 and C-3.<sup>2</sup> One of the reasons for this selectivity may be a greater reactivity of the secondary hydroxyl group at C-3 than the primary one. An other explanation could be that in a cyclic form, the hydroxyl groups at C-2 and C-3 are fixed in a relative orientation particularly suitable for degradation.

It has been interesting in this connection to find that 1,3-dihydroxy acetone (XV), with two primary hydroxyl groups next to the ketone function, needs almost 1 h for a complete oxidation to methyl glycolate (III) at 55°C. This compound is also obviously oxidized by diol cleavage of its hemiacetal (XVI). The possibility of two subsequent oxidation steps of the dimeric form, in which the compound is known to crystallize, to give the glycolic acid dimer is excluded for the same reasons as in the case of glycolaldehyde (I).

The results presented have shown that the presence of methyl esters of glycolic, glyoxylic, and glyceric acid after oxidation of aldopentoses may be due to direct oxidation of the corresponding aldehydes. It is further seen that dimethyl oxalate may possibly arise from methyl glycerate, in particular because a temperature of 45°C has been found to be "critical" for this reaction, and dimethyl oxalate was not formed from the aldopentoses at reaction temperatures lower than this temperature.

The present work has also established that silver carbonate on Celite in methanol is a convenient oxidant for the conversion of  $\alpha$ -hydroxy aldehydes, and possibly other activated aldehydes, to the corresponding carboxylic acid methyl esters.

#### EXPERIMENTAL

Paper chromatography was performed on Whatman No. 1 paper in the solvent system (v/v) (A) butanone – acetone – formic acid – water 40:2:1:6. Thin-layer chromatography (TLC) was run on Silica gel G in (B) benzene – ethanol 5:1 and (C) benzene – ethanol 10:1. As spray reagents were used hydroxylamine – ferric chloride<sup>6</sup> for esters, sulphanilamide –  $\beta$ -naphthol – sodium nitrite<sup>7</sup> for acids and diphenylamine – aniline – phosphoric acid<sup>8</sup> for the other compounds.

*Oxidation of glycolaldehyde (I).* Glycolaldehyde (I) (100 mg) in methanol (50 ml) was stirred with silver carbonate on Celite<sup>9</sup> (6 g) for 35 min at 35°C. The solution was then filtered, and from a part of it, the solvent was evaporated to give chromatographically homogeneous (TLC, solvent C) methyl glycolate (III), indistinguishable from an authentic sample of methyl glycolate. The infrared spectrum was identical with that of authentic methyl glycolate.

To the solution containing methyl glycolate (III) was added sodium hydroxide (200 mg) in water (2 ml). After 2 h, the solution was diluted with water (10 ml), neutralized with Dowex 50 W (H<sup>+</sup>) ion exchange resin and the solvents were evaporated. Glacial acetic acid was evaporated from the residue, which was then kept at 2–3°C over night to give crystalline glycolic acid (IV), the yield was 69 mg (54%), m.p. 75–77°C, after sublimation *in vacuo* m.p. 77.5–78.5°C (lit.<sup>10</sup> 80°).

*Oxidation of glycolaldehyde (I). Colorimetric determination of glycolaldehyde and formaldehyde.* Glycolaldehyde (30 mg) in methanol (20 ml) was stirred with silver carbonate on Celite (2 g) at 35°C. Aliquots (100  $\mu$ l) were withdrawn at intervals, diluted with water (to 1 ml) and the amounts of glycolaldehyde and formaldehyde determined colorimetrically with the  $\alpha$ -naphthol–sulphuric acid reagent<sup>4</sup> and the acetylacetone–ammonium acetate reagent,<sup>3</sup> respectively. The results are shown in Fig. 1.

*Oxidation of formaldehyde (VII).* Formaldehyde (VII) (6.5 mg) in methanol (10 ml) was stirred with silver carbonate on Celite (1 g) at 50°C. Aliquots (10  $\mu$ l and 250  $\mu$ l) were withdrawn at intervals, and the amounts of formaldehyde and formate were determined colorimetrically with the acetylacetone–ammonium acetate reagent and the hydroxylamine–ferric perchlorate reagent,<sup>5</sup> respectively. The results are shown in Fig. 2.

After 1 h, the solid material was filtered off. A mixture of the product and methanol was distilled into chloroform by keeping the solution at 60°C for a few min. The infrared spectrum of the resulting chloroform solution showed strong absorption at 1720 cm<sup>-1</sup>, characteristic of formic esters.<sup>11</sup>

*Oxidation of DL-glyceraldehyde (IX).* DL-Glyceraldehyde (200 mg) in methanol (100 ml) was oxidized with silver carbonate on Celite (10 g) at 35°C for 45 min. Filtration of the solution and evaporation of the solvent gave syrupy methyl DL-glycerate (X). The compound was chromatographically (TLC, solvent B) indistinguishable from an authentic sample, and the infrared spectra were identical. The product contained traces of a compound with mobility (TLC, solvent C) corresponding to that of methyl glycolate (III).

Hydrolysis of the ester (X) with 0.2 M trifluoroacetic acid at 40°C for 48 h and removal of the acid by repeated distillations with water, afforded syrupy DL-glyceric acid (133 mg). The syrup was chromatographically homogeneous (paper chromatography, solvent A) and the mobility corresponded to that of authentic DL-glyceric acid. M.p. of the derived<sup>12</sup> amide was 86–89°C (lit.<sup>12</sup> 91.5–92°C).

*Oxidation of methyl-DL-glycerate (X).* Methyl DL-glycerate (190 mg) in methanol (100 ml) was stirred with silver carbonate on Celite (12 g) for 1 h at 45°C. After filtration of the solution and evaporation of the solvent, the residue was dissolved in chloroform (30 ml). The chloroform layer was extracted with water (6  $\times$  5 ml), dried with sodium sulphate and the solvent evaporated to give dimethyl oxalate (XI) (20 mg) indistinguishable from authentic dimethyl oxalate by TLC (solvent C); the infrared spectrum was identical with that of the authentic sample. The water extracts Nos. 3 to 6 from the extraction mentioned above contained methyl glyoxylate (XII) (14 mg), identical with an authentic sample (TLC, infrared spectrum).

The water extracts Nos. 1 and 2 contained a mixture of starting material and methyl glyoxylate (XII).

*Oxidation of glyoxal (XIII).* Glyoxal (200 mg) in methanol (100 ml) was oxidized with silver carbonate on Celite (10 g) for 1 h at 45°C. Filtration of the solution and evaporation of the solvent yielded methyl glyoxylate (XII), indistinguishable from an authentic sample (prepared by periodate oxidation of dimethyl tartrate) by TLC (solvent B). The infrared spectrum was identical with that of authentic methyl glyoxylate.

Hydrolysis of the ester (XII) in water (4 ml) containing sodium bicarbonate (0.5 g) for 48 h at room temperature, afforded glyoxylic acid (XIV) (165 mg) as a chromatographically homogeneous syrup (paper chromatography, solvent A). Treatment of this syrup in water (4 ml) with dimedone (300 mg) in ethanol (7.5 ml) and water (7.5 ml) over night yielded the dimedone derivative (133 mg), crystallizing directly from the solution, m.p. 232°C, after sublimation *in vacuo* m.p. 234–238°C (lit.<sup>13</sup> 236–238°C).

*Oxidation of 1,3-dihydroxy-acetone (XV).* 1,3-Dihydroxy-acetone (200 mg) in methanol (100 ml) was treated with silver carbonate on Celite (10 g) at 55°C for 1 h. After filtration, the solvent was evaporated from a part of the solution, yielding methyl glycolate (III), homogeneous by TLC (solvent C). The chromatographic mobility corresponded to that of authentic methyl glycolate, and the infrared spectra ( $\text{CHCl}_3$ ) were identical.

To the solution was added sodium hydroxide (400 mg) in water (4 ml). After 2 h at room temperature, the solution was neutralized with Dowex 50 W ion exchanger ( $\text{H}^+$  form) and the solvent evaporated. From the residue was distilled acetic acid twice, the residue crystallized in refrigerator. The yield was 107 mg (63 %, based on dihydroxy acetone) of glycolic acid (IV), m.p. 72–75°C, after sublimation *in vacuo* m.p. 78.5–79.5°C (lit.<sup>10</sup> 80°).

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