ACTA CHEMICA SCANDINAVICA 27 (1973) 1557–1564

Oxidation of Carbohydrate Derivatives with Silver Carbonate on Celite.

VI. 2-Ketoses

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D-Fructose is oxidized by silver carbonate on Celite in methanol to give a glycolic ester of D-erythrose. Derivatives of D-glyceraldehyde and D-erythronic acid are also formed by further oxidation of the primary product.

The five other 2-ketoses examined are also oxidized. The products after hydrolysis and removal of acidic compounds were the aldoses resulting from cleavage of the ketoses between C-2 and C-3, and varying amounts of the aldoses produced by one further step of degradation.

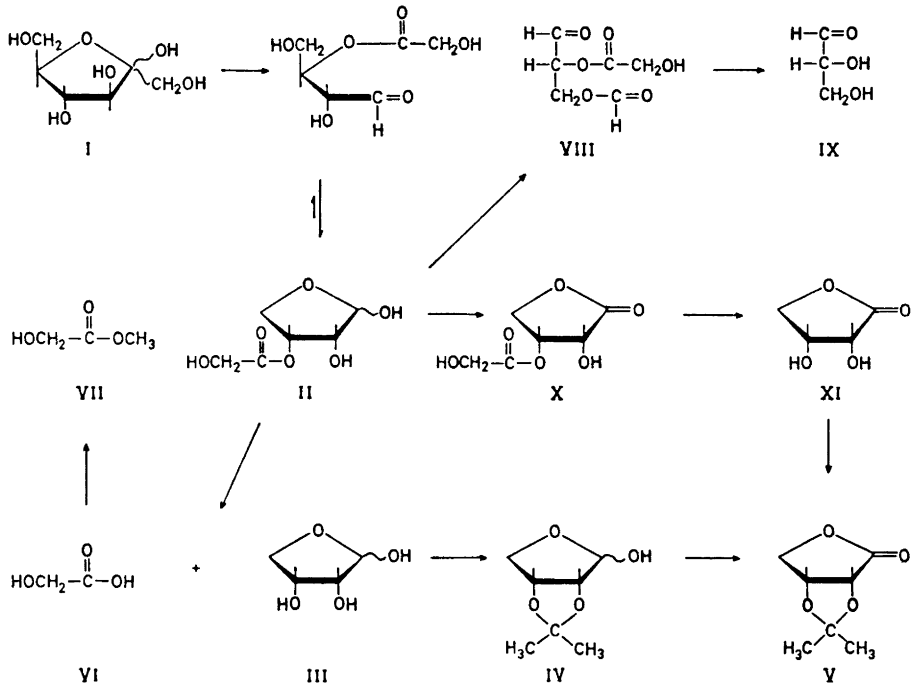
D-*manno*-Heptulose and D-*glycero*-D-*manno*-octulose are found to be oxidized with greater difficulty than the hexuloses and D-*altro*-heptulose.

Silver carbonate on Celite, the oxidant introduced by Fetizon and co-workers,[1] has shown similarities to periodate and lead tetraacetate in its ability to cleave the diol group between C-1 and C-2 in reducing aldose derivatives.[2,3] Lead tetraacetate is known to cleave fructose and other 2-ketoses in furanose form between C-2 and C-3.[4,5] From D-fructose is formed 3-*O*-glycolyl-D-erythrose, which in turn is rapidly degraded to 3-*O*-formyl-2-*O*-glycolyl-D-glyceraldehyde. Acid hydrolysis liberates D-glyceraldehyde from this compound, and the method thus offers a convenient way to the triose. In addition to its synthetic applicability, this reaction has been widely used in identification of heptuloses, octuloses, and nonuloses isolated from plants.[6,7] Periodate has been reported to give a more complex oxidation pattern in the case of 2-ketoses because of its greater tendency to cause cleavage between C-1 and C-2.[8,9]

An investigation of the effect of silver carbonate on Celite on 2-ketoses seemed in light of these facts to be of interest, and has now been undertaken. In a previous paper in this series, the application of the oxidant in the synthesis of L-threose from L-sorbose has already been described.[10]

RESULTS AND DISCUSSIONS

D-Fructose (I) gave in analogy to L-sorbose on oxidation in methanol as major product a glycolic ester of D-erythrose (II) from which the tetrose (III) was liberated on acid hydrolysis. D-Erythrose (III) was characterized by



acetonation to 2,3-*O*-isopropylidene-D-erythrose (IV), which was subsequently oxidized to 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone (V) by silver carbonate on Celite in benzene.

Glycolic acid (VI), formed on hydrolysis of the primary oxidation product, was isolated after conversion to its methyl ester (VII). The methyl ester was identified by chromatography and infrared spectroscopy.

The primary oxidation product, the glycolic ester of D-erythrose (II), shows that the oxidation occurs in cyclic form (or forms) of fructose. In order to obtain information about the ring form, the glycolic ester was subjected to oxidation with lead tetraacetate. The main product resulting from this treatment was a derivative (VIII) of D-glyceraldehyde with chromatographic mobility corresponding to that of 3-*O*-formyl-2-*O*-glycolyl-D-glyceraldehyde. This compound was also formed on prolonged oxidation of D-fructose with an excess silver carbonate on Celite. D-Glyceraldehyde (IX) was formed from this derivative on acid hydrolysis. The formation of a diester of glyceraldehyde from fructose by two steps of degradation, as well as with lead tetraacetate from the primary degradation product, is consistent with an initial oxidation of fructose mainly in furanose form.

Infrared spectroscopy of the reaction mixture after oxidation of D-fructose indicated the presence of small amounts of a γ-lactone. This was confirmed by the isolation of D-erythrono-1,4-lactone (XI) after acid hydrolysis. The 3-*O*-glycolyl derivative (X) is presumably the precursor of this compound, and its formation is in agreement with the assumption that D-fructose initially is cleaved between C-2 and C-3 in furanose form. It is in this connection worth to mention that the formation of aldonolactones has been observed in this laboratory to be a competing reaction to degradation when aldopentoses are treated with silver carbonate on Celite in methanol,[11] and recently the formation of D-galactono-1,4-lactone and D-lyxose was reported by Fetizon and Moreau when D-galactose was oxidized with the same oxidant in ethanol.[12]

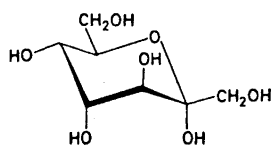
One octulose, two heptuloses, and two hexuloses, in addition to D-fructose, have also been oxidized. The main products obtained after hydrolysis and removal of acidic compounds were the aldoses resulting from glycol cleavage between C-2 and C-3 of the ketoses, as shown by chromatography and electrophoresis. Varying amounts of the aldoses, formed by one subsequent degradation, were also detected (Table 1).

Table 1. Products obtained from the ketoses with silver carbonate on Celite in methanol after hydrolysis and removal of acidic compounds, detected by electrophoresis and chromatography.

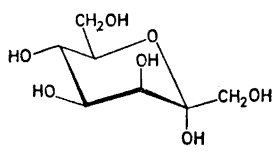
2-Ketose	Major product	Minor product
D-Tagatose	Threose	Glyceraldehyde
D-Psicose	Erythrose	Glyceraldehyde
D-*altro*-Heptulose	Ribose	Erythrose
D-*manno*-Heptulose	Arabinose	Erythrose
D-*glycero*-D-*manno*-Octulose	Altrose	Ribose [a]

[a] The yield of the minor product in this case was relatively high.

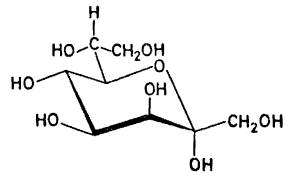
The product mixture after oxidation of the hexuloses did not contain detectable amounts of pentonolactones. Since the pentonolactones seem to be relatively stable to the oxidant under the reaction conditions employed,[11] the possibility of significant initial cleavage between C-1 and C-2 is excluded. The oxidant thus seems to be nearer related to lead tetraacetate than to periodate in degradation of ketoses. In the case of *manno*-heptulose, however, traces of a compound with chromatographic behaviour corresponding to that of mannonolactone were detected. This compound is the product expected after initial cleavage of the heptulose between C-1 and C-2.



XII



XIII



XIV

The approximate minimum reaction temperatures at which detectable degradation of the ketoses occurred within 15 min are shown in Table 2. It is seen that three of the hexuloses and D-*altro*-heptulose (XII) are oxidized at about 20°C, whereas D-*manno*-heptulose (XIII) and its homomorphous sugar D-*glycero*-D-*manno*-octulose (XIV) need considerably higher temperatures.

Table 2. Approximate temperatures below which no degradation product could be detected within 15 min on treatment of the ketoses with silver carbonate on Celite in methanol.

2-Ketose	Approximate minimum reaction temperature (°C)	Initial cleavage between C-2 and C-3 with periodate [9] (%)
D-Fructose	20	53
L-Sorbose	22	31
D-Tagatose	20	20
D-Psicose	27	–
D-*altro*-Heptulose	22	–
D-*manno*-Heptulose	35	0
D-*glycero*-D-*manno*-Octulose	40	–

D-Tagatose [13] and especially D-fructose are known to exist in solution as a mixture of different forms, and L-sorbose has been reported to exhibit small, complex mutarotation.[14] D-*manno*-Heptulose, however, does not show mutarotation,[9] and it is assumed to be very stable in α-pyranose form in the *C1* (D) conformation having the two hydroxy-methyl groups, as well as two of the secondary hydroxyl groups, equatorially attached. The *trans* diaxial arrangement of the hydroxyl groups at C-2 and C-3 is a favorable situation as a result of the anomeric and the *Δ*2 effect. The same must be supposed for the homomorphous sugar D-*glycero*-D-*manno*-octulose (XIV). For D-*altro*-heptulose (XII) on the other hand, the steric situation is less favorable in the pyranose form, because of the diaxial interaction between the hydroxyl groups at C-2 and C-4.

The explanation of the low reactivity to the oxidant of the sugars with *manno*-configuration is possibly that relatively much energy is required to bring these sugars from their stable form into a ring form and conformation suitable for cleavage between C-2 and C-3. It is in this connection worth to recognize that initial cleavage with periodate does not occur between C-2 and C-3 in the heptuloses and octuloses which on steric grounds must be assumed to be most stable in chair conformation in pyranose form, notably those with *manno*- and *gluco*-configurations, and their homomorphous sugars. D-Fructose, L-sorbose, and D-tagatose, on the other hand, are cleaved initially also between C-2 and C-3 by this reagent [9] (Table 2). It seems by inspection of the table that some correlation exists between the degree of initial C-2 – C-3 cleavage with periodate and the reactivity with silver carbonate on Celite for three of the ketoses investigated with both oxidants. D-Tagatose, however, is oxidized at a lower temperature than L-sorbose with silver carbonate on Celite, whereas the degree of cleavage between C-2 and C-3 of this sugar with periodate is less

than for L-sorbose. It seemed desirable to examine nearer the rate of oxidation of the hexuloses with silver carbonate on Celite, and the oxidation of these sugars at 30°C was followed using a colorimetric method. The results (Fig. 1) support the observation that D-tagatose is easily oxidized. At this temperature, D-tagatose is oxidized with the highest initial rate of the hexuloses.

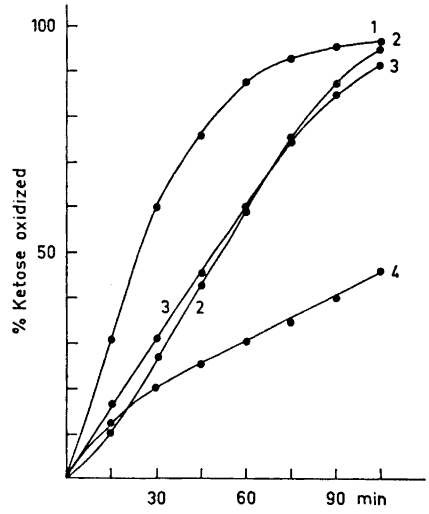


Fig. 1. Oxidation of the hexuloses at 30°C with silver carbonate on Celite in methanol. 1, D-Tagatose; 2, D-fructose; 3, L-sorbose; 4, D-psicose.

In addition to its applicability in synthesis of L-threose from L-sorbose,[10] silver carbonate on Celite may be an alternative to lead tetraacetate in identification of heptuloses and octuloses. The latter oxidant seems to cleave the primary degradation product more rapidly than it reacts with the ketoses. Silver carbonate on Celite, on the other hand, gives mainly one degradation under the conditions employed. Information about the configuration at one carbon atom more (C-4 of the ketoses) is thus obtained with this oxidant.

EXPERIMENTAL

Paper chromatography was performed on Whatman No. 1 and 3 MM papers in the solvent systems (v/v): (A) butanol-pyridine-water 5:3:2, (B) butanol-ethanol-water 40:11:19, and (C) butanone-acetone-formic acid-water 40:2:1:6. Thin-layer chromatography (TLC) was run on Silica gel G in (D) benzene-ethanol 3:1, (E) benzene-ethanol 5:1, (F) chloroform-methanol 15:1, and (G) chloroform-methanol 30:1. Paper electrophoresis was performed on Whatman No. 1 paper in borate buffer, pH 10. As spray reagents were used hydroxylamine-ferric chloride [15] for esters and lactones, diphenylamine-aniline-phosphoric acid [16] and aniline hydrogenphthalate for reducing sugars, and sulphanilamide-β-naphthol-sodium nitrite [17] for acids.

Oxidation of D-*fructose (I).* D-Fructose (I) (500 mg) in methanol (100 ml) was stirred with silver carbonate on Celite [18] (11 g) at 35°C for 35 min. The solution was filtered and the solvent evaporated under reduced pressure. The syrupy residue showed strong infrared absorption at 1735 cm^{-1} and a shoulder at 1770 − 1780 cm^{-1}. The syryp contained as major component a compound which was detectable with hydroxylamine-ferric chloride as well as with diphenylamine-aniline-phosphoric acid after TLC (solvent D). At least

three faster moving compounds were also present in small amounts. The syrup was treated with sulphuric acid, 0.2 M, for 48 h at room temperature, the solution was then neutralized with Dowex 1 (bicarbonate) ion exchanger, filtered and the solvent evaporated. The resulting syrup (192 mg) contained as major component a compound with electrophoretic, paper- (solvent A), and thin-layer (solvent D) chromatographic mobilities corresponding to those of erythrose. TLC and electrophoresis showed in addition the presence of a compound with mobilities and colours after spraying corresponding to those of glyceraldehyde. Traces of two compounds with higher mobility (TLC) were also present.

2,3-O-Isopropylidene-D-erythrose (IV). The syrup obtained as described above was shaken with acetone (20 ml) containing sulphuric acid (0.15 ml) for 3 h. The solution was then neutralized with solid sodium bicarbonate, filtered and the solvent evaporated. The residue was dissolved in benzene (50 ml), the benzene solution extracted with water (3 × 20 ml) and the water evaporated to give syrupy 2,3-*O*-isopropylidene-D-erythrose (IV); the yield was 165 mg (37 % based on fructose). The product was indistinguishable from authentic 2,3-*O*-isopropylidene-L-erythrose [3] by TLC (solvent F), $[\alpha]_D$ −72° (*c* 1, water) {lit.[19] −78°}.

2,3-O-Isopropylidene-D-erythrono-1,4-lactone (V). 2,3-*O*-Isopropylidene-D-erythrose (IV), obtained as described above, (125 mg) in benzene (30 ml), was refluxed with silver carbonate on Celite (3.5 g) for 2 h. The solution was filtered and the solvent evaporated. Crystallization of the residue from petroleum ether (b.p. 40 − 65°C) afforded 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone (V), 101 mg (82 %). After recrystallization from the same solvent it had m.p. 67 − 69°C (lit.[20] 65 − 67.5°C), and $[\alpha]_D$ −114° (*c* 1, water) {lit.[20] −116°}. The compound was indistinguishable by TLC (solvent G) from a sample of the L-enantiomeric compound.[3]

Identification of glycolic acid (VI). D-Fructose (I) (500 mg) was oxidized as described above, and the product mixture was hydrolyzed in trifluoroacetic acid, 0.2 M, at 75°C overnight. The solvent was evaporated, and the residue stirred with Dowex 50 W (H^+ form) ion exchanger in methanol (50 ml) for 4 h. After filtration and evaporation of the solvent, the residue was extracted with benzene (5 × 15 ml). The benzene extracts were combined, and the solvent removed to give a syrup (67 mg), containing mainly methyl glycolate (VII). The chromatographic mobility (TLC solvents E and F) corresponded to that of authentic methyl glycolate, and the infrared spectrum was identical with that of the authentic sample, except for one small additional absorption band, presumably resulting from impurity.

The syrup was hydrolyzed overnight in 0.5 M trifluoroacetic acid (5 ml) at 60°C. The trifluoroacetic acid and the water were removed under reduced pressure, and the residue subjected to paper chromatography (solvent C). The major component was indistinguishable from glycolic acid; small amounts of a compound with lower mobility were also present.

Prolonged oxidation of D-fructose (I), identification of D-glyceraldehyde (IX). D-Fructose (I) (250 mg) was stirred at 35°C with silver carbonate on Celite (10 g) in methanol (80 ml) for 50 min. After filtration of the solution, a few drops of acetic acid were added (to prevent cleavage of formic ester during work up), and the solvent was removed under reduced pressure. The residue contained a major component with chromatographic mobility (TLC solvent E) corresponding to that of 3-*O*-glycolyl-2-*O*-formyl-D-glyceraldehyde, prepared from D-fructose by oxidation with lead tetraacetate.[21] The residue was hydrolyzed in 0.2 M sulphuric acid (5 ml) for 48 h at room temperature. The solution was neutralized with Dowex 1 (bicarbonate) ion exchanger, and the water removed under reduced pressure to give a syrupy residue (54 mg). The syrup contained mainly a compound with chromatographic (TLC solvent D) and electrophoretic mobilities corresponding to those of glyceraldehyde. The compound was purified by preparative TLC (solvent D), the resulting product (34 mg) gave a dimedone derivative (3 mg after recrystallization from ethanol-water) m.p. 194 − 198°C, (lit.[21] 196 − 198°), $[\alpha]_D$ +175° ± 25° (*c* 0.2 ethanol) {lit.[21] +210°}.

Identification of D-erythrono-1,4-lactone (XI). D-Fructose (I) (250 mg) was oxidized with silver carbonate on Celite (6 g) in methanol (50 ml) at 38 − 39°C for 40 min. After filtration of the solution, the solvent was removed and the residue hydrolyzed in trifluoroacetic acid, 0.5 M (5 ml), overnight at 60°C. After removal of water and trifluoroacetic acid under reduced pressure, the resulting residue was subjected to preparative paper chromatography (solvent A). The fraction with mobility corresponding to that of

erythrono-1,4-lactone was purified further by TLC (solvent D), affording D-erythrono-1,4-lactone (XI) as a chromatographically homogeneous syrup (18 mg). Treatment of the syrup with acetone-anhydrous cupric sulphate overnight, filtration and evaporation of the solvent gave a partially crystalline residue. Extraction of the residue with petroleum ether (b.p. 40 – 65°), evaporation of the solvent and recrystallization from the same solvent afforded 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone (V) (2 – 3 mg), m.p. 68°C (lit.[20] 65 – 67.5°), $[\alpha]_D$ $-90° \pm 15°$ (*c* 0.2, water) {lit.[20] $-116°$}. The compound was chromatographically indistinguishable (TLC solvent G) from authentic 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone.

Oxidation of the primary oxidation product from D-*fructose with lead tetraacetate.* D-Fructose (I) (250 mg) was oxidized at 35°C with silver carbonate on Celite in methanol (50 ml) for 35 min. The solution was filtered and the solvent evaporated after addition of a few drops of acetic acid. The reaction mixture did not contain any unreacted fructose as shown by TLC (solvent D). The residue was dissolved in acetic acid (12 ml) and stirred with lead tetraacetate (1 g) for 10 min at 16 – 18°C and further 10 min at room temperature. A solution of anhydrous oxalic acid (0.2 g) in acetic acid (2 ml) was then added, the solution was filtered and the solvent evaporated. The residue was by TLC (solvent E) shown to contain as main component a compound with mobility corresponding to that of 3-*O*-formyl-2-*O*-glycolyl-D-glyceraldehyde. The residue was hydrolyzed in 0.2 M sulphuric acid at room temperature for 48 h, the solution was then neutralized with Dowex 1 (bicarbonate) resin. Electrophoresis of the solution indicated the presence of exclusively one component, TLC (solvent D) showed the presence of a major product; the mobilities corresponded to those of glyceraldehyde. The colours with the spray reagent were identical with those given by authentic glyceraldehyde. TLC showed in addition the presence of minor amounts of a faster moving component.

Oxidation of the other 2-ketoses. The ketoses were oxidized in the same manner as described for D-fructose. The temperatures employed were from 35 to 45°C. After hydrolysis in 0.2 M sulphuric acid at room temperature for 48 h and neutralization with Dowex 1 (bicarbonate) resin, the products were detected by electrophoresis, paper chromatography (solvent A) and in part by TLC (solvent D); the results are shown in Table 1.

For determination of the approximate minimum reaction temperatures, TLC was used to detect the presence of degradation products. The results are shown in Table 2.

Oxidation rate of the hexuloses. The hexuloses (50 mg) in methanol (10 ml) were oxidized after completion of mutarotation with silver carbonate on Celite (1.2 g) at 30°C. Aliquots (10 µl) were withdrawn at intervals, diluted with water (to 1 ml) and the amount of unreacted hexulose present determined colorimetrically with the thiobarbituric acid reagent.[22] The results are shown in Fig. 1.

Acknowledgements. The author is indebted to Cand. pharm. Guri Haustveit for a gift of D-*altro*-heptulose and D-*glycero*-D-*manno*-octulose, and to Miss Astrid Fosdahl for valuable technical assistance.

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Received December 7, 1972.