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The Oxidation of Glycosides

IV*. Oxidation of Methyl β-D-Glucoside with Dichromate

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Methyl β-D-glucopyranoside has been oxidized with dichromate in the presence of oxalic acid, and from the resulting mixture two carbonyl derivatives have been isolated. One of these, a crystalline product, has the structure of methyl β-D-3-ketoglucopyranoside. On reduction it yields a mixture of methyl glucoside and methyl alloside, which proves the position of the keto group. The other substance, methyl β-D-6-aldehydoglucopyranoside, is amorphous and on reduction yields methyl β-glucoside only. The substances are of interest as models for oxycelluloses.

As part of our program on the study of oxycelluloses, the oxidation of methyl β-D-glucopyranoside (I) with dichromate has been investigated. It is known that when cellulose is oxidized with chromate in the presence of oxalic acid[1], an extreme type of oxycellulose with high copper number and practically no carboxyl groups is obtained, and as we were interested in the carbonyl derivatives, this oxidizing agent was used. From the neutral part of the reaction mixture, after separations on carbon and thick filter paper (See Experimental) two oxidized products were isolated.

The first product (II) was crystalline, m.p. 127—128° and specific rotation −68° in water. It was strongly reducing and gave positive reactions with 2,4-dinitrophenylhydrazine as well as with typical sugar reagents. The analyses were consistent with the formula $C_7H_{12}O_6$, that is a methyl glucoside with one of the hydroxyl groups oxidized to a carbonyl group. On reduction with Raney nickel[2] it yielded a mixture of methyl β-glucoside and another substance (III), m.p. 150—151° and specific rotation −53° in water. With the carbonyl group in C_2, C_3 or C_4, a mannoside, alloside or galactoside, respectively, should be formed, but the data for the substance do not agree with those for methyl β-mannoside or methyl β-galactoside. On hydrolysis the substance (III) yielded a reducing sugar with colour reactions and R_F-values in different

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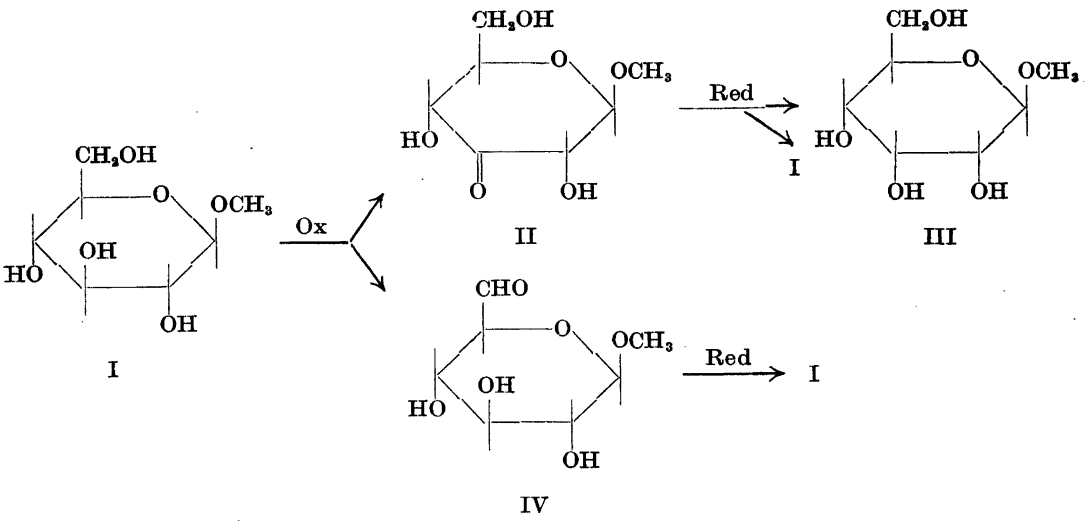


solvents indistinguishable from those of allose. Methyl β-D-allopyranoside (III) has not been described previously in the literature, but the data in Table 1 show that the rotation observed for the substance is in good agreement with that expected.

Table 1. Specific rotations of some β-hexoses and their methyl β-glucosides.

Hexose	$[\alpha]_D$ of free sugar in β-form	$[\alpha]_D$ of methyl β-glycoside	Δ
D-Glucose	19	−34	53
D-Galactose	54	0	54
D-Allose [a]	1	−53 [b]	54

[a] Ref.[3] [b] Present investigation.

It is consequently proved that II has the structure of methyl β-D-3-keto-glucopyranoside, and by these reactions an interconversion from the D-glucose to the D-allose series has been accomplished.

The other product (IV), an amorphous powder, was also strongly reducing and gave positive reactions with 2,4-dinitrophenylhydrazine and sugar reagents. It gave two spots and considerable trailing between them on the paper chromatogram, but when either of these was cut out, extracted and rechromatographed, the same picture was obtained. A probable explanation of this behaviour is that the substance occurs in different forms, the equilibrium between which is set up rather slowly. This rendered the purification of it difficult and it is questionable whether the substance is quite pure. In contra-

distinction to the first substance (II) it gave positive reaction with Schiff's reagent and on reduction yielded methyl β-glucoside only. These facts, as well as the result of the periodate oxidation of the substance, are in agreement with the structure of methyl β-D-6-aldehydoglucopyranoside (IV). The percentage of IV in the amorphous powder, which probably contained small amounts of salts and water, was estimated to be 79 % by hypoiodite oxidation. Similar substances, methyl glycosides of D-mannohexodialdose, have recently been prepared by Ballou and Fischer[4].

As considerable losses could not be avoided during the isolation of the substances described above, it is difficult to estimate how much of the total oxidized, non-acidic material they represent. It seems, however, as if they are the two most important constituents and that the yield of the aldehyde derivative is the higher. The presence of both aldehyde and keto groups in oxidized cellulose and starch have been demonstrated analytically by Purves and coworkers[5,6]. As they point out, there is no definite proof that the aldehyde groups occupy the sixth position, but they regard it as very probable, and this is strongly supported by the result of the present investigation. They have also proved that a considerable part of the carbonyl groups, at least 17 % in an oxidized starch, occurred as 2-keto glucose residues. In the present investigation no 2-keto glucoside was isolated but the corresponding 3-keto derivative isolated amounted to about 15 % of the total carbonyl derivatives. Both substances described above are thus of interest as model substances for oxycelluloses and will be further investigated in this respect.

EXPERIMENTAL

Melting points uncorrected. Evaporations performed under reduced pressure and a bath temperature of 40°. Whatman 1 and Whatman 3 MM filter papers used for paper chromatography. Solvents used:

A. Butanol-ethanol-water, 5:1:4.
B. Ethyl acetate-acetic acid-water, 3:1:1.
C. Butanol-pyridine-water, 3:1:1.5.

Oxidation of methyl β-glucoside and fractionation of product. Methyl β-glucoside (30 g) was dissolved in a mixture of 0.1 *N* potassium dichromate (1 300 ml) and 0.5 *N* oxalic acid (1 300 ml). After 20 hours at room temperature excess of calcium carbonate was added and the mixture stirred overnight, filtered, the solids washed with water of 50° and the combined filtrates concentrated to 100 ml. The solution was then diluted with 90 % ethanol (300 ml) and kept at 5° for 4 hours. The precipitated chromium salts were removed by filtration and washed with 75 % ethanol. By this treatment practically all the chromium salts were removed and no neutral carbonyl compounds could be found in the precipitate. The filtrate and washings were concentrated to a thick sirup, from which unchanged methyl β-glucoside (22 g) could be recovered by crystallisation from ethanol. From the mother liquors a thick sirup (8 g) was obtained by concentration. The recovered methyl β-glucoside plus fresh material (8 g) was oxidized and worked up as described above. This procedure was repeated a third time.

The combined sirups (25 g) were dissolved in 1 % aqueous ethanol (100 ml) and added to the top of a column (50 × 6 cm), built up of equal parts of carbon (Darco 60) and Celite. The column was eluted with aqueous ethanol, 6 000 ml, the concentration of which was continuously increased from 1 % to 8 %, then 8 000 ml, 8—20 %, then 8 000 ml, 20—30 %, and finally 4 000 ml 75 % ethanol. The eluate was divided into fractions and investigated by paper chromatography. The main amount of the sirup (19.1 g) eluted with 1—6 % ethanol, consisted of unchanged methyl-β-glucoside, which was almost

completely separated from the carbonyl compounds. There were also small amounts of glucose and chromium salts in this fraction. The carbonyl compounds (1.7 g) were eluted with 6—10 % ethanol. The material which appeared after 10 % ethanol (1.0 g) was a complex mixture, probably containing only small amounts of mono-carbonyl compounds. Attempts to separate the carbonyl compounds on cellulose columns were not successful. However, a separation was accomplished using thick filterpaper. About 2 mg per cm paper (Whatman 3 MM) was used and the chromatograms were run for 7 hours in solvent B, dried and then run for 7 hours in solvent A. The substances were located and isolated in the ordinary manner. From the separation on thick paper the ratio of substance II to IV was calculated to be 1:4.

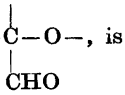
Methyl β-D-3-ketoglucopyranoside (II). The eluate from the thick papers containing methyl β-D-3-ketoglucopyranoside was deionised by passing it through the ion exchange resins Amberlite IR 120 and IR 4B and concentrated to dryness. The residue, which crystallised and amounted to about 15 % of the total carbonyl compounds, was recrystallised from ethanol. M. p. 127—128°. $[\alpha]_D^{20}$ −68° (water, c = 2). (Found: C 43.9; H 6.25; OCH_3 15.1. Calc. for $C_7H_{12}O_6$ (192.2): C 43.7; H 6.29; OCH_3 16.1).

On periodate oxidation with 0.1 *M* solution, buffered with acetate to pH 4.0, at room temperature, the substance overnight consumed 0.7 moles of reagent. By oxidation with sodium metaperiodate under similar conditions, 1.0 moles of acid were formed. (These oxidations, as well as those described below, were made with a very small amount of material and thus a better agreement with the calculated values, 1 mole periodate and 1 mole acid, could hardly be expected.)

The $R_{glucose}$-values for the substance were 1.98 (Solvent A), 1.82 (B) and 2.70 (C). The corresponding values for methyl β-glucoside were 1.77, 1.67 and 2.02. Colour reactions: Anisidine phosphate, first yellow then greyish brown; Aniline hydrogen phthalate, greyish brown; Resorcinol-hydrochloric acid, dark brown.

Hydrogenation of II. II (45 mg) was dissolved in 70 % ethanol (5 ml) and Raney nickel (500 mg) was added. The mixture was refluxed on the steam bath for 3 hours, filtered and concentrated. A small amount of the reaction product was hydrolysed with 0.1 *N* hydrochloric acid at 100° overnight. The hydrolysate gave two spots on the chromatogram, indistinguishable from those of glucose and allose. Crystalline methyl β-D-alloside separated when the product of hydrogenation was dissolved in ethanol and was purified by recrystallisation from the same solvent. Yield, 16 mg. M. p. 150—151°. $[\alpha]_D^{20}$ −53° (water, c = 2). From the mother liquors a small amount of pure methyl β-glucoside (6 mg) was isolated. M. p. 109—110°, undepressed on admixture with authentic material.

The methyl alloside on hydrolysis yielded only one reducing sugar, chromatographically indistinguishable from allose. On periodate oxidation the alloside consumed 1.7 moles of reagent, under the formation of 0.9 moles of acid. The required values are 2 and 1 respectively.

Methyl β-D-6-aldehydoglucopyranoside (IV). The purification of IV was rather difficult as it gave several spots with trailing between them on the chromatogram. The eluates from the thick filter paper were concentrated without previous ion exchange and thus the amorphous product contained some salts from the paper in addition to water. The amount of this substance was about 60 % of the total carbonyl compounds. The product consumed hypoiodite[7] corresponding to a purity of 79 %. On periodate oxidation it consumed 4.6 moles of reagent (corrected to pure substance). As a group containing "active" hydrogen,  , is formed during the oxidation[8], a consumption of 5 moles is required by IV.

The $R_{glucose}$-values for the substance were 0.73, 2.35 (A), long band with centre at 1.05 (B) and 0.98, 2.90 (C).

Colour reactions: Anisidine phosphate, first yellow, then reddish brown; Aniline hydrogen phthalate, reddish brown; Resorcinol-hydrochloric acid, pink.

IV (20 mg) on reduction with Raney nickel as described above, yielded pure methyl β-glucoside (6 mg), identical with authentic material. Glucose was the only reducing sugar detected in the hydrolysate of the crude reaction product.

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