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REACTIONS OF METHYL ALDOHEXOPYRANOSIDES WITH ALKALINE HYDROGEN PEROXIDE*

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ABSTRACT

Reaction of methyl α-D-glucopyranoside and methyl α-D-mannopyranoside with alkaline hydrogen peroxide and a ferrous salt, at room temperature and below, afforded the corresponding D-glycosiduronic acids. On dehydration, the acids gave the corresponding gamma lactones, with a shift of the pyranoid ring to a furanoid ring. Surprisingly, the glycosidic methyl group was retained during the oxidation reactions and pyranose–furanose interconversions. This retention is rationalized by a mechanism involving formation of a pseudo-acyclic intermediate. Another unexpected reaction was the conversion of slightly moist methyl D-glucopyranosiduronolactone syrup, on standing for 5–6 days at room temperature, into crystalline D-glucofuranurono-6,3-lactone, and of methyl α-D-mannopyranosidurono-6,3-lactone into crystalline D-mannofuranurono-6,3-lactone.

INTRODUCTION

The oxidative degradation of carbohydrates by alkaline hydrogen peroxide in the presence and absence of iron salts has been the object of study for many years. In 1894, Fenton[2] discovered that the oxidative power of hydrogen peroxide is greatly enhanced by a ferrous salt. Shortly thereafter, Fenton and Jackson[3] found that the reaction of D-mannitol with hydrogen peroxide and a ferrous salt affords D-mannose in substantial yield.

With aldohexopyranosides, the primary hydroxyl group is attacked preferentially, but not exclusively. Thus, Smolenski[4], in 1924, reported the preparation of methyl D-glucosiduronic acid, in yields of up to 30%, by oxidation of methyl α-D-glucopyranoside with hydrogen peroxide in the presence of a ferric salt. Later, Fraser-Reid and co-workers[5] found that, with the Fenton reagent, 3,4-di-*O*-methyl-D-mannitol affords 3,4-di-*O*-methyl-D-mannose, 3-*O*-methyl-D-mannose, 3-*O*-methyl-

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D-mannitol, and D-mannitol. In 1974, Ericson *et al.*[6] reported that, on treatment with alkaline hydrogen peroxide at 95°, methyl β-D-glucopyranoside gives the following major products: methanol, two dicarboxylic acids, two methyl 2-*C*-carboxy-β-D-pentofuranosides, glycolic acid, and formic acid. These results show that, under certain conditions, the Fenton reagent attacks the glycosidic structure at several points, and that the initial, oxidation step is followed by processes of enolization, beta elimination, fragmentation, and saccharinic acid formation. More recently, Weaver *et al.*[7] reported that, on treatment with alkaline hydrogen peroxide at 60°, methyl α-D-glucopyranoside gives rise to an organic peroxide, and, possibly, a 3-ketone derivative. Apparently, the reaction products depend, in part, on the experimental conditions employed.

In accordance with a hypothesis developed by Isbell and co-workers[8], the degradation of a nonreducing carbohydrate by the Fenton reagent, under alkaline conditions, begins with oxidation of one of the hydroxylated carbon atoms of the substrate to a carbonyl group. Nucleophilic addition of hydroperoxide anion to the carbonyl group affords a hydroperoxide adduct which, in the presence of an alpha-hydroxyl group, decomposes by the so-called alpha-hydroxy–hydroperoxide cleavage reaction[9,10]. In the absence of an alpha-hydroxyl group (or a similar electron-releasing group), the adduct decomposes by rupture of either the adjoining C–C bond or a C–H bond[11]. The reactions of alditols and aldonic acids were found to follow this general course. The principal objective of the present investigation was to obtain information on the reactions of aldohexopyranosides under conditions resembling those used for study of alditols and aldonic acids.

TABLE I

OXIDATION[a] OF METHYL GLYCOSIDES BY ALKALINE HYDROGEN PEROXIDE AT 25°

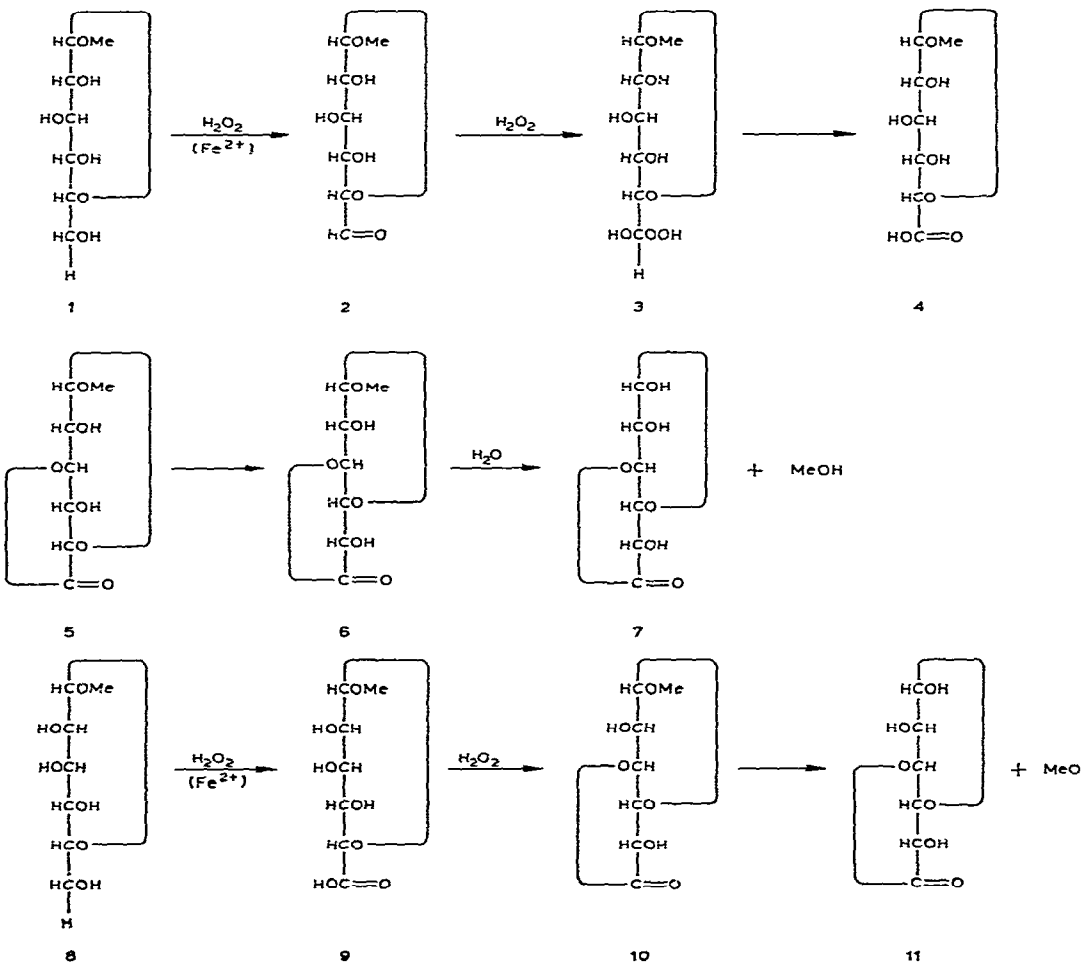
Substrate	*Reaction mixture*	*Reaction time (h)*	$[\alpha]_D^{25}$ *(degrees)*	*Formic acid (mmol/mmol of substrate)*
Methyl α-D-glucopyranoside	(a)	0	+158	—
	(a)	48	+156	0.06
	(b)	66	+143	0.32
Methyl β-D-glucopyranoside	(a)	0	−34	—
	(a)	48	−31	0.26
	(b)	66	−24	0.62
Methyl α-D-mannopyranoside	(a)	0	+79	—
	(a)	48	+78	0.08
	(b)	66	+70	0.29

[a]Reaction mixtures and conditions are fully described in the Experimental section. Reaction mixtures (a) and (b) were similar, except for the presence of ferrous sulfate in (b).

RESULTS AND DISCUSSION

In preliminary experiments, the glycosides were treated, at 25°, with alkaline hydrogen peroxide in the presence, and in the absence, of an iron catalyst. Under the conditions used, optical rotations and determinations of formic acid (see Table I) revealed little reaction in the absence of the iron catalyst, and only partial reaction in its presence. After suitable periods of time, the reaction was stopped, the excess of hydrogen peroxide was decomposed by treatment with activated carbon, and the products were separated by means of ion-exchange resins into a nonvolatile, acid portion and a nonionic portion.

The reaction mixture from the oxidation of methyl α-D-glucopyranoside (**1**) yielded, from the nonionic portion, 89.3% of unreacted glycoside. The major compo-



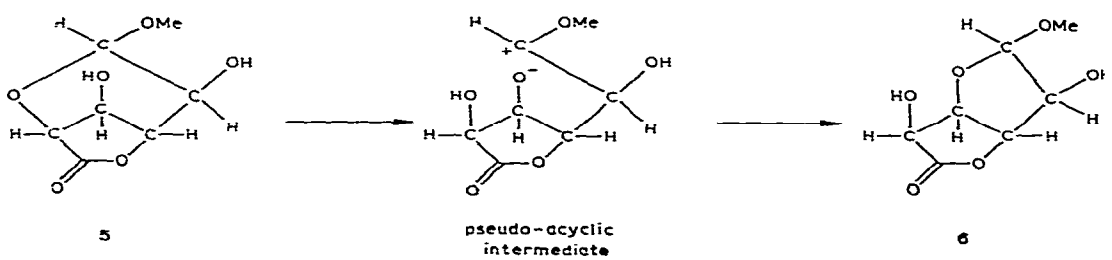
Scheme 1

nent of the acid portion was found to be the methyl glycoside (**4**) of D-glucuronic acid. On treatment with cation-exchange resin, and concentration of the solution, acid **4** was converted into the 6,3-lactone **6**. Formation of **6** may be rationalized by the process depicted in Scheme 1. The process involves abstraction of a hydrogen atom from the primary hydroxyl group of glycoside **1**, followed by production of carbonyl compound **2**. This compound forms the hydroperoxide adduct **3**, which decomposes, to afford methyl α-D-glucopyranosiduronic acid (**4**). On dehydration, acid **4** lactonizes to compound **5**, which undergoes a shift in ring structure to give compound **6**. The properties of **6** were found to be identical to those of syrupy methyl α-D-glucofuranosidurono-6,3-lactone, prepared, for reference, from D-glucofuranurono-6,3-lactone (**7**) by the method of Cadotte *et al.*[12].

Under the same experimental conditions, the reaction mixture from the oxidation of methyl α-D-mannopyranoside (**8**) yielded, from the nonionic portion, 67.5% of unreacted glycoside. The major component of the acid fraction was methyl α-D-mannopyranosiduronic acid (**9**), which, after lactonization and rearrangement, gave compound **10**, isolated as a chromatographically pure syrup. The properties of **10** were found to be the same as those of syrupy methyl D-mannofuranosidurono-6,3-lactone, prepared[12], for reference, from D-mannofuranurono-6,3-lactone (**11**).

Isolation of methyl aldohexofuranosidurono-6,3-lactones **6** and **10** from the reaction products of **1** and **8**, respectively, is noteworthy, because it shows that the methoxyl group of the glycoside is retained during both the oxidation and the isolation process, despite a change in ring structure. Retention of the methoxyl group during the oxidation step is not surprising, but its retention during the conversion of the pyranosiduronic acids **4** and **9** into the furanosiduronolactones **6** and **10** is unusual. The results show that the change in ring structure does not take place through an open-chain, aldehydo modification of the uronic acid. The change may be rationalized by the formation of[13] a "pseudoacyclic intermediate", or transition state, depicted in Scheme 2. By a slight shift in the position of C-1, the pyranoside is converted into the more thermodynamically stable furanoside.

Surprisingly, on standing for five to six days at room temperature, intermediate methyl furanosiduronolactones **6** and **10** decomposed spontaneously, with formation of crystalline D-glucofuranurono-6,3-lactone (**7**) and D-mannofuranurono-6,3-lactone (**11**), respectively. At present, the cause of this unusual instability of the glycosidurono-



Scheme 2. Pyranose–furanose interconversion.

lactones is not known. It is noteworthy that crystalline **7** and **11** have a furanoid structure for the sugar rings, and a gamma structure for the lactone rings[14,15].

EXPERIMENTAL

General methods. — The glycosides studied were commercial products whose purity was checked by measurement of their optical rotation. The reagents used were of the highest commercial grade. The hydrogen peroxide was represented as containing <0.005% of Fe, and the potassium hydroxide, <0.001% of Fe. Silica gel 7731 (Merck) was used for t.l.c., detection being effected by charring with sulfuric acid. Preparative chromatography (p.l.c.) was performed on plates (20 × 20 cm, 250 μm thick) of silica gel; constituents were located by comparison with a developed plate (5 × 20 cm, 250 μm thick). Large-scale, paper chromatography was performed on Whatman No. 3M paper (46 × 57 cm) with 3:2:1:1 butyl acetate–acetic acid–ethanol–water. Column chromatography was conducted on silica gel 7734 (Merck). Optical rotations were determined with a Perkin–Elmer 141 polarimeter by use of 1-dm tubes. I.r. spectra were recorded with a Perkin–Elmer 727 spectrophotometer. ^{13}C-N.m.r. spectra were recorded with a Bruker-WP-80 instrument; solutions containing 50–100 mg/mL were made up in D_2O, with 1,4-dioxane as the internal standard, and the temperature of the sample was 34 ±2°.

Preparation of reference compounds. — Methyl D-glucofuranosidurono-6,3-lactone (**6**) was prepared[12] as a syrup by refluxing D-glucofuranurono-6,3-lactone (**7**, 2 g) with methanol (100 mL) for 6 h in the presence of Dowex 50W-X4 resin. The mixture was filtered, and the filtrate evaporated to dryness, giving almost pure **6** as a syrup; yield, 1.4 g (70%). The optical rotation of the syrup, $[\alpha]_D^{25}$ −54.8° (*c* 2, H_2O), was slightly lower than that reported[12] for crystalline methyl β-D-glucofuranosidurono-6,3-lactone, namely, $[\alpha]_D^{20}$ −56.5° (*c* 1.4, H_2O); it agreed, however, with that (−54.5°) of the product obtained in the present study by oxidation of methyl α-D-glucopyranoside.

Methyl α-D-mannofuranosidurono-6,3-lactone (**10**) was similarly prepared as a syrup from D-mannofuranurono-6,3-lactone (2 g); yield, 1.48 g (74%). The optical rotation of the product, $[\alpha]_D^{25}$ +49.6° (*c* 1.0, H_2O), was somewhat higher than that reported[12] (+46°) for methyl α-D-mannofuranosidurono-6,3-lactone, but was in good agreement with that found by us (+49.2°) for the oxidation product of methyl α-D-mannopyranoside.

Measurements in Table I. — The following ice-cold reagents were added successively to Pyrex test-tubes cooled in ice–water: (*a*) substrate (1 mmol) in ice–water (4 mL), 3M potassium hydroxide (8 mL), and, finally, 30% hydrogen peroxide (4 mL), added dropwise during 10 min; (*b*) reaction mixtures as in (*a*), except for the presence of ferrous sulfate (20 μmol) in the aqueous substrate. The mixtures were held at 25° for the times cited. The excess of hydrogen peroxide was decomposed by adding ~0.5 g of Norit to each tube, and heating the mixtures in a hot-water bath until evolution of oxygen ceased. Each reaction mixture was filtered, and the filtrate was

diluted with water to 100 mL. The measurements of optical rotation and determinations of formic acid reported in Table I were then made. Specific rotations are based on the weight of the original substrate.

Usual procedure for conducting oxidations and separating products. — The substrate in each experiment was treated with hydrogen peroxide under the conditions cited. After the requisite time, activated charcoal (~0.5 g of Norit) was added to the reaction mixture; this was followed by aqueous barium hydroxide (to remove any sulfate present). The mixture was heated in a hot-water bath until evolution of oxygen ceased, and was then filtered. The filtrate was passed successively through a column of Amberlite IR-120 (H^+) cation-exchange resin and one of Duolite A-4 anion-exchange resin. The salt-free eluate and washings from the Duolite column were combined, and evaporated to dryness, and the resulting nonionic fraction was treated as described in the individual experiments.

After separation of the nonionic fraction, the Duolite column was eluted with ammonium hydroxide, and then washed with water. The eluate and washings were combined, concentrated to ~25 mL, and passed through a column of Amberlite IR-120 (H^+) resin. The resulting solution was concentrated to a small volume, and four 5-mL portions of toluene were added and evaporated. Treatment of this acid fraction is described in specific experiments.

Reaction of methyl α-D-glucopyranoside with alkaline hydrogen peroxide. — To an ice-cold solution of methyl α-D-glucopyranoside (0.582 g, 3 mmol) in a mixture of water (18 mL) and 1.0M potassium hydroxide solution (12 mL) was added 30% hydrogen peroxide (3 mL) dropwise. The mixture was kept in ice water for 5 min and for 2 days at 25°, after which it was treated in the usual way for separation of the products. When the neutral fraction was evaporated to a thick syrup, crystalline, unreacted methyl α-D-glucopyranoside (0.520 g, 89.3%) was recovered. Paper chromatography of the acid fraction showed two components. The major, faster-moving component was separated by large-scale, paper chromatography. The eluate was concentrated, and freed of water by the successive addition and evaporation of four 0.5-mL portions of toluene; yield, 0.021 g (3.6%); $[\alpha]_D^{25}$ −55.4° (*c* 0.5, H_2O). The i.r. spectrum and chromatographic behavior of the syrupy product were the same as those of methyl D-glucofuranosidurono-6,3-lactone (**6**) prepared by us, for reference, from D-glucofuranurono-6,3-lactone.

On being kept for 5–6 days at room temperature, the syrupy **6** afforded crystalline D-glucofuranurono-6,3-lactone (**7**), m.p. 168–170°, $[\alpha]_D^{25}$ +18.7° (equil.; *c* 1.0, H_2O); lit.[14] m.p. 167–172°, $[\alpha]_D$ +19.4° (equil.; H_2O).

Reaction of methyl α-D-mannopyranoside with alkaline hydrogen peroxide. — The oxidation was conducted on 0.194 g (1 mmol) of substrate, under the conditions described for the oxidation of methyl α-D-glucopyranoside. The neutral fraction yielded 0.131 g (67.5%) of unreacted substrate. The acid fraction was isolated as a syrup (0.0247 g, 12.7%) that contained two components (paper chromatography). The major, faster-moving component was separated by large-scale paper-chromatography (0.017 g, 8.7%), $[\alpha]_D^{25}$ +49.2° (*c* 1.0, H_2O). It was identified as methyl

α-D-mannofuranosidurono-6,3-lactone (**10**) by comparison of its properties with those of the authentic compound prepared by us from D-mannofuranurono-6,3-lactone (**11**).

On being kept for 5–6 days at room temperature, the syrupy glucoside **10** afforded crystalline **11**, m.p. and mixed m.p. 188–189°, $[\alpha]_D^{25}$ +94.4° (equil.; *c* 0.8, H_2O); lit.[15] $[\alpha]_D^{20}$ +92.2° (equil.; *c* 4, H_2O).

Anal. Calc. for $C_6H_8O_6$: C, 40.91; H, 4.58. Found: C, 40.98; H, 4.76.

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