A Convenient Synthesis of 2,3,6-Tri-*O*-methyl-D-galactose

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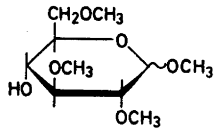
In connection with structural work on oligo- and polysaccharides, 2,3,6-tri-*O*-methyl-D-galactose was needed as a reference substance. A synthesis of this compound from the methyl pyranosides of 2,3-di-*O*-methyl-D-galactose by partial methylation has been reported.[1] The present paper describes an alternative, convenient synthesis in 15 % yield from the methyl pyranosides of 2,3,6-tri-*O*-methyl-D-glucose, a starting material easily obtainable from commercial methyl cellulose.[2]

Oxidation of the methyl 2,3,6-tri-*O*-methyl-D-glucopyranosides (I) with dimethyl sulphoxide-acetic anhydride gave the methyl 2,3,6-tri-*O*-methyl-D-*xylo*-hexo-



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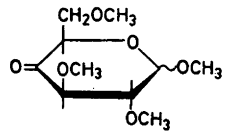

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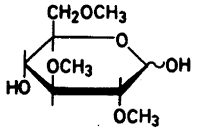

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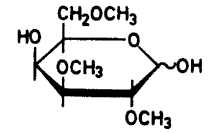

IV

pyranosid-4-uloses (II), which were not characterized. The crude hexopyranosid-ulose mixture was reduced with sodium borohydride and subsequently hydrolyzed. The resulting 2,3,6-tri-*O*-methyl ethers of glucose (III) and galactose (IV) were separated on silica gel, the former could be transformed to the methyl pyranosides again and reused. 2,3,6-Tri-*O*-methyl-D-galactose (IV) was characterized as its aldono-1,4-lactone, and demethylation with boron tribromide gave galactose.

Borohydride reductions of unsubstituted pyranosid-2- and 3-uloses where β-axial interactions do not interfere, are reported to give at least 50 % of the isomers with axial hydroxyl groups,[3,4] and trityl cellulose, partially oxidized to the 2-keto derivative, on reduction with the same reagent and subsequent hydrolysis gives more than 50 % mannose per oxidized unit.[5] In the present case, however, the glucose derivative with an equatorial hydroxyl group preponderated, and this is in accordance with the reported results of a borohydride reduction of an other fully substituted *xylo*-hexopyranosid-4-ulose.[6]

Hydrogenation over Adams catalyst, the method which usually results in formation of most of the isomer with an axial hydroxyl group from pyranosidic ketones,[3,7] was also attempted, but no reduction of the pyranosid-uloses could be recognized. This is most probably due to inactivation of the catalyst by contaminating materials in the crude pyranosid-ulose mixture obtained by oxidation with dimethyl sulphoxide-acetic anhydride. Since a previous chromatographic purification of the pyranosid-uloses would complicate the procedure, the borohydride reduction method was chosen in spite of the unfavorable product ratio.

In a preliminary investigation, the methyl 2,3,6-tri-*O*-methyl-D-glucosides were used in the synthesis without prior removal of the small amounts of furanosides present in the equilibrium mixture, a third product was then recognized chromatographically. When a prior removal of the furanosides from the starting material was performed by weak hydrolysis, followed by extraction of the formed 2,3,6-tri-*O*-methyl-D-glucose from a benzene solution with small amounts of water, this third compound could not be detected among the products. This fact indicates that the compound is 2,3,6-tri-*O*-methyl-L-idose, the 5-epimer of the glucose derivative. Work is going on to modify the above procedure to give this compound in reasonable yield.

Experimental. Thin layer chromatography was performed on silica gel plates in the following solvent systems (v/v): (A) benzene-ethanol, 20:3, (B) benzene-ethanol, 10:1, (C) butanone saturated with 10 % aqueous ammonia, (D) benzene-acetone, 1:1, and (E) propanol-nitromethane-water, 5:4:1. Paper chromatograms were run on Whatman No. 1 papers in the solvent systems: (F) butanol-pyridine-water, 5:3:2, and (G) ethyl acetate-

acetic acid-formic acid-water, 18:3:1:4. Electrophoresis was carried out on Munktells paper for chromatography No. 302 in 0.1 M borate buffer, pH 10. Localization of the spots was attained with aniline oxalate, diphenylamine-aniline-phosphoric acid, *p*-anisidine hydrochloride, and hydroxylamine-ferric chloride (for lactones) reagents. Evaporations were performed under reduced pressure.

*Methyl 2,3,6-tri-*O*-methyl-*D*-glucopyranosides* (*I*). The methyl glycoside mixture of 2,3,6-tri-*O*-methyl-D-glucose, prepared essentially as described by Hess and Neumann,[2] was heated for 2 h at 90° in 1 % oxalic acid, the solution was neutralized with calcium carbonate, filtered and evaporated to dryness. The residue was taken up in benzene, and the benzene solution was extracted once with one part of water to thirty parts of benzene. The water extract was reextracted with an equal amount of benzene, the combined benzene solutions were dried over sodium sulphate and the solvent evaporated. A small amount of the pyranosidic mixture obtained in this way was separated on thin layer plates (solvent A), giving the anomers as colourless syrups. The slowest moving anomer had $[\alpha]_D$ +147° (*c* 1, methanol), lit. value [8] +149° for methyl 2,3,6-tri-*O*-methyl-α-D-glucopyranoside. The fastest moving anomer had $[\alpha]_D$ −43° (*c* 1, chloroform), lit. value [9] −48° for methyl 2,3,6-tri-*O*-methyl-α-D-glucopyranoside.

*Oxidation of methyl 2,3,6-tri-*O*-methyl-*D*-glucopyranosides* (*I*). A mixture of the methyl 2,3,6-tri-*O*-methyl-D-glucopyranosides (I) (2.5 g) in dimethyl sulphoxide (30 ml) and acetic anhydride (20 ml) was kept at room temperature over night, and then at 40° for 45 min. After cooling, chloroform (300 ml) was added, and the solution was shaken with saturated bicarbonate (50 ml) for 1 h. The two layers were separated and the chloroform layer washed four times with water (40 ml portions). The chloroform solution was dried over sodium sulphate and the solvent evaporated, giving a sypury residue. Thin layer chromatography (solvent B) showed the presence of mainly two components; both gave immediately a violet colour with the diphenylamine-aniline-phosphoric acid reagent after heating of the plates for 3−4 min at 110° before spraying, conditions insufficient to give colour with sugars containing no free carbonyl groups. Small amounts of the pyranosid-ulose mixture were purified by thin layer chromatography (solvent B), giving an oil which showed a strong infrared absorption at 1730 cm^{-1} ($CHCl_3$).

*2,3,6-Tri-*O*-methyl-*D*-galactose* (*IV*). The crude methyl 2,3,6-tri-*O*-methyl-D-*xylo*-hexopyranoside-4-ulose (II) was dissolved in 0.05 M borate buffer, pH 9.2, (50 ml) and treated with sodium borohydride (2 g) for 2 h at room temperature. Excess borohydride was decomposed with Amberlite IR-120 (H^+) ion exchange resin, the solution filtered and the solvent removed. The boric acid formed was removed by repeated distillations of methanol from the residue, which was subsequently heated in 0.5 N sulphuric acid (60 ml) at 50° for 40 h. After neutralisation of the solution with barium carbonate, filtration and evaporation of the water, the syrupy product was added to a column (4 × 45 cm) of boric acid impregnated silica gel (200 g of the gel treated with 400 ml 0.02 M boric acid, dried and activated at 110° for one hour). Elution was performed with butanone saturated with 10 % aqueous ammonia; fractions of 6 ml were collected. The carbohydrate containing fractions were localized by thin layer chromatography (solvent C), and fractions 39−49, 50−54, and 55−67 were combined. After evaporation of the solvent, the residues were taken up in water (200 ml), the water solutions were extracted twice with benzene (15 ml portions), and subsequently filtered through a small coloumn of Dowex 50 W (H^+) ion exchange resin. This procedure removed small amounts of coloured material which had been formed during the chromatographic process. Fractions 39−49 contained 2,3,6-tri-*O*-methyl-D-glucose (1.55 g), fractions 50−54 a mixture (220 mg) of the same compound and 2,3,6-tri-*O*-methyl-D-galactose (IV), and fractions 55−67 contained 2,3,6-tri-*O*-methyl-D-galactose as the sole component (250 mg). From fractions 50−54, more of the galactose derivative (IV) was obtained (100 mg) on preparative thin layer chromatography (solvent C), the total yield of 2,3,6-tri-*O*-methyl-D-galactose was 350 mg (15 %) as an almost colourless oil; $[\alpha]_D$ +85° (*c* 1, water), lit. values +80°,[10] +87°,[11] +95°,[1] chromatographically indistinguishable from an authentic specimen, which was on hand in small amounts, in solvents A, C, and D. Demethylation with boron tribromide [12] gave galactose as main product, as shown by thin layer chromatography (solvent E); small amounts of oligosaccharides also seemed to have been formed. The galactose was purified by paper chromarography (solvent F) giving a syrup which crystallized slowly, and which was indistinguishable from authentic galactose by paper chromatography (solvents F and G) and electrophoresis.

Oxidation of 2,3,6-tri-*O*-methyl-D-galactose (IV) (30 mg) with bromine water,[1] separation of the formed lactone from unoxidized material by thin layer chromatography (solvent B),

and recrystallization from ethyl ether-petroleum ether gave 2,3,6-tri-*O*-methyl-D-galactono-1,4-lactone (8 mg) as colourless crystals; m.p. 101–102°, lit. value[1] 100–101°, $[\alpha]_D$ −26° (*c* 0.7, water), lit. value[1] −29°. A strong infrared absorption was observed at 1785 cm^{-1} (in chloroform), which is characteristic of γ-lactones.

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Substituent Effects of Sulfur Groups

V. Note on the Influence of Positive Sulfur on the ESCA Shifts of Adjacent Carbon and Oxygen

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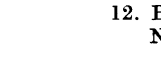
In previous papers various types of substituent effects on ESCA shifts in sulfur substituted compounds have been investigated and discussed.[1,2] In Ref. 1 it has been shown that sulfur in oxygen-carrying sulfur groups has a positive character, and in the present communication the influence of the positive character of the sulfur on the electron binding energies on adjacent atoms within the groups themselves is considered.

The positive character of sulfur in oxygen-carrying groups would be expected to exert a substituent effect on the electron spectra of adjacent atoms. The existence of substituent effects are best proved with elements without lone electron pairs and aliphatic saturated carbon would be a suitable model. As extensive ESCA data on carbon are available,[3] it is possible to establish that such an effect of sulfur on carbon exists. For instance, the electron binding energies of the methyl groups in the compounds listed in Table 1 are

Table 1. The influence of positive sulfur groups on the C1*s* electron binding energy of adjacent carbon (shifts, eV).

Compound	Δ C1*s*	Δ S2*p*
H_3C-CH_3	0	
		0
$H_3C-SO-CH_3$	+0.4	+3.3
H_3C-SO_2Cl	+0.6	+6.1

significantly shifted due to the influence of the sulfur substituent. This proves the existence of the expected substituent effect from positive sulfur, and it can be seen that the effect of the charge on sulfur increases the C1*s* binding energy of the adjacent carbon about 1/10 of the value of the shift in the sulfur S2*p* level.

In Ref. 1 a large amount of electron binding energy data on oxygen adjacent to sulfur is available. Table 2 summarizes the data for oxygen and sulfur in oxygen-carrying sulfur groups. When the same group is represented by more than one compound, the average values are given. In Fig. 1 the O1*s* electron binding energies have been plotted against the S2*p* electron binding energies. With increasing S2*p* binding energy an increase in the O1*s* binding energy occurs. The >S=O and