Synthesis of 2,3,6-Tri-*O*-methyl-L-idose

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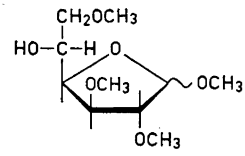
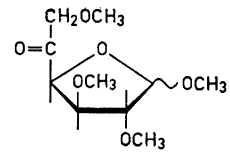
During synthesis of 2,3,6-tri-*O*-methyl-D-galactose from the methyl glycosides of the corresponding trimethyl ether of D-glucose by oxidation-reduction epimerization of the free hydroxyl group,[1] the presence in minor amounts of a compound, easily separated from the trimethyl ethers of galactose and glucose on silica gel, was observed in the product mixture. Since this compound was not formed when the furanosides were removed from the starting material, it was reasonable to believe that the compound in question was 2,3,6-tri-*O*-methyl-L-idose, the C-5 epimer of the glucose trimethyl ether. A synthesis of this idose derivative has been claimed earlier;[2] doubt has, however, been thrown on the identity of the product of this synthesis by others.[3] A 1,5-anhydro 2,3,6-tri-*O*-methyl hexose, which was proposed to have the D-*gluco* configuration, has, on the other hand, been prepared.[4] This compound has later, in light of present day knowledge, been assumed to have the L-*ido* configuration.[5]

L-Iduronic acid is a component of chondroitin sulphate B;[6] recently it has also been found to be a major constituent of heparin.[7,8] One of the methods utilized in structure determinations of polysaccharides of this type, is removal of sulphate groups and reduction of the esterified carboxyl groups followed by conventional methods.[7,9] Methylation studies on mucopolysaccharides modified in this way would require 2,3,6-tri-*O*-methyl-L-idose as a reference substance, since the most usual linkage type to uronic acids in these mucopolysaccharides is 1 – 4. It was for this reason found of some value to modify the procedure leading to 2,3,6-tri-*O*-methyl-D-galactose [1] in such a way that the L-idose derivative could be obtained.

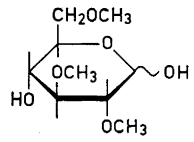
Oxidation with dimethyl sulphoxide – acetic anhydride of the anomeric methyl furanosides of 2,3,6-tri-*O*-methyl-D-glucose (I), followed by reduction of the uncharacterized methyl 2,3,6-tri-*O*-methyl-D-*xylo*-hexofuranosid-5-uloses (II) with sodium borohydride and subsequent hydrolysis, gave a mixture of 2,3,6-tri-*O*-methyl-D-glucose (III) and 2,3,6-tri-*O*-methyl-L-idose (IV). The compounds were easily separable on a silica gel column. This method gives 20 % of the idose isomer, a result which is in contrast with some reported borohydride reductions of 1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose derivatives [10,11] which give the product with the L-*ido* configuration in preponderance.



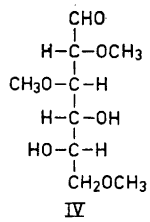
I



II



III



IV

Demethylation of the prepared compound gave a product which was chromatographically indistinguishable from L-idose. Besides the synthetic route this fact makes the identity unquestionable. A configuration inversion at C-4 during the borohydride reduction of the hexofuranos-5-ulose derivative (II) is not very likely in the weakly alkaline solution, and it has not been reported to take place in reduction of analogous compounds.[10,11] If an inversion had occurred, however, the D-galactose trimethyl ether should have been among the products, but this compound was not detected. The demethylated sugar showed in accordance with this to be well separated from D-altrose by chromatography, the 2,3,6-trimethyl hexose with the L-*altro* configuration is the other product that would result from an inversion at C-4 prior to, or during reduction of the keto derivative (II). Acetolysis followed by saponification of the above-mentioned 1,5-anhydro 2,3,6-trimethyl hexose,[4] later assumed to have the L-*ido* configuration,[5] was reported to afford a product with an optical rotation + 9.4°; this is in very good agreement with that of the product in the present work.

To obtain a crystalline derivative of the syrupy trimethyl sugar, it was oxidized to

its corresponding aldonolactone with silver carbonate on Celite;[12] the lactone was then converted to the phenylhydrazide which crystallized easily.

Experimental. Thin layer chromatography was performed on silica gel with the solvent systems (v/v): (A) benzene-ethanol, 10:1, (B) benzene-ethanol, 20:3. Paper chromatograms were run in (C) butanol-pyridine-water, 5:3:2, and (D) butanol-ethanol-water, 40:11:19. As spray reagents were used aniline oxalate and diphenyl amine–aniline–phosphoric acid[13] for the reducing sugar derivatives, and hydroxylamine-ferric chloride[14] for the lactone.

Oxidation of the anomeric methyl 2,3,6-tri-O-methyl-D-glucofuranosides (I). The anomeric methyl 2,3,6-tri-*O*-methyl-D-glucofuranosides (I)[15] (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, the mixture was poured into chloroform (300 ml), and the solution was shaken with saturated sodium bicarbonate (50 ml) for 1 h. The two layers were separated, and the chloroform layer washed four times with water (40 ml portions). After drying over sodium sulphate, the solution was evaporated giving a syrupy residue. Thin layer chromatography (solvent A) showed the presence of two components, both moving faster than the two starting compounds, and both gave immediately colour with diphenylamine–aniline–phosphoric acid after the plates had been heated for 3 min at 110° before they were sprayed.

2,3,6-Tri-O-methyl-L-idose (IV). The crude reaction mixture of the anomeric methyl 2,3,6-tri-*O*-methyl-D-*xylo*-hexofuranosid-5-uloses (II) was treated with sodium borohydride (2 g) in 0.05 M borate buffer, pH 9.2, (50 ml) for 40 h at room temperature. Excess borohydride was decomposed with Amberlite IR-120 (H) ion exchange resin, the solution filtered and the solvent evaporated. The boric acid formed was removed by repeated distillations of methanol from the residue, which was subsequently heated in 1 % oxalic acid (200 ml) for 90 min at 90°. The solution was neutralized with calcium carbonate, filtered and evaporated to a syrupy product. Chromatography on a silica gel column (4×45 cm) with solvent B gave two well separated fractions; from the second fraction 2,3,6-tri-*O*-methyl-D-glucose (III) crystallized upon evaporation of the solvent. The first fraction gave 2,3,6-tri-*O*-methyl-L-idose (IV) (510 mg, 20 % of theoretical) as a slightly yellowish oil, chromatographically homogeneous. $[\alpha]_D + 8.5°$ (*c* 1, water, initial). Demethylation with boron tribromide[16] yielded a compound indistinguishable from L-idose by paper chromatography (solvents C and D); the mobility was lower than that of altrose in both solvents.

2,3,6-Tri-O-methyl-L-idonic acid phenylhydrazide. 2,3,6-Tri-*O*-methyl-L-idose (IV) (35 mg) in benzene (50 ml) was refluxed with silver carbonate on Celite[17] (1.2 g) for 40 min. Filtration of the solution and evaporation of the solvent gave a syrupy residue which was chromatographically homogeneous (solvent A). $[\alpha]_D + 88°$ (*c* 1.7, chloroform), infrared absorption was observed at 1790 cm^{-1} (chloroform) which is characteristic of γ-lactones. The syrup was heated with phenylhydrazine (16 mg) on a water bath for 2 h, the product crystallized on trituration with ethyl acetate; recrystallization from benzene yielded 2,3,6-tri-*O*-methyl-L-idonic acid phenylhydrazide as colourless crystals (20 mg, 38 %) m.p. 120°. (Found C 54.61; H 7.40; N 8.48. Calc. for $C_{15}H_{24}N_2O_6$: C 54.86; H 7.37; N 8.53.)

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