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Alkaline Degradation of Methyl 2,4,6-Tri-*O*-methyl-α- and -β-D-*ribo*-hexosid-3-ulose. Part II. Isolation and Characterization of Degradation Products

LENNART KENNE, OLLE LARM and SIGFRID SVENSSON

Department of Organic Chemistry, The Arrhenius Laboratory, P.O.B., S-104 05 Stockholm 50, Sweden

Treatment of methyl 2,4,6-tri-*O*-methyl-α- or -β-D-*ribo*-hexosid-3-ulose with sodium ethoxide in ethanol-dichloromethane yielded a labile 4,6-di-*O*-methyl-1-deoxy-2-methoxy-D-hex-1-ene-3-ulose (A) and several isomeric ethyl 2,4,6-tri-*O*-methyl-hexosid-3-uloses (B – G).

The synthesis and alkaline degradation of methyl 2,4,6-tri-*O*-methyl-α-D-*ribo*-hexosid-3-ulose and the corresponding β-glycoside were reported in a previous communication.[1] Elimination of the aglycone was complete after 30 min at room temperature in 0.1 M ethanolic sodium ethoxide. The product was complex and isolation of the individual components was not attempted. We have now observed that a simpler reaction product is obtained when the reaction is performed with 0.1 M sodium ethoxide in ethanol-dichloromethane (1:1, v/v). GLC of the reaction product (Table 1) showed the presence of seven components (A – G). The proportions of these components were independent of whether the starting material had the α- or β-configuration.

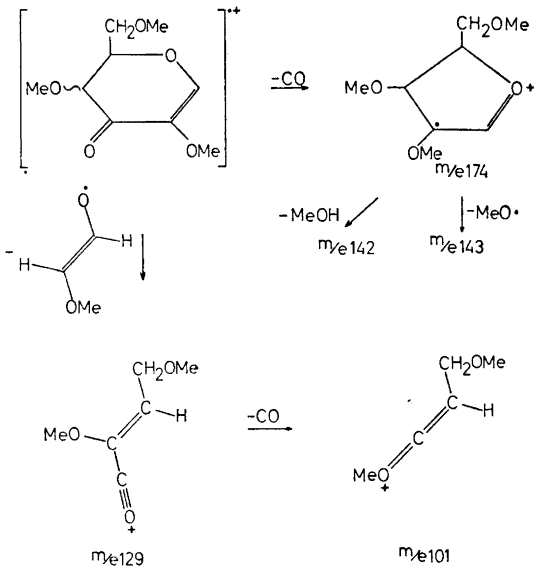
Two of the main components (B and G) were obtained pure by Silica Gel chromatography. Two other components, D and F, were obtained pure by preparative GLC. Components C and E were enriched by this latter method but were still contaminated by B and D, respectively. Component A could not be isolated owing to its extreme lability. The response factors of B and G were determined, relative to an inert internal standard, and the yields of the various components were determined by GLC (Table 1).

The reaction products were further investigated by GLC-MS. The MS of A indicated that it was a 4,6-di-*O*-methyl-1-deoxy-2-methoxy-hex-1-ene-3-ulose. Possible routes for the formation of some fragments are given in Scheme 1.

Table 1. Composition and properties of the reaction products.

Compound	T^a	Yield[b]	$[\alpha]_D$ (c 0.3, $CHCl_3$)	τ, H-1	*J* 1.2	Derived alditols[c]	Configuration
A	0.34	5					
B	1.00	29	+113	4.89	1.8	D-altritol-D-mannitol (20:1)	α-D-*arabino*
C	1.19	4					
D	1.38	7	+ 33	4.72	4.0	D-galactitol-D-gulitol (1:11)	α-D-*xylo*
E	1.50	1					
F	2.00	6	− 19	5.60	8.0	D-allitol-D-glucitol (49:1)	β-D-*ribo*
G	3.59	42	+138	4.71	4.0	D-allitol	α-D-*ribo*

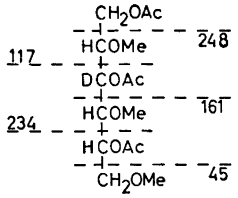
[a] Retention time, relative to ethyl 2,4,6-tri-*O*-methyl-α-D-*arabino*-hexosid-3-ulose.
[b] Response factors were determined for B and G relative to the internal standard (methyl 2,3,4-tri-*O*-methyl-β-D-xyloside). The response factors were the same for both B and G and they are therefore assumed to be valid for C–F.
[c] Obtained by reduction, hydrolysis, reduction and demethylation.



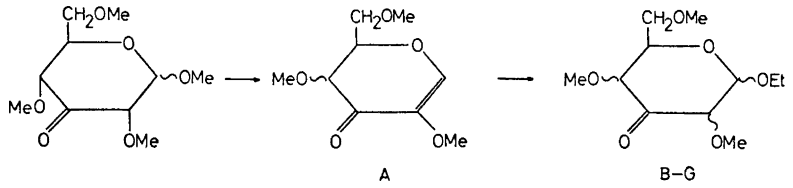
Components B – G all gave similar mass spectra, differing only in the intensities of some of the peaks. The composition of the molecular ion (for component F) as determined by high resolution MS was $C_{11}H_{20}O_6$. Authentic ethyl 2,4,6-tri-*O*-methyl-α/β-D-*ribo*-hexosid-3-ulose was prepared. This, on GLC gave two peaks with the same retention time as components F and G, and the corresponding MS were also indistinguishable. Components B – G are therefore isomeric ethyl 2,4,6-tri-*O*-methyl-hexosid-3-uloses.

The NMR data (relative proportions of methyl, ethyl, and other protons) were consistent with the proposed structures. Chemical shifts and coupling constants for the anomeric protons are given in Table 1.

Borodeuteride reduction of each isolated component and acid hydrolysis yielded mixtures of 2,4,6-tri-*O*-methyl-hexoses-3-*d*, which were analysed, as their alditol acetates, by GLC-MS.[2] The primary fragments formed on MS of these substances are indicated below.



The alditol mixtures were also demethylated by treatment with boron tribromide [3] and analysed as acetates by GLC-MS [4,5] (Table 1). From these



results, the NMR evidence and the optical rotations of the compounds, their configurations could be established (Table 1).

The formation of these compounds by β-elimination of methanol followed by addition of ethanol yielding B – G in a total yield of 90 %, is depicted below in Scheme 2. Reversible enolisation leading to epimerization at C-4 may also occur, at any stage of the transformation. Six of the eight possible ethyl 2,4,6-tri-*O*-methyl-hexosid-3-uloses were observed in the reaction product. The two missing isomers are probably formed in low percentages only and their GLC traces may be hidden in the peaks of other components. The predominating components were the α-glycosides with the D-*ribo*- and D-*arabino*-configurations. It seems reasonable that in an equilibrium mixture, the α-anomers should predominate because of the anomeric effect. Those with bulky equatorial substituents (D-*ribo*) at C-2, C-3, C-4, and C-5 should be favoured over those with one axial substituent only (D-*arabino* and D-*xylo*) as is actually observed.

EXPERIMENTAL

Concentrations were performed at reduced pressure at bath temperatures not exceeding 40°. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. NMR spectra were recorded with a Varian A60 A and a Varian XL 100 spectrometer, using tetramethylsilane as internal reference. Chemical shifts (τ) are given as ppm downfield from tetramethylsilane. GLC separations were performed on a Perkin-Elmer model 990 instrument using a glass column packed with 3 % ECNSS-M on Gas-Chrom Q. Peak areas were measured with a Hewlett-Packard 3370 electronic integrator. The preparative GLC separations were performed on a Varian aerograph series 1400, column size: 0.3 × 250 cm. For GLC-MS the compounds were injected into a Perkin-Elmer 270 gas chromatograph-mass spectrometer fitted with the appropriate column. The mass spectra were recorded at a manifold temperature of 200°, ionisation potential of 70 eV, ionisation current of 80 μA and an ion source temperature of 120°. High resolution MS was performed by the peak matching technique on an Atlas SM 1 instrument.

Ethyl 2,4,6-tri-O-*methyl-α/β*-D-ribo-*hexosid-3-ulose* was prepared from 2,4,6-tri-*O* methyl-D-glucose, using the same procedure as previously described for the corresponding anomeric mixture of methyl glycosides.[1]

Alkaline degradation of methyl 2,4,6-tri-O-*methyl-α- and β*-D-ribo-*hexosid-3-ulose.* A. *Preparative experiments.* Ethanolic 0.1 M sodium ethoxide (12.5 ml) was added to a solution of methyl 2,4,6-tri-*O*-methyl-β-D-*ribo*-hexosid-3-ulose (500 mg) in dichloromethane (12.5 ml) and the solution was kept for 20 min at room temperature. The yellow solution was then neutralised by addition of Dowex 50 (H^+) and concentrated. The product, which gave seven peaks on GLC (Table 1) was fractionated on a silicic acid column (40 × 3 cm), irrigated with ethyl acetate-light petroleum (2:1). The separation was monitored by polarimetry and TLC. The first fraction eluted (36 mg) consisted of pure B. The second fraction (16 mg) contained B, D, and small amounts of C and E. Pure D was obtained from this fraction by preparative GLC. The third fraction (43 mg) contained F together with small amounts of D and E. Pure F, m.p. 83 – 84°, was ob-

tained by preparative GLC. It gave a molecular ion of *m/e* 248.1262, in agreement with the composition $C_{11}H_{20}O_6$ (248.1260). The last fraction (104 mg) consisted of pure G. All the isolated components showed a strong band at 1750 (C=O) in their IR spectra.

Each component (2 mg) was reduced with sodium borodeuteride (10 mg) in ethanol (5 ml) at room temperature overnight. The glycosides obtained after processing were hydrolysed in 0.25 M sulphuric acid at 100° for 18 h, and the product obtained after neutralization was reduced with sodium borohydride. One third of each alditol mixture was acetylated and analysed by GLC-MS,[2] using the ECNSS-M column at 170°. All components gave similar mass spectra, typical for the 2,4,6-tri-*O*-methyl-hexitol-3-*d* derivatives. The retention times, relative to 1,5-di-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-D-glucitol, and percentages of the derivatives were: B, 2.00(95), 2.09(5); D, 2.00(91), 2.30(9); F, 1.45(98), 1.94(2); G, 1.45(100).

The remainder of the above products was demethylated with boron tribromide in dichloromethane,[3] acetylated and investigated by GLC-MS.[4,5] The products, which were all hexitol-3-*d* hexaacetates, had the following retention times (relative to peracetylated D-glucitol) on the ECNSS-M column at 200°: (B), D-altritol 0.785, D-mannitol 0.790 (separated at 170°); (D), D-galactitol 0.90, D-gulitol 1.00; (F), D-allitol 0.72, D-glucitol 1.00; (G), D-allitol 0.72.

B. *Quantitative experiments.* Ethanolic 0.1 M sodium ethoxide (0.5 ml) was added to a solution of methyl 2,4,6-tri-*O*-methyl-β-D-*ribo*-hexosid-3-ulose (19.6 mg) and methyl 2,3,4-tri-*O*-methyl-β-D-xyloside (1.8 mg) in dichloromethane (0.5 ml). Samples were withdrawn, neutralized (Dowex 50, H^+) and analysed by GLC. The composition of the product after 20 min, when no starting material remained, is given in Table 1. The response factors of B and G, relative to the xyloside, were determined in separate experiments. They were similar and it was assumed that the same response factors were valid for the other components. This is almost certainly incorrect for the extremely labile component A.

Almost identical results were obtained when the above experiment was repeated with methyl 2,4,6-tri-*O*-methyl-α-D-*ribo*-hexosid-3-ulose.

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