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Note

Selective C-1 ethanethiolysis and deuteration in *keto*-hexulose penta-acetates

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Treatment of 1,3,4,5,6-penta-*O*-acetyl-D-fructose[1] and -L-sorbose[2] with ethanethiol in the presence of zinc chloride has been reported to give moderate yields of the corresponding diethyl dithioacetals. When, in the course of our studies of the thiolysis of carbohydrate esters[3], the reaction of the latter acetate was repeated, it was observed that, as well as the diethyl dithioacetal, one main, and several minor, chromatographically more-mobile products were formed. This major product has been isolated in 19% yield and characterised by n.m.r. methods as 3,4,5,6-tetra-*O*-acetyl-1-*S*-ethyl-1-thio-L-sorbose diethyl dithioacetal. When room temperature thiolysis was then applied to 1,3,4,5,6-penta-*O*-acetyl-D-fructose diethyl dithioacetal, the analogous 1-thio derivative was obtained crystalline in 37% yield. The n.m.r. spectra of these products are largely similar to those of the corresponding acyclic penta-*O*-acetyl hexulose derivatives from which they are derived, but the H-1 resonances are specifically moved to higher fields (Table I). The n.m.r. data are consistent with those obtained by Angyal and James[4], who have discussed the preferred conformation of such compounds.

The minor products of these reactions were mixtures of more highly thiolated compounds which were found (n.m.r. data) to have retained their C-5 and C-6 ester groups. Replacement of the ester functions in the starting materials therefore occurs preferentially at the primary site adjacent to the acetal function, and then can proceed at the other adjacent site and thence, conceivably, in a relay fashion down the chain[3b]. Several examples are known of the replacement by alkylthio groups of hydroxyl groups which are adjacent to thioacetal centres, and it has been shown that the reactions involve neighbouring-group displacements of the hydroxyl function by a thioacetal sulphur atom[3]. Displacement of α-ester functions is less well known. However, acid-catalysed ethanethiolysis of penta-*O*-acetyl-β-D-glucopyranose gives some acetylated 2-*S*-ethyl-2-thioaldose diethyl dithioacetal[5], and an indication that this type of reaction may proceed by way of a 1,2-episulphonium ion is provided by the fact that reduction of various esterified aldose dialkyl dithioacetals with Raney nickel

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TABLE I

N.M.R. PARAMETERS OF 3,4,5,6-TETRA-*O*-ACETYLHEXULOSE DERIVATIVES

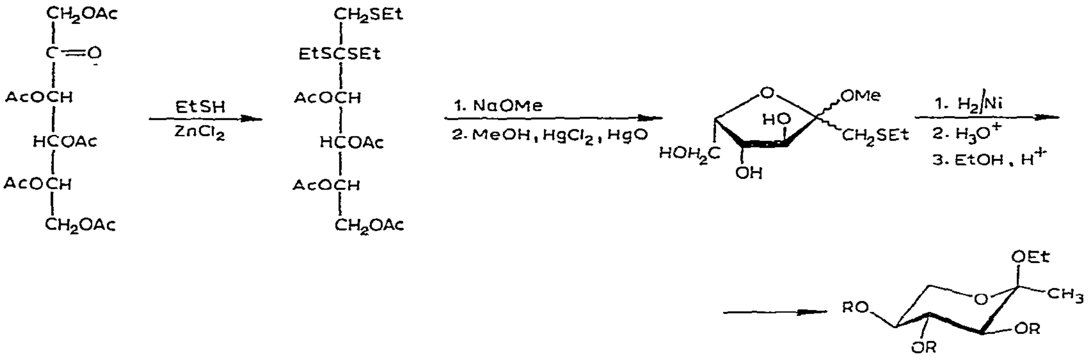
Compound	*Chemical shifts*[a] (*τ scale*)						
	H-1	*H-1'*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*
D-Fructose, 1-*O*-acetyl[b]	4.65	4.98	3.98	3.83	4.38	5.39	5.71
D-Fructose, 1-*O*-acetyl	5.05	5.41	4.51	4.34	4.81	5.68	5.95
D-Fructose, 1-*O*-acetyl, diethyl dithioacetal	5.40	5.73	4.43	4.18	4.99	5.64	5.94
D-Fructose, 1-*S*-ethyl-1-thio, diethyl dithioacetal	6.80	7.02	4.32	4.30	5.10	5.73	5.93
L-Sorbose, 1-*O*-acetyl[b]	5.11	5.31	4.59	4.42	4.69	5.66	6.00
L-Sorbose, 1-*O*-acetyl, diethyl dithioacetal	5.48	5.81	4.65	4.19	4.75	5.66	5.92
L-Sorbose, 1-*S*-ethyl-1-thio, diethyl dithioacetal	6.88	7.06	4.50	4.28	4.83	5.64	5.93

Compound	*Coupling constants*[a] (*Hz*)					
	$J_{1,1'}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6}$
D-Fructose, 1-*O*-acetyl	17.0	2.0	8.5	3.0	5.0	12.5
D-Fructose, 1-*O*-acetyl, diethyl dithioacetal	12.5	1.8	7.0	3.5	5.0	12.0
D-Fructose, 1-*S*-ethyl-1-thio, diethyl dithioacetal	12.5	1.0	7.0	3.0	4.5	12.0
L-Sorbose, 1-*O*-acetyl	17.5	3.7	6.0	6.5	6.0	12.5
L-Sorbose, 1-*O*-acetyl, diethyl dithioacetal	12.0	2.5	6.0	4.0	6.0	12.0
L-Sorbose, 1-*S*-ethyl-1-thio, diethyl dithioacetal	13.0	1.8	6.8	4.0	6.0	12.5

[a] Measured in deuteriochloroform. [b] Measured in pyridine.

can give 1,2-dideoxyalditol derivatives[6]. In view of these observations, and of the present report, doubt is perhaps thrown on the nature of the dideoxyhexitol obtained from 1,3,4,5,6-penta-*O*-acetyl-D-psicose on thiolysis followed by reduction with Raney nickel and de-esterification[7]. For a thio group to be introduced at C-5 by a neighbouring-group mechanism, a 5-membered, cyclic sulphonium ion would have been necessary, and although such intermediates are known[8], it seems possible that a 1,2-dideoxyhexitol would have been formed, and that the evidence provided in favour of 2,5-dideoxy-*erythro*-hexitol (its lack of optical activity in the visible region of the spectrum) is inadequate.

The 1-*S*-ethyl-1-thio compounds here described offer a new means of obtaining 1-deoxyhexuloses and their derivatives[9], as is illustrated. Attempts to prepare 1-deoxy-L-sorbose, however, resulted in the isolation of an ethyl glycoside (**1**, R = H), shown by n.m.r. examination of the derived triacetate (**1**, R = Ac) to have the pyranoid-ring form ($J_{3,4}$ 9.8, $J_{4,5}$ 9.4, $J_{5,6a}$ 10.8 Hz). The α-L-anomeric configuration is assigned on the grounds of its stability relative to the β-L anomer[10]; the negative optical rotations of both the glycoside (**1**, R = H) and its acetate (**1**, R = Ac) are consistent with this inference. It is assumed that glycosidation occurred during heating of the free sugar with ethanol, which was used as a drying agent, and that a catalytic amount of acid was present. The same compound was obtainable by ethanolysis of 1-deoxy-L-sorbose prepared by the method of James and Angyal[9b].



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1,3,4,5,6-Penta-*O*-acetyl-D-fructose and -L-sorbose were also found to react specifically at C-1 with deuterium oxide, as was evidenced by the loss of the signals for H-1 and H-1′ in the n.m.r. spectrum. This observation is in accord with the earlier conclusion that D-fructose is specifically deuterated at C-1 on standing in alkaline deuterium oxide[11,12], and with the recognised generalisation that 1,2-enediolate ions are more readily formed from 2-uloses than are the isomeric 2,3-ions[13]. On the grounds of other findings[13,14], it would be anticipated that further incorporation of deuterium would occur at the secondary positions in the order of their proximity to the carbonyl group, and thus thiolysis and deuteration of the carbonyl compounds, although mechanistically unrelated reactions, occur with the same selectivity.

EXPERIMENTAL

*Ethanethiolysis of 1,3,4,5,6-penta-*O*-acetyl-L-sorbose.* — The penta-acetate (7.8 g) was ethanethiolysed under the conditions of Zinner and Schneider[2], being allowed to stand for 2 days at room temperature. T.l.c. then indicated the presence of two major products, together with smaller amounts of starting material and chromatographically mobile compounds. The mixture was neutralised with saturated, aqueous sodium hydrogen carbonate and extracted with chloroform, and the extracts were washed with water, dried, and taken to dryness to leave a syrup (8.2 g) which was resolved on a column of silica gel (800 g). Elution with ether–light petroleum (b.p. 60–80°, 1:2) afforded three fractions. Fraction *1* (0.1 g) contained more than one compound; n.m.r. spectroscopy revealed that additional thio-groups had been introduced, and resonances for H-5,6,6′ indicated that the ester groups were retained at these positions. Fraction *2* gave 3,4,5,6-tetra-*O*-acetyl-1-*S*-ethyl-1-thio-L-sorbose diethyl dithioacetal (1.87 g, 19%), m.p. *ca.* −20°, $[\alpha]_D$ −13° (*c* 1.5, chloroform). For n.m.r. data, see Table I.

Anal. Calc. for $C_{20}H_{34}O_8S_3$: C, 48.2; H, 6.8; S, 19.3. Found: C, 48.1; H, 6.8; S, 18.4%.

Fraction *3* was a syrup (2.8 g, 23%), which gave an n.m.r. spectrum consistent with its being 1,3,4,5,6-penta-*O*-acetyl-L-sorbose diethyl dithioacetal, and had $[\alpha]_D$ −8° (*c* 1.0, chloroform); lit.[2] m.p. 94–95°, $[\alpha]_D$ −12.3°.

The residual starting-ketone was not eluted from the column.

Ethyl 1-deoxy-α-L-sorbopyranoside (**1**, R = H). — (*a*) *From 3,4,5,6-tetra-O-acetyl-1-S-ethyl-1-thio-L-sorbose diethyl dithioacetal.* The 1-ethylthio compound (1.23 g) was dissolved in dry methanol (20 ml) and deacetylated by the addition of a catalytic amount of sodium methoxide. The sodium ions were removed with a cation-exchange resin, mercury(II) oxide (1.3 g) and a saturated solution of mercury(II) chloride (1.35 g, 2.1 mol. equiv.) in dry methanol were added, and the suspension was stirred at room temperature for 0.5 h. Removal of the solids and solvent afforded a glass which gave an n.m.r. spectrum consistent with its comprising two 1-ethylthio methyl glycosides (probably furanosides[15]; methoxyl resonances τ 6.54, 6.44) in the ratio 2:1. The glass was dissolved in ethanol (30 ml), and a slurry of active Raney nickel (30 g) in ethanol was added. After heating of the suspension under reflux for 0.5 h, the nickel was removed and thoroughly washed, and the filtrate and washings were taken to dryness to give a syrup which showed *C*-methyl singlets at τ 8.44 and 8.30, and *O*-methyl singlets at τ 6.66 and 6.60 (ratios 2:1; the higher-field signals were more intense in both cases). The residue was taken up in water (20 ml) and heated with Dowex-50W x8 (H^+) resin (3 g) for 1 h on a steam bath. The resin was then removed and the water was evaporated under diminished pressure, the last traces being removed by several codistillations with ethanol. Crystallisation of the residue from ethyl acetate (in which 1-deoxysorbose is largely insoluble) gave ethyl 1-deoxy-α-L-sorbopyranoside (0.21 g, 44%), m.p. 160–164°, $[\alpha]_D$ −89° (*c* 0.5, water). The n.m.r. spectrum revealed the presence of an ethyl group and a *C*-methyl group, and the mass spectrum showed an intense ion with *m/e* 147 $(M-OEt)^+$.

Anal. Calc. for $C_8H_{16}O_5$: C, 50.0; H, 8.3. Found: C, 49.9; H, 8.3%.

(*b*) *From 1-deoxy-L-sorbose.* The free sugar[9b] (0.20 g) was heated at 40–50° in ethanolic hydrogen chloride (10 ml, 0.07M) until dissolution had been effected and for a further 5 min; t.l.c. then showed that all the free sugar had reacted. The acid was neutralised with anion-exchange resin, and the alcohol was removed to give a solid residue. Recrystallisation from ethyl acetate gave the ethyl glycoside (0.17 g, 72%), and further, similar purification yielded a product with m.p. 166–170°, $[\alpha]_D$ −84° (*c* 0.5, water). It had the same n.m.r. characteristics as the material produced by method (*a*).

Ethyl 3,4,5-tri-O-acetyl-1-deoxy-α-L-sorbopyranoside (**1**, *R* = *Ac*). — The ethyl glycoside prepared by method (*b*) (75 mg) was left for 20 h in pyridine–acetic anhydride (2 ml, 2:1). Ice was added and, after 2 h, the solution was acidified with dilute hydrochloric acid and extracted with chloroform (×4). The extracts were washed with saturated, aqueous sodium hydrogen carbonate and dried, and the solvent was removed to give the crystalline triacetate (**1**, R = Ac) (0.122 g, 98%). Recrystallised from ether–light petroleum and then water, (**1**, R=Ac) had m.p. 90–91°, $[\alpha]_D$ $-77°$ (*c* 0.7, chloroform). N.m.r. data ($CDCl_3$): τ 8.69 (*s*, 3, H-1), 6.53 (*t*, 1, $J_{6a,6e}$ 10.8, $J_{5,6a}$ 10.4 Hz, H-6a), 6.19 (*q*, 1, H-6e), 5.10 (*d*, 1, $J_{3,4}$ 9.8 Hz, H-3), 5.02 (*o*, 1, $J_{5,6e}$ 6.4, $J_{4,5}$ 9.4 Hz, H-5), 4.50 (*t*, 1, H-4).

Anal. Calc. for $C_{14}H_{22}O_8$: C, 52.8; H, 6.9. Found: C, 52.8; H, 6.8.

*Ethanethiolysis of 1,3,4,5,6-penta-*O*-acetyl-*D*-fructose diethyl dithioacetal.* — The acetal (3.7 g) was dissolved in ethanethiol (12 ml) containing fused zinc chloride (1.5 g), and the mixture was stirred at room temperature for 6 h. T.l.c. then indicated that the major fraction of the acetal had been converted into one main product together with smaller amounts of chromatographically more-mobile compounds. The mixture was treated with saturated, aqueous sodium hydrogen carbonate and extracted with chloroform. The extract was dried, and removal of the solvent gave a semi-crystalline residue which was resolved on a column of silica gel (400 g) eluted with ether–light petroleum (b.p. 60–80°, 1:2). Fraction *1* (0.31 g) contained several components which were shown (n.m.r. spectroscopy) to contain more than three thio groups. Resonances for H-5,6,6′ indicated that the ester groups remained at these positions. Fraction *2* crystallised from light petroleum (b.p. 60–80°) to give 3,4,5,6-tetra-*O*-acetyl-1-*S*-ethyl-1-thio-D-fructose diethyl dithioacetal (1.35 g, 37%), m.p. 74–75°, $[\alpha]_D$ $-1°$ (*c* 1.2, chloroform). For n.m.r. data, see Table I.

Anal. Calc. for $C_{20}H_{34}O_8S_3$: C, 48.2; H, 6.8; S, 19.3. Found: C, 48.3; H, 7.1; S, 19.1%.

Fraction *3* gave starting material (0.29 g, 8%), m.p. and mixture m.p. 79–80°, $[\alpha]_D$ $+20°$ (*c* 1, chloroform); lit.[1] m.p. 83°, $[\alpha]_D$ $+20°$.

*Deuteration of 1,3,4,5,6-penta-*O*-acetyl-*D*-fructose and -*L*-sorbose.* — The acetates (0.1 g) were separately dissolved in dry pyridine–deuterium oxide (1 ml, 2:1), and the deuteration was followed by n.m.r. spectroscopy (see Table I). In each case, the signals for H-1 were removed specifically, and the members of each pair were replaced concurrently, the reactions being complete in *ca.* 5 h.

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