Deoxy-sugars. Part XXVI. The Cleavage of Sulphonic Esters with Lithium Aluminium Hydride.*

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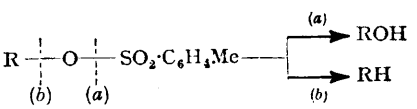
Cleavage with lithium aluminium hydride of the 2-toluene-*p*-sulphonates and 2-methanesulphonates of methyl β-L-arabinoside and its 3 : 4-*O*-*iso*propylidene derivative has been studied. Both esters of the latter sugar undergo direct cleavage and methyl 3 : 4-*O*-*iso*propylidene-β-L-arabinoside is regenerated. Methyl 2-*O*-methanesulphonyl(or 2-*O*-toluene-*p*-sulphonyl)-β-L-arabinoside gave methyl β-L-arabinoside, 2 : 3-anhydro-β-L-riboside, 2-deoxy-β-L-riboside, and 3-deoxy-β-L-xyloside (-riboside). These results are compared with those obtained by the hydrogenolysis of sulphonic esters of sugars with sodium amalgam (Vargha, Puskás, and Nagy, *J. Amer. Chem. Soc.*, 1948, **70**, 261) and with Raney nickel and hydrogen (Kenner and Murray, *J.*, 1949, S 178).

THE reduction of toluene-*p*-sulphonic esters has been studied by Schmid and Karrer (*Helv. Chim. Acta*, 1949, **32**, 1371) (cf. also Vis and Karrer, *ibid.*, 1954, **37**, 378), using lithium aluminium hydride, and by Kenner and Murray (*J.*, 1949, S 178) using Raney nickel and hydrogen. The Swiss authors concluded that there are two distinct reactions with lithium aluminium hydride, namely, hydrogenolysis (*a*) with preservation of the hydroxyl group and (*b*) with fission of the hydroxyl group, as depicted :



From the examples studied it appeared that although aryl toluene-*p*-sulphonates react according to scheme (*a*), alkyl toluene-*p*-sulphonates (including esters of carbohydrates) react according to either scheme. Kenner and Murray (*loc. cit.*; see also *J.*, 1950, 406), however, reported that hydrogenation in the presence of Raney nickel converts aryl toluene-*p*-sulphonates into aromatic hydrocarbons and the alkyl esters into alcohols; in agreement with Trevoy and Brown (*J. Amer. Chem. Soc.*, 1949, **71**, 1675), they regard lithium aluminium hydride as a source of potential hydride ions and ascribe to steric hindrance the exceptional reductions noted in the sugar series with this reagent. In this paper we report the action of lithium aluminium hydride on other toluene-*p*-sulphonates and methanesulphonates of some L-arabinose derivatives.

By heating under reflux a suspension of methyl 3 : 4-*O*-*iso*propylidene-2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside in dry ether with lithium aluminium hydride, a syrup (A) was

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formed, which on mild acidic hydrolysis yielded only methyl β-L-arabinoside and on complete hydrolysis only arabinose. From these and other tests it became apparent that the syrup was methyl 3 : 4-*O*-*iso*propylidene-β-L-arabinoside (see Honeyman, *J.*, 1946, 990; Overend and Stacey, *J.*, 1949, 1235). Methyl 3 : 4-*O*-*iso*propylidene-2-*O*-methanesulphonyl-β-L-arabinoside gave a similar result. Clearly both compounds reacted with lithium aluminium hydride according to scheme "*a*."

Hydrogenolysis of methyl 2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside with lithium aluminium hydride also yielded a syrup, but in this case chromatography of a hydrochloric acid hydrolysate revealed the presence of L-arabinose, 2-deoxy-L-ribose, 3-deoxy-L-xylose (-ribose), and 3-chloro-3-deoxy-L-xylose. In another experiment on a larger scale methyl β-L-arabinoside, methyl 2 : 3-anhydro-β-L-riboside, and methyl 2-deoxy-β-L-riboside were isolated, and chromatography of the syrupy residue revealed that it contained some methyl 3-deoxy-β-L-xyloside (-riboside). It is interesting in this connection that Vargha, Puskás, and Nagy (*J. Amer. Chem. Soc.*, 1948, **70**, 261) report that in sodium amalgam reduction of toluene-*p*-sulphonic esters of compounds containing some free hydroxyl groups competitive reactions occur: in addition to reduction products, anhydro-bodies may be formed by the loss of toluene-*p*-sulphonic acid. Kenner and Murray (*loc. cit.*) found that such esters (*e.g.*, methyl 2-toluene-*p*-sulphonyl-α-L-arabinoside) were readily converted by Raney nickel and hydrogen into sulphur-free materials, but that only small quantities of the expected products could be separated in the pure state, probably owing to the formation of anhydro-sugars. The treatment of the syrupy product with hydrochloric acid before the chromatographic examination results not only in hydrolysis of the glycoside group, but also in rupture of the anhydro-ring in methyl 2 : 3-anhydro-β-L-riboside, with the formation predominantly of 3-chloro-3-deoxy-L-xylose (Allerton and Overend, *J.*, 1951, 1480). Similarly it is probable that at least part of the methyl 2-deoxy-β-L-riboside arises from the action of excess of lithium aluminium hydride on the methyl 2 : 3-anhydro-β-L-riboside previously formed, it being well known that 2 : 3-anhydro-sugars are cleaved by lithium aluminium hydride with the formation of deoxy-sugars (Prins, *J. Amer. Chem. Soc.*, 1948, **70**, 3955) and, in particular, that methyl 2 : 3-anhydro-β-D-riboside gives methyl 2-deoxy-β-D-riboside and methyl 3-deoxy-β-D-xyloside (-riboside) (Allerton and Overend, *loc. cit.*). Although in the experiments described above, methyl 3-deoxy-β-L-xyloside was not isolated in crystalline form, its undoubted presence in the syrupy reaction mixture was demonstrated by chromatography. It is difficult to conceive how this 3-deoxy-sugar could arise except by the action of lithium aluminium hydride on methyl 2 : 3-anhydro-β-L-riboside, which would yield also methyl 2-deoxy-β-L-riboside.

However some of the methyl 2-deoxy-β-L-riboside is probably formed by direct reduction of methyl 2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside according to a reaction of type (*b*) as noted by Schmid and Karrer (*loc. cit.*). From previous investigations it is apparent that treatment of methyl 2 : 3-anhydro-D(or L)-riboside with nucleophilic reagents leads mainly to the formation of 3-substituted xylose derivatives, together with much smaller amounts of derivatives of arabinose substituted at $C_{(2)}$, and indeed we have already demonstrated (Allerton and Overend, *loc. cit.*) that lithium aluminium hydride converts methyl 2 : 3-anhydro-β-D-riboside mainly into methyl 3-deoxy-β-D-xyloside. In the present experiments, however, methyl 2-deoxy-β-L-riboside was formed in much larger amount than was the 3-deoxy-analogue, indicating that at least part of the former probably arises by some reaction other than that of excess of lithium aluminium hydride on the 2 : 3-anhydro-pentoside. Furthermore the action of the hydride on methyl 3 : 4-di-*O*-acetyl-2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside gives only methyl β-L-arabinoside and methyl 2-deoxy-β-L-riboside. Since in these experiments cleavage of the acetyl groups also occurred (this was also shown in a separate experiment by treating methyl 2 : 3 : 4-tri-*O*-acetyl-β-L-arabinoside with lithium aluminium hydride: the product was methyl β-L-arabinoside; cf. Jones, Henbest, and Lovell, B.P. Appl. 8549/51 and 8550/51, for reductive cleavage of benzoates), the possibility of anhydro-ring formation must be considered. However, neither methyl 2 : 3-anhydro-β-L-riboside nor methyl 3-deoxy-β-L-xyloside was isolated or even detected chromatographically, which strongly suggests that direct reductive cleavage of the toluene-*p*-sulphonyloxy-group had occurred.

Essentially similar results have been obtained with the corresponding 2-*O*-methanesulphonyl derivatives of L-arabinose, except that relatively greater amounts of methyl β-L-arabinoside and smaller amounts of methyl 2-deoxy-β-L-riboside were formed generally (*i.e.*, reaction " *a* " was even more predominant).

Although the experiments now described lead to a derivative of 2-deoxyribose, they are not useful for its preparation, owing to difficulties encountered in separating the syrupy reaction mixture and the low yield.

Experimental

Treatment of Methyl 2-O-*Toluene*-p-*sulphonyl*-β-L-*arabinoside with Lithium Aluminium Hydride.*—(a) *Initial experiment.* Reduction of methyl 2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside (1 g.) with lithium aluminium hydride (2 g.) was followed by hydrolysis and chromatography, which showed the presence of arabinose, 2-deoxyribose, 3-deoxyxylose, and 3-chloro-3-deoxyxylose.

(b) *Larger-scale experiment.* Lithium aluminium hydride (10 g., 17·5 mols.) was suspended in dry ether (300 c.c.), and methyl 2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside (19 g.) was added during 3 hr., the final 5 g. in solution in dry ether (400 c.c.). After 24 hours' heating under reflux, additional lithium aluminium hydride (5 g.) and dry ether (150 c.c.) were added, and heating was continued for 48 hr. Excess of hydride was eliminated by cautious addition of water. The mixture was filtered and the residue washed thoroughly with water. The combined filtrate and washings were accurately neutralised with 2N-sulphuric acid. A precipitate which formed was removed and the filtrate concentrated to dryness. The white solid residue was extracted with hot ethyl acetate. The small amount of syrupy residue was dissolved in water, and the solution filtered and then concentrated. The syrupy residue (0·864 g.) was separated by ethanol fractionation into an unidentified syrup and methyl β-L-arabinoside (m. p. 169—170°, $[\alpha]_D$ +244·5° in H_2O). On cooling of the ethyl acetate extract a further amount of methyl β-L-arabinoside was deposited (total yield 1·1 g.). Evaporation of the ethyl acetate extract, after separation of the glycoside, afforded a yellow syrup (1·28 g.). A portion (0·173 g.) of this was heated at 100° in 0·05N-hydrochloric acid (3 c.c.) for 40 min. and, after neutralisation (Ag_2O), chromatography in the usual manner showed the presence of methyl β-L-arabinoside, 2 : 3-anhydro-β-L-riboside, 2-deoxy-β-L-riboside, and 3-deoxy-β-L-xyloside. The remainder of the syrup was fractionally distilled and afforded the following fractions: (i) a syrup (0·2936 g.), b. p. 85—95° (bath-temp.)/0·03 mm., which crystallised on nucleation with methyl 2 : 3-anhydro-β-L-riboside, and after recrystallisation from ether had m. p. 46—48°, $[\alpha]_D^{18}$ +52·3° (*c*, 1·26 in $CHCl_3$) {Allerton *et al.*, *J.*, 1951, 1480, report, m. p. 52—53°, $[\alpha]_D^{18}$ −49·2° (*c.*, 1·38 in $CHCl_3$) for the D-isomer}; (ii) a syrup (0·117 g.), b. p. 100—110° (bath-temp.)/0·02 mm., from which a small amount of anhydro-compound was isolated (the remainder did not crystallise); and (iii) a syrup (0·19 g.), b. p. 110—140° (bath-temp.)/0·03—0·04 mm., which crystallised and after recrystallisation from ether was identical with methyl 2-deoxy-β-L-riboside, m. p. 81—83°, $[\alpha]_D^{20}$ +181·8° (*c*, 0·55 in $CHCl_3$) (Deriaz *et al.*, *J.*, 1949, 2836, give m. p. 83—84°, $[\alpha]_D^{20}$ +193°).

Methyl 2-O-*Methanesulphonyl*-β-L-*arabinoside.*—Methyl 3 : 4-*O*-*iso*propylidene-2-*O*-methanesulphonyl-β-L-arabinoside (0·9 g.) (cf. Jones, Kent, and Stacey, *J.*, 1947, 1341) was heated at 100° in N-acetic acid (10 c.c.) for 3 hr. Concentration at 45° then gave a syrup which crystallised. Recrystallisation from ethanol yielded *methyl* 2-O-*methanesulphonyl*-β-L-*arabinoside* (0·75 g., 97%), m. p. 86°, $[\alpha]_D^{15}$ +163° (*c.*, 0·97 in $CHCl_3$) (Found: C, 34·7; H, 6·0. $C_7H_{14}O_7S$ requires C, 34·7; H, 5·8%).

Reduction of Methyl 2-O-*Methanesulphonyl*-β-L-*arabinoside.*—The mixture resulting from the action of lithium aluminium hydride on methyl 2-*O*-methanesulphonyl-β-L-arabinoside was hydrolysed (0·05N-hydrochloric acid). Chromatography then revealed arabinose, 2-chloro-2-deoxyarabinose, 3-chloro-3-deoxyxylose, 2-deoxyribose, and 3-deoxyxylose (mean R_F values respectively were 0·216, 0·250, 0·571, 0·417, and 0·472).

Then methyl 2-*O*-methanesulphonyl-β-L-arabinoside (8·9 g.) was added during 3 hr. to a suspension of powdered lithium aluminium hydride (5 g.) in dry ether (500 c.c.). The mixture was heated under reflux for 3 days and then worked up as described above. Some methyl β-L-arabinoside (m. p. 169—170°) was isolated and concentration of the ethyl acetate extract afforded a syrup (3·61 g.) which crystallised at 0°. This material did not reduce Fehling's solution and gave a positive Dische diphenylamine test. A portion was separated by fractional

distillation in a high vacuum into (i) methyl 2 · 3-anhydro-β-L-riboside, which was obtained as a colourless syrup [b. p. 85—95° (bath-temp.)/0·01 mm.], m. p. 48—50° (after recrystallisation once from ether), $[\alpha]_D^{21}$ +51·6° (*c*, 0·97 in $CHCl_3$) (Found : C, 49·9; H, 6·95. Calc. for $C_6H_{10}O_4$: C, 49·3; H, 6·85%), and (ii) methyl 2-deoxy-β-L-riboside, m. p. 81—83°.

Reduction of Methyl 3 : 4-O-iso*propylidene*-2-O-*methanesulphonyl*-β-L-*arabinoside*.—Powdered lithium aluminium hydride (2 g.) was suspended in dry ether (150 c.c.) in a Soxhlet apparatus. Methyl 3 : 4-*O*-*iso*propylidene-2-*O*-methanesulphonyl-β-L-arabinoside (1 g.) was placed in a thimble in the extractor and the solution refluxed for 4 hr. The mixture was worked up in the usual manner and a sticky solid (A) (0·478 g.) was obtained from which, on mild acidic hydrolysis followed by trituration, only methyl β-L-arabinoside (m. p. 169—170°) was isolated. When the material (A) (0·126 g.) was heated at 100° for 1 hr. in 0·05N-hydrochloric acid no hydrolysis of the glycosidic residue occurred. In N-acid during 7 hr. hydrolysis occurred, as revealed by the onset of reducing power towards Fehling's solution. Chromatography of the hydrolysate after neutralisation with silver oxide revealed arabinose only; no 2-deoxy-L-ribose was detectable.

Repetition of the experiment but with methyl 3 : 4-*O*-*iso*propylidene-2-*O*-toluene-*p*-sulphonyl β-L-arabinoside (1 g.) gave only methyl β-L-arabinoside (0·2 g.).

Reduction of Methyl 3 : 4-*Di*-O-*acetyl*-2-O-*toluene*-p-*sulphonyl*-β-L-*arabinoside*.—Powdered methyl 3 : 4-di-*O*-acetyl-2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside (2 g.) was added to an ice-cold suspension of powdered lithium aluminium hydride (3·82 g.) in dry ether (130 c.c.). The mixture was heated under reflux for 24 hr. and then the excess of hydride was destroyed by water. The suspension was filtered through Filter-cel, and the residue was washed thoroughly with ether and water. The ethereal layer in the combined filtrate and washings was separated and the aqueous phase was re-extracted with ether. After being washed successively with 2N-sulphuric acid, sodium hydrogen carbonate solution, and water, and dried, the ethereal extracts were evaporated to dryness. A negligible residue was obtained. The aqueous layer was neutralised with dilute sulphuric acid and filtered, and the filtrate was evaporated to dryness. The white solid residue was extracted continuously with ethyl acetate for 16 hr. On cooling and nucleation of the extract, crystalline methyl β-L-arabinoside separated and was collected {0·34 g.; m. p. 169—171°, $[\alpha]_D^{20}$ +242·8° (*c*, 1·32 in H_2O)}. The ethyl acetate filtrate therefrom was concentrated to dryness, furnishing a syrup (0·184 g.) which gave a positive Dische test. The syrup was hydrolysed at 100° for 40 min. with 0·05N-hydrochloric acid (3 c.c.), and, after neutralisation, the hydrolysate was examined chromatographically in the usual manner. This showed the presence of arabinose and 2-deoxy-L-ribose only.

When methyl 3 : 4-di-*O*-acetyl-2-*O*-methanesulphonyl-β-L-arabinoside (0·96 g.) was treated similarly, methyl β-L-arabinoside (0·08 g.) was isolated. Chromatography showed that no sugars other than derivatives of L-arabinose were present.

Action of Lithium Aluminium Hydride on Methyl 2 : 3 : 4-*Tri*-O-*acetyl*-β-L-*arabinoside*.—Powdered methyl tri-*O*-acetyl-β-L-arabinoside (2 g.) was added to an ice-cold suspension of lithium aluminium hydride (6·3 g.) in ether (350 c.c.), and the mixture was heated under reflux for 24 hr. The product, isolated in the usual way, was methyl β-L-arabinoside (0·68 g., 61%), m. p. and mixed m. p. 169—170°.

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