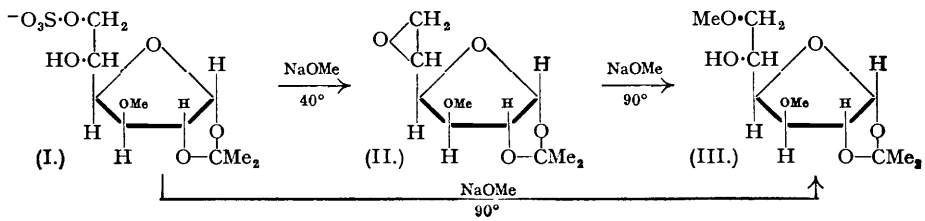
334. *Carbohydrate Sulphuric Esters. Part IV. Production of a Derivative of* 5 : 6-*Anhydroglucose by the Hydrolysis of a Sulphate.*

By R. B. Duff and E. G. V. Percival.

By the hydrolysis of *barium* 3-*methyl* 1 : 2-*monoacetone glucofuranose* 6-*sulphate* (I), 3-methyl 1 : 2-monoacetone 5 : 6-anhydroglucose (II) has been obtained. Unsuccessful attempts to prepare anhydrides from *barium* 4 : 6-*benzylidene* α-*methylglucoside sulphate* and *barium* 6-*methyl* β-*methylgalactopyranoside* 2-*sulphate* (VI) are recorded.

In Part III (*J.*, 1945, 119) it was shown that the hydrolysis with alkali of barium 1 : 2-monoacetone glucofuranose 6-sulphate yielded 1 : 2-monoacetone glucofuranose and 1 : 2-monoacetone 3 : 6-anhydroglucofuranose. The failure to identify any *l*-idose derivatives among the products of this hydrolysis was held to prove that no 5 : 6-anhydride was formed, since Ohle and von Vargha (*Ber.*, 1928, **61**, 1203; 1929, **62**, 2435) had claimed that, from the corresponding 6-toluene-*p*-sulphonate, 1 : 2-monoacetone *l*-idofuranose could be obtained *via* the 5 : 6-anhydride. The basis for this conclusion was destroyed, however, by Seebeck, Meyer, and Reichstein (*Helv. Chim. Acta*, 1944, **27**, 1142) who showed that *l*-idose derivatives could not be obtained in this way and that 1 : 2-monoacetone 5 : 6-anhydroglucose underwent transformation into the corresponding 3 : 6-anhydride with great ease. The possibility arose therefore that the 1 : 2-monoacetone 3 : 6-anhydroglucose isolated in the experiments from the 6-sulphate (Part III, *loc. cit.*) might have arisen from the 5 : 6-anhydride as an intermediate.

In order to arrive at an unequivocal decision, a derivative of glucose substituted on C_3 was chosen, to prevent the formation of a 3 : 6-anhydro-ring. The compound selected, *barium* 3-*methyl* 1 : 2-*monoacetone glucofuranose* 6-*sulphate* (I) had the added advantage of solubility in organic solvents which enabled the hydrolysis to be carried out with sodium methoxide instead of aqueous barium hydroxide as in the previous cases (Part III, *loc. cit.*; Part II, *J.*, 1941, 830). Although the method of preparation of (I) does not exclude the possibility that the sulphate group is on C_5, on general grounds, and by analogy with the reaction with toluene-*p*-sulphonyl chloride (Ohle and von Vargha, *loc. cit.*; Vischer and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 1332), this is thought to be highly improbable. Furthermore, it has been shown that by the deacylation of 6-benzoyl 3-benzyl 1 : 2-monoacetone 5-toluene-*p*-sulphonyl *d*-glucose, 3-benzoyl 1 : 2-monoacetone 5 : 6-anhydro-*l*-idose is obtained (Meyer and Reichstein, *Helv. Chim. Acta*, 1946, **29**, 152). The possible reaction products in the present case are 3-methyl 1 : 2-monoacetone glucofuranose by direct hydrolysis and 3-methyl 1 : 2-monoacetone 5 : 6-anhydroglucose (II) followed by 3 : 6-dimethyl 1 : 2-monoacetone glucofuranose (III) by reaction of (II) with sodium methoxide since the entering methoxyl anion invariably attaches itself to the primary carbon atom (Peat, *Ann. Reports*, 1939, **36**, 264).



Experimentally, it was found that although the sulphate group was not removed quite so readily as for the corresponding toluene-*p*-sulphonate, (I) with sodium methoxide (5%) after three hours at 40° gave a transparent barium sulphate gel, and from the reaction mixture 3-methyl 1 : 2-monoacetone 5 : 6-anhydroglucose (II, 50%) was obtained, characterised by conversion by sodium methoxide into 3 : 6-dimethyl 1 : 2-monoacetone glucofuranose (III)

which on hydrolysis gave crystalline 3 : 6-dimethyl glucose, identical with an authentic specimen kindly provided by Dr. D. J. Bell, and with specimens prepared by us from 3-methyl 1 : 2-monoacetone glucofuranose 6-toluene-*p*-sulphonate and the corresponding 5 : 6-ditoluene-*p*-sulphonate.

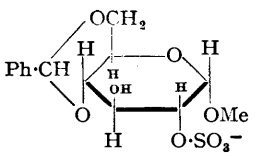
The following table gives the properties of these compounds with the relevant references.

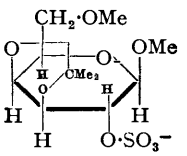
Derivatives prepared from the sulphate (I).	*Derivatives prepared from toluene*-p-*sulphonates.*
3-Methyl monoacetone anhydrohexoside; $n_D^{15°}$ 1·4610; $[\alpha]_D^{12°}$ −67° (*c*, 4·0 in chloroform)	3-Methyl 1 : 2-monoacetone 5 : 6-anhydroglucose; $n_D^{15°}$ 1·4610; $[\alpha]_D^{15°}$ −65° ± 2 (*c*, 2·0, in acetone) (Vischer and Reichstein, *loc. cit.*).
Dimethyl monoacetone hexose; $[\alpha]_D^{15°}$ −46·5° (*c*, 4·5 in chloroform)	3 : 6-Dimethyl 1 : 2-monoacetone glucofuranose; $[\alpha]_D^{20°}$ −45·8° (*c*, 4·0 in chloroform) (Bell, *J.*, 1936, 1553)
Dimethyl hexose; m. p. 115—116°; $[\alpha]_D^{15°}$ +61° (*c*, 0·8 in water at equilibrium)	3 : 6-Dimethyl glucose; m. p. 114—115° ; $[\alpha]_D^{20°}$ +61·6° (in water at equilibrium) (Bell, *loc. cit.*)

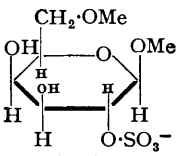
There is thus no doubt that ethylene oxide derivatives can be produced from carbohydrate sulphates, and by analogy with the toluene-*p*-sulphonates and methanesulphonates it would be expected that, when the sulphate group is removed from an asymmetric carbon atom with an adjacent *trans*-hydroxyl group, an ethylene oxide ring would be produced with Walden inversion. It is true that the opposite conclusion was reached by one of us (Part III, *loc. cit.*) since the alkaline hydrolysis of barium methylglucofuranoside 3-sulphate gave only glucose and 3 : 6-anhydroglucose derivatives, but this could be attributed to the preferential formation of the pentaphan ring.

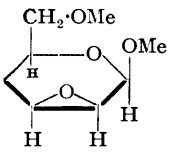
To test the hypothesis, 4 : 6-benzylidene α-methylglucoside was treated with chlorosulphonic acid in pyridine to give a *barium* 4 : 6-*benzylidene* α-*methylglucoside sulphate*. When this was treated in methanol with sodium methoxide, 4 : 6-benzylidene α-methylglucoside (85%) was recovered and the methoxyl content (10%) of the partly crystalline residue showed that no methoxyl groups had entered the molecule, so that it must be presumed that no ethylene oxide rings had been formed. Whether the product used was a 2-sulphate (IV) or a 3-sulphate, if either had given 2 : 3-anhydrides, these would certainly have been decomposed by the excess of sodium methoxide with the entry of an additional methoxyl group.

As a further test, 6-*methyl* 3 : 4-*monoacetone* β-*methylgalactoside* was synthesised and its structure confirmed by conversion into the known 2 : 6-dimethyl 3 : 4-monoacetone β-methylgalactoside (Bell, *J.*, 1945, 692). *Barium* 6-*methyl* 3 : 4-*monoacetone* β-*methylgalactoside* 2-*sulphate* (V) was then prepared and removal of the *iso*propylidene residue gave *barium* 6-*methyl* β-*methylgalactoside* 2-*sulphate* (VI). When this substance, in methanolic solution, was treated with sodium methoxide, however, no reaction was observed until 90° was reached, whereupon, instead of the production of 6-methyl 2 : 3-anhydro-β-methyltaloside (VII) followed by 2 : 6-dimethyl β-methylgalactoside or 2 : 6-dimethyl β-methylidoside, or both, rapid darkening of the solution took place with extensive decomposition and the formation of reducing products; no increase in methoxyl content could be detected.


(IV.)


(V.)


(VI.)


(VII.)

So far, therefore, there is no direct support for the suggestion (*Nature*, 1946, **158**, 29) that sugars may undergo interconversion in Nature by way of sulphuric esters and their hydrolysis, even though ethylene oxide formation does occur when the sulphate group on a primary carbon atom is removed. Further work is necessary, however, before this possibility can be abandoned since the behaviour of sulphate residues on C_2 might be anomalous. In connexion with the hydrolysis of (VI) it may be recalled that Helferich and Schnorr (*Annalen*, 1941, **547**, 201) recorded the hydrolysis of a 2-hydroxyethanesulphonic acid glycoside with alkali, and Isbell (*Ann. Rev. Biochem.*, 1943, **12**, 205) has suggested an explanation of this effect in terms of electron displacement initiated by the electronegative sulphonyl group. Until more evidence is available it would be premature to attempt an explanation of the present result, but it is clear that the adjacent sulphate group renders the glycosidic methoxyl labile to alkali. In (VI) it will be noted

that these two groupings are *trans*- to one another which recalls the fact that the alkali fission of the phenylglycosides proceeds most readily when the phenoxy-group is in the *trans*-position with respect to the hydroxyl residue on C_2, as in β-phenylglucoside (Montgomery, Richtmyer, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 1848; *J. Org. Chem.*, 1945, **10**, 194; McCloskey and Coleman, *ibid.*, p. 184). If, as is quite likely, the barium 4 : 6-benzylidene α-methylglucoside sulphate is the 2-sulphate (IV), the sulphate and methoxyl groups are in the *cis*-positions, and this might explain why fission of the glycosidic methoxyl was not observed; it is hoped that further work will illuminate these points.

Experimental.

Barium 3-Methyl 1 : 2-Monoacetone Glucofuranose 6-Sulphate.—3-Methyl 1 : 2-monoacetone glucofuranose was prepared as a colourless syrup by the methods of Freudenberg *et al.* (*Ber.*, 1923, **56**, 2125; 1926, **59**, 104). The product had $n_D^{16°}$ 1·4740, $[\alpha]_D^{15°}$ − 54° (*c*, 3·1, in chloroform) [Found : OMe, 12·8; $(CH_3)_2CO$, 23·3. Calc. for $C_{10}H_{16}O_6$: OMe, 13·2; $(CH_3)_2CO$, 24·8%].

Sulphation with chlorosulphonic acid (approx. 1 mol.) in pyridine was carried out as described in Part III (*loc. cit.*). In a typical experiment the above syrup (10·1 g.) in dry pyridine (80 c.c.) was vigorously stirred and treated with chlorosulphonic acid (3·65 c.c.) in chloroform (40 c.c.) at − 15°. The mixture was neutralised with barium hydroxide solution, the excess being removed with carbon dioxide; it was found necessary to add alcohol to obtain a homogeneous solution, owing to the solubility of the free 1 : 2-monoacetone 3-methyl glucofuranose sulphate in chloroform with the resulting danger of incomplete neutralisation; in some experiments chloroform was removed under reduced pressure at 15°. The crude *barium* salt (15 g.) was isolated in the usual way and purified by dissolving in twice the minimum volume of acetone followed by partial precipitation (8·1 g.) with light petroleum (b. p. 60—80°); $[\alpha]_D^{12°}$ − 19° (*c*, 1·0, in water) [Found : Ba, 18·5; OMe, 8·7; SO_4, 23·2; $(CH_3)_2CO$, 15·0. $(C_{10}H_{17}OS)_2Ba$ requires Ba, 18·0; OMe, 8·1; SO_4, 25·2; $(CH_3)_2CO$, 15·2%].

3-Methyl 1 : 2-Monoacetone 5 : 6-Anhydroglucose.—The above barium salt (3·53 g.) was dissolved in warm anhydrous methanol (10 c.c.) and cooled to room temperature. A solution (6·5 c.c.) of sodium (5%) in methanol was added with stirring and the mixture heated at 40° for 3 hours, whereby the mobile liquid was completely converted into a stiff transparent gel owing to separation of colloidal barium sulphate. The gel was treated with excess of a mixture of chloroform and methanol (1 : 1), and carbon dioxide bubbled through until wet phenolphthalein paper was no longer affected. Water (300 c.c.) was then added followed by repeated extraction with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated at 40°/15 mm.; the residual syrup was distilled at 120—130°/0·02 mm. in the presence of barium carbonate (0·2 g.), to give a colourless mobile oil (1·0 g.), $[\alpha]_D^{12°}$ − 63° (*c*, 4·5, in chloroform) (Found : OMe, 16·5. Calc. for $C_{10}H_{16}O_5$: OMe, 14·4%). Since it was suspected that this product was contaminated with 3 : 6-dimethyl 1 : 2-monoacetone glucose, the crude oil in chloroform (20 c.c.) was adsorbed on a column of aluminium oxide (30 cm. × 1 cm.). The column was eluted with 5 portions (20 c.c.) of chloroform, and the syrup (0·4 g.) obtained after removing chloroform from the second fraction gave at 120°/0·01 mm. an oil (0·3 g.) which had the properties required for 3-methyl 1 : 2-monoacetone 5 : 6-anhydroglucose; namely $n_D^{15°}$ 1·4610, $[\alpha]_D^{12°}$ − 67° (*c*, 4·0 in chloroform) (Found : OMe, 14·3. Calc. for $C_{10}H_{16}O_5$: OMe, 14·4%).

3 : 6-Dimethyl 1 : 2-Monoacetone Glucofuranose and 3 : 6-Dimethyl Glucose.—3-Methyl 1 : 2-monoacetone 5 : 6-anhydroglucose (0·5 g.) obtained as described above was heated at 90° with a solution of sodium (0·5 g.) in anhydrous methanol (10 c.c.) for 18 hours. Neutralisation by carbon dioxide, dilution with water, and extraction with chloroform was followed by distillation at 110—120°/0·01 mm. to give an oil (0·3 g.), $n_D^{14°}$ 1·4622, $[\alpha]_D^{15°}$ − 46·5° (*c*, 4·5 in chloroform) (Found : OMe, 21·5. Calc. for $C_{11}H_{20}O_6$: OMe, 25·0%).

The above product (0·2 g.) was left at 37° for 48 hours with sulphuric acid (200 c.c.; 0·2N). Neutralisation with barium carbonate followed by filtration and evaporation at 40°/15 mm. gave a sugar which was twice recrystallised from hot ethyl acetate to give crystals (0·1 g.), $[\alpha]_D^{15°}$ + 61° (*c*, 0·8 in water; equilibrium value) (Found : C, 46·0; H, 7·5; OMe, 29·8. Calc. for $C_8H_{16}O_6$: C, 46·1; H, 7·7; OMe, 30·0%), m. p. 115—116°, unchanged on admixture with an authentic specimen of 3 : 6-dimethyl glucose provided by Dr. D. J. Bell, and with specimens prepared by the action of sodium methoxide on 3-methyl 1 : 2-monoacetone glucofuranose 6-toluene-*p*-sulphonate (Found : OMe, 7·4. Calc. for $C_{17}H_{24}O_8S$: OMe, 8·0%), and from 3-methyl 1 : 2-monoacetone glucose 5 : 6-ditoluene-*p*-sulphonate (Found : OMe, 5·5. Calc. for $C_{24}H_{30}O_{10}S_2$: OMe, 5·7%).

In another experiment the sulphate (2·0 g.) was heated at 90° for 24 hours with sodium in methanol (25 c.c.; 5%). Neutralisation and isolation as previously described gave an oil (0·5 g.), $n_D^{13°}$ 1·4637 (Found : OMe, 22·8%) which was treated with sulphuric acid (0·2N) as before, and the sugar purified by filtration through a column of aluminium oxide to give crystals of 3 : 6-dimethyl glucose, m. p. 114°, not depressed on admixture with an authentic specimen.

Barium 4 : 6-Benzylidene α-Methylglucoside Sulphate.—4 : 6-Benzylidene α-methylglucopyranoside, m. p. 163° (10·5 g.), was sulphated as previously described to yield a *product* (9·5 g.) having $[\alpha]_D^{12°}$ + 39·5° (*c*, 1·2 in water) [Found : Ba, 17·6; SO_4, 23·0; OMe, 8·4. $(C_{14}H_{17}O_8S)_2Ba$ requires Ba, 15·9; SO_4, 22·4; OMe, 7·2%]. This was hydrolysed as previously described with excess of a solution of sodium (5%) in methanol at 15° and at 90°. Four such experiments were conducted and in none was any material other than 4 : 6-benzylidene α-methylglucoside obtained from the hydrolysate. In one experiment barium 4 : 6-benzylidene α-methylglucoside sulphate (8·8 g.) was hydrolysed for 18 hours at 90° with sodium methoxide in methanol. The product was dissolved in ethyl acetate and three crops (5·0 g.) of 4 : 6-benzylidene α-methylglucoside were isolated. The residues gave a partly crystalline substance (0·9 g.) which was chiefly 4 : 6-benzylidene α-methylglucoside (Found : OMe, 10·1%).

6-Methyl 3 : 4-Monoacetone β-Methylgalactoside.—6-Methyl β-methylgalactoside (11·0 g.) was

converted into the monoacetone derivative by the method of Ohle and Thiel (*Ber.*, 1933, **66**, 525) as modified by McPhillamy and Elderfield (*J. Org. Chem.*, 1939, **4**, 150). Distillation at 120°/0·01 mm. gave an oil which crystallised at 0°; recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave a *product*, m. p. 72—74°, $[\alpha]_D^{15°}$ + 11° (*c*, 1·4 in chloroform) [Found : C, 52·8; H, 8·1; OMe, 23·1; $(CH_3)_2CO$, 25·9. $C_{11}H_{20}O_6$ requires C, 53·2; H, 8·1; OMe, 25·0; $(CH_3)_2CO$, 23·4%].

Two methylations (0·4 g.) with Purdie's reagents followed by distillation at 120°/0·01 mm. gave 2 : 6-dimethyl 3 : 4-monoacetone β-methylgalactoside (0·35 g.), $[\alpha]_D^{15°}$ + 2° (*c*, 1·0 in chloroform), m. p. 55—56°, unchanged on mixing with an authentic specimen prepared by Dr. D. J. Bell.

Barium 6-Methyl 3 : 4-Monoacetone β-Methylgalactoside 2-Sulphate.—6-Methyl 3 : 4-monoacetone β-methylgalactoside (1·7 g.) was sulphated as previously described to yield a *barium* salt (3·1 g.), $[\alpha]_D^{15°}$ + 10° (*c*, 1·0 in water) [Found : Ba, 18·0; SO_4, 24·8; $(CH_3)_2CO$, 13·2. $(C_{11}H_{19}O_9S)_2Ba$ requires Ba, 17·4; SO_4, 24·3; $(CH_3)_2CO$, 14·6%].

Barium 6-Methyl β-Methylgalactoside 2-Sulphate.—The above product (2·7 g.) was treated with sulphuric acid (0·2N) at 37° as previously described to yield a non-reducing *barium* salt (2·3 g.), $[\alpha]_D^{15°}$ ± 0° (*c*, 1·0 in water) [Found : Ba, 17·5; SO_4, 25·6; OMe, 15·4. $(C_8H_{15}O_9S)_2Ba,4H_2O$ requires Ba, 17·5; SO_4, 24·5; OMe, 15·8%]. To this substance (2·0 g.) in methanol (25 c.c.), a solution of sodium in methanol (50 c.c.; 5%) was added. No reaction took place during 24 hours at 15°, 24 hours at 40°, or 6 hours at 60°. When the temperature was raised to 90°, however, the solution rapidly darkened. After 18 hours at 100° the product was worked up in the usual way to give a dark reducing syrup (0·5 g.; OMe, 25·3%). The syrup obtained from a second experiment had OMe, 21·8%. It is thought probable therefore that the syrups obtained were specimens of 6-methyl β-methylgalactoside (OMe, 29·9%) contaminated with reducing material formed by the fission of the glycosidic methoxyl group.

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