## 187. 1 : 2-5 : 6-*Di*-O-isopropylidene-α-D-glucofuranose 3-(*Methyl Sulphate*).

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1 : 2-5 : 6-Di-*O-iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) is obtained by oxidation of the corresponding methyl sulphite ester, and is converted into the 3-(sodium sulphate) by sodium iodide in acetone. The value of this new synthetical route is limited by the acid lability of the 3-(methyl sulphate).

Methods developed [1] for the preparation of carbohydrate sulphates involve the direct introduction of the sulphate residue. Subsequent reactions are frequently rendered difficult by the inconvenient properties conferred by the $RO{\cdot}SO_2{\cdot}O$ grouping. Thus, there is a need for methods which employ protected sulphate groups so that the salt of the free sugar sulphate ($RO{\cdot}SO_2{\cdot}O^-Y^+$) can be formed as the final stage of synthesis. From this viewpoint we have examined the reaction sequence

$$ROH \xrightarrow{A} \underset{(I)}{RO{\cdot}SO{\cdot}OMe} \xrightarrow{B} \underset{(II)}{RO{\cdot}\overset{a}{\downarrow}SO_2{\cdot}\overset{b}{\downarrow}OMe} \xrightarrow{C} RO{\cdot}SO_2{\cdot}O^-X^+$$

Stage *A* and some reactions of methyl sulphite esters (I) have been described elsewhere,[2] stages *B* and *C* and some properties of the hitherto unknown carbohydrate derivatives (II) are now outlined.

Oxidation of methyl sulphite esters (I) to methyl sulphate esters (II) may be accomplished, in moderate yield, by the use of calcium permanganate in aqueous acetic acid.[3] Crystalline 1 : 2-5 : 6-di-*O-iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) was obtained thus but oxidation of (—)-menthyl methyl sulphite and 1 : 2-3 : 4-di-*O-iso*propylidene-α-D-galactopyranose 6-(methyl sulphite) gave only oily products. Dimethyl sulphite and di*iso*propyl sulphite were readily oxidized to the corresponding dialkyl sulphates. Active manganese dioxide [4] had no effect on dimethyl sulphite. All these dialkyl sulphates decompose on storage: the only stable dialkyl sulphates so far encountered are the cyclic sulphates of *cis*- and *trans-cyclo*hexane-1 : 2-diol.[5]

1 : 2-5 : 6-Di-*O-iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) and sodium iodide in acetone yield the corresponding 3-(sodium sulphate) although the solubility of the salt in acetone complicates the isolation procedure. Cholesteryl 3-(methyl sulphate) is reported [6] to yield the 3-(sodium sulphate) by reaction with sodium iodide in acetone although no experimental details were provided. In this case the 3-(methyl sulphate) was prepared by the action of diazomethane on cholesteryl 3-(pyridinium sulphate). (—)-Menthyl methyl sulphate and dimethyl sulphate react readily with sodium iodide in acetone to yield sodium (—)-menthyl sulphate and sodium methyl sulphate, respectively; di*iso*propyl sulphate reacts less readily to give sodium *iso*propyl sulphate.

Hydrolysis by acid, or by alkali followed by acid, of 1 : 2-5 : 6-di-*O-iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) gave mainly D-glucose together with traces of unidentified substances. Similar products were obtained when 1 : 2-5 : 6-di-*O-cyclo*hexylidene-α-D-glucofuranose 3-(barium sulphate) [7] was treated similarly. D-Allose, which would be expected to be formed if Walden inversion occurred at $C_{(3)}$ during hydrolysis of the D-glucose sulphate derivatives, could not be detected in the reaction mixtures. Walden

[1] Percival, *Quart. Rev.*, 1949, **3**, 369.
[2] Foster, Hancock, Overend, and Robb, *J.*, 1956, 2589.
[3] Garner and Lucas, *J. Amer. Chem. Soc.*, 1950, **72**, 5497.
[4] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.
[5] Foster, Hancock, and Overend, *Chem. and Ind.*, 1956, 1144.
[6] McKenna and Norymberski, *ibid.*, 1954, 961.
[7] Bera and Foster, unpublished results.

inversion does occur in simpler compounds: thus sodium (+)-1-methylpropyl sulphate yields (−)-butan-2-ol on basic hydrolysis.[8]

Dissolution of 1 : 2-5 : 6-di-*O*-*iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) in aqueous acetic acid at 40° revealed (by paper-chromatographic and paper-ionophoretic analysis[9]) that the methyl ester group was much more labile in acid than were the *O*-*iso*propylidene residues and that in the main the following reaction sequence occurred: 1 : 2-5 : 6-di-*O*-*iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) $\xrightarrow{\text{fast}}$ 1 : 2-5 : 6-di-*O*-*iso*propylidene-α-D-glucofuranose 3-(sulphate) ⟶ D-glucose 3-sulphate $\xrightarrow{\text{slow}}$ D-glucose. The alternative initial reacton (*i.e.* cleavage at *a* in II) is negligible. The lability of the methyl ester group in acid media largely deprives the reaction sequence *A* ⟶ *B* ⟶ *C* of value as a method for carbohydrate sulphate synthesis and in view of this, alternative methods for synthesizing compounds of type (II) were not investigated.

## Experimental

1 : 2-5 : 6-*Di*-O-iso*propylidene*-α-D-*glucofuranose* 3-(*Methyl Sulphate*).—To a solution of 1 : 2-5 : 6-di-*O*-*iso*propylidene-D-glucofuranose 3-(methyl sulphite)[2] (10 g.) in glacial acetic acid (20 ml.) cooled to 0° was added a solution of calcium permanganate (7·4 g.) in water (10 ml.) so that the temperature was kept below 15°. Reaction was complete when a permanent colour was produced. Thereafter the mixture was poured slowly into a cold solution of sodium carbonate (25 g.) in water (50 ml.), excess of permanganate was decomposed with sodium dithionite, and the mixture was extracted with ether (6 × 50 ml.). Evaporation of the dried ($MgSO_4$) extracts and crystallization from ether gave the *product* (4·5 g., 43%), m. p. 120—126° (decomp.), $[\alpha]_D^{22}$ −84·0° (*c*, 0·762 in $CHCl_3$) (Found: C, 43·6; H, 6·6; S, 9·15. $C_{13}H_{22}O_9S$ requires C, 44·1; H, 6·2; S, 9·0%). After 2 weeks at room temperature extensive decomposition had occurred. By a similar procedure dimethyl sulphate (24%) and di*iso*propyl sulphate (42%) were obtained from the corresponding sulphites. Application to 1 : 2-3 : 4-di-*O*-*iso*propylidene-α-D-galactopyranose 6-(methyl sulphite)[2] and (−)-menthyl methyl sulphite[2] gave oils which decomposed on attempted distillation or on storage at room temperature.

*Action of Sodium Iodide in Acetone on* 1 : 2-5 : 6-*Di*-O-iso*propylidene*-α-D-*glucofuranose* 3-(*Methyl Sulphate*).—A solution of sodium iodide (0·34 g.) in acetone (5 ml.) was added to one of 1 : 2-5 : 6-di-*O*-*iso*propylidene-α-D-glucofuranose 3-(methyl sulphate) (0·4 g.) in acetone (10 ml.), and the mixture stored at room temperature overnight. The solution was evaporated, the residue dissolved in water, and the aqueous solution extracted with ether and then diluted to 50 ml. Iodide ion was removed by addition of the exact amount (determined by titration) of aqueous silver nitrate, and the remaining solution freeze-dried. The residue was extracted with boiling acetone and the extract concentrated to give 1 : 2-5 : 6-*di*-O-iso*propylidene*-α-D-*glucofuranose* 3-(*sodium sulphate*) (0·29 g., 71%), m. p. 135—136° (decomp.), $[\alpha]_D^{19}$ 0° (in water) (Found: S, 8·3. $C_{12}H_{19}O_9SNa$ requires S, 8·8%).

Dimethyl sulphate, di*iso*propyl sulphate, and (−)-menthyl methyl sulphate reacted rapidly with sodium iodide in acetone and after 1 min. at room temperature sodium methyl sulphate, (93%), sodium *iso*propyl sulphate (42%) and *sodium* (−)-*menthyl sulphate* {42%; m. p. 146° (decomp.), $[\alpha]_D^{17\cdot5}$ −61·8° (*c*, 1·0 in water) (Found: S, 11·6. $C_{10}H_{19}O_4SNa$ requires S, 12·4%)} had separated. The last is appreciably soluble in acetone.

*Hydrolysis of* 1 : 2-5 : 6-*Di*-O-iso*propylidene*-α-D-*glucofuranose* 3-(*Methyl Sulphate*).—(a) A solution of the methyl sulphate ester (0·123 g.) in N-sulphuric acid (5 ml.) was boiled under reflux for 1·5 hr. and then neutralized with barium hydroxide. Paper ionophoresis[9] of the solution in borate buffer (pH 10) for 2·5 hr. at 900 v showed the presence of D-glucose and traces of other, unidentified reducing substances (aniline hydrogen phthalate[10]): D-allose was absent from the hydrolysate. A mixture of apparently similar composition was obtained by the acidic hydrolysis of 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-α-D-glucofuranose 3-(barium sulphate)[6] {m. p. 220—260° (charring), $[\alpha]_D^{19}$ *ca.* 0° (*c*, 1·28 in water)}.

(b) A solution of the ester sulphate (0·120 g.) in 2N-sodium hydroxide (5 ml.) was boiled

[8] Burwell and Holmquist, *J. Amer. Chem. Soc.*, 1948, **70**, 878.
[9] Foster, *Chem. and Ind.*, 1952, 1050; *J.*, 1953, 982.
[10] Partridge, *Nature*, 1949, **164**, 443.

under reflux for 1·5 hr. (extensive liberation of sulphate ion) and then de-ionized [Amberlite IR-120($H^+$)]. *iso*Propylidene residues were removed by acidic hydrolysis and the neutralized solution was examined by paper ionophoresis; a composition similar to that in (*a*) was observed. Identical results were obtained with 1 : 2-5 : 6-di-*O*-*cyclo*hexylidene-α-D-glucofuranose 3-(barium sulphate).

(c) A solution of the ester sulphate (0·275 g.) in acetic acid (12·5 ml.) and water (7·5 ml.) was maintained at 40° {$[\alpha]_D$ $-0·34° \longrightarrow +0·12°$ (constant value) in 9 hr.}. From time to time the composition of the solution was examined (1) by paper chromatography: after irrigation with the organic phase of a butanol–ethanol–water (5 : 1 : 4) mixture and development with aniline hydrogen phthalate [10] (reducing sugars), *iso*propylidene derivatives could be detected by spraying with trichloroacetic acid (25% solution in 50% aqueous methanol), heating, and then spraying with aniline hydrogen phthalate; and (2) by paper ionophoresis, the previously described [9] apparatus and technique being used, with borate (pH 10) and glycine (pH 11) buffers and development as in (1). Suitable reference compounds were always included. It was apparent that in the main the reaction sequence was that outlined in the Discussion.

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