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REACTION OF SOME ALDOSES WITH ANHYDROUS CUPRIC SULPHATE–ACETONE PREPARATION OF 3,4-*O*-ISOPROPYLIDENE DERIVATIVES

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ABSTRACT

3,4-*O*-Isopropylidene derivatives are obtained in yields of 40–60% when D-fucose and 6-*O*-methyl-D-galactose are treated with acetone and anhydrous cupric sulphate. 3,4-*O*-Isopropylidene-D-ribose is isolated in 15–20% yield after treatment of the parent aldose with the same reagent, whereas 4,6-*O*-isopropylidene-D-glucose is formed in low yield from D-glucose in the presence of *N*,*N*-dimethylformamide

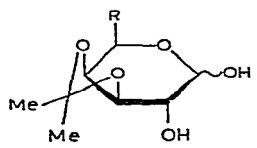
INTRODUCTION

Anhydrous cupric sulphate in acetone has long been known as a mild reagent for the preparation of *O*-isopropylidene derivatives from glycols, and it has found application in the synthesis of such derivatives from glycosides[1] It has also been found favourable in synthesis of *O*-isopropylidene derivatives which are not formed, or are formed in small amounts only, from free aldoses in the presence of acid[2,3] Despite the reported formation of 3,4-*O*-isopropylidene-D-arabinose with anhydrous cupric sulphate in acetone from the parent aldose in the absence of acid[3], little attention seems to have been focused on the potential applicability of this reagent in syntheses of otherwise inaccessible mono-*O*-isopropylidenealdoses. The aim of the present work was to investigate the possibility of preparing mono-*O*-isopropylidene derivatives of some analogues of D-arabinose using acetone in the presence of anhydrous cupric sulphate.

RESULTS AND DISCUSSION

D-Fucose and 6-*O*-methyl-D-galactose gave the corresponding 3,4-*O*-isopropylidene derivatives (**1** and **2**) in yields of ~40 and ~60%, respectively, no other mono-*O*-isopropylidene derivatives could be detected after treatment with anhydrous cupric sulphate in acetone for 3–4 h Prolonged reaction time gave increasing amounts of di-*O*-isopropylidene derivatives. D-Ribose which, in the presence of minute amounts of acid, reacts with acetone to give the 2,3-*O*-isopropylidene derivative (**3**), was found to react completely with cupric sulphate in acetone within one hour. The

products were 2,3- (**3**) and 3,4-*O*-isopropylidene-D-ribose (**4**) in approximately equal proportions Slightly prolonged reaction time caused extensive conversion of **4**→**3**, and it was only possible to isolate crystalline **4** in 15–20% yield.



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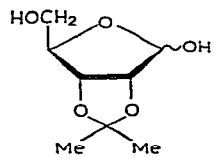

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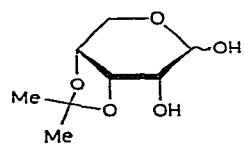

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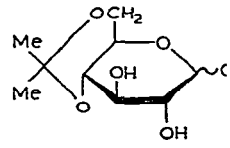

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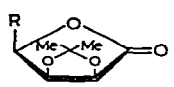
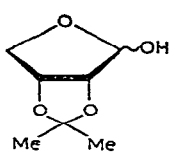
For comparison with these aldoses which have the *erythro* configuration at positions 3 and 4, D-glucose was treated with anhydrous cupric sulphate in acetone The reaction occurred considerably more slowly, presumably due in part to the low solubility in acetone of D-glucose The primary product was 4,6-*O*-isopropylidene-D-glucose (**5**), which was isolated in low yield after the reaction had been carried out in the presence of *N*,*N*-dimethylformamide This solvent prevented further reaction of the primary product, but also slowed down the rate of its formation

Identification of the *O*-isopropylidene derivatives was based on methylation, periodate oxidation, and, in part, on mass spectrometry That HO-1 and HO-2 were unsubstituted was shown by a positive Fehling's reaction and the response to periodate

Methylation of 3,4-*O*-isopropylidene-D-fucose (**1**) and 3,4-*O*-isopropylidene-6-*O*-methyl-D-galactose (**2**) with methyl iodide–silver oxide and subsequent acid hydrolysis gave 2-*O*-methyl-D-fucose and 2,6-di-*O*-methyl-D-galactose, respectively Periodate oxidation of **1** and **2** and subsequent oxidation of the products with silver carbonate–Celite–benzene yielded fully substituted aldono-1,4-lactones, the structures of which must therefore be 5-deoxy (**6**) and 5-*O*-methyl (**7**) derivatives of 2,3-*O*-isopropylidene-D-lyxono-1,4-lactone, respectively



6 R = Me
7 R = CH_2OMe



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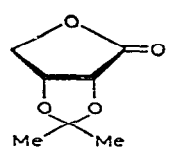

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The mass spectrum of 3,4-*O*-isopropylidene-D-fucose (**1**) showed the $(M-Me)^+$ ion at *m/e* 189, which is characteristic of *O*-isopropylidene derivatives[4] Fragments with *m/e* 129 (189−AcOH), 85 (), 59 (Me_2COH^+), and 43 ($MeCO^+$),

all expected ions from a compound having this structure, were also observed A fragment of low intensity with *m/e* 187 was also seen, presumably $(M-OH)^+$; such fragments are indicative of unsubstituted hemiacetal hydroxyl-groups[4].

The identity of 3,4-*O*-isopropylidene-D-ribose (**4**) was established by periodate oxidation to 2,3-*O*-isopropylidene-D-erythrose (**8**), which was further oxidized with silver carbonate–Celite–benzene to 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone (**9**) The identity of **4** was supported by the mass spectrum, which showed only small, quantitative differences from that of the configurational isomer 3,4-*O*-isopropylidene-L-arabinose

4,6-*O*-Isopropylidene-D-glucose (**5**) has previously been prepared by treatment of D-glucose with 2,2-dimethoxypropane in *N,N*-dimethylformamide–toluene-*p*-sulphonic acid, but the product was isolated as a triacetate[5] When the work reported herein was complete, an elegant synthesis of **5** was described using the system D-glucose–*N,N*-dimethylformamide–ethyl isopropenyl ether–toluene-*p*-sulphonic acid[6] The identity of **5** was supported by the fact that periodate oxidation yielded an *O*-isopropylidene-D-erythrose which was different from the 2,3-*O*-isopropylidene derivative (**8**), and was isomerized to this compound on treatment with acetone in the presence of acid

The preferred formation of the 3,4- over the 1,2-*O*-isopropylidene derivatives from D-fucose, 6-*O*-methyl-D-galactose, and D- and L-arabinose[3 7 8] seems to be due to low reactivity of the glycol group involving the anomeric hydroxyl group That the low reactivity is not due to the *trans* relationship of HO-1 and HO-2 is indicated by the fact that α-D-glucopyranose, in v hich HO-1 and HO-2 are *cis*, yields a 4,6-*O*-isopropylidene derivative (**5**) Moreover, **5** contains a 1,3-dioxane ring, and acetone usually reacts preferentially with vicinal *cis*-diols to give 1,3-dioxolane rings[1] The recently reported formation[6] of 4,6-*O*-isopropylidene-D-glucose (**5**) using ethyl isopropenyl ether was suggested to be due to greater reactivity of the primary hydroxyl group It is of interest to note the resistance to reaction of the anomeric hydroxyl group in D-glucose and other aldoses with acetone–cupric sulphate, particularly in the presence of *N,N*-dimethylformamide Similar, low reactivity was also observed with 2,2-dimethoxypropane–*N,N*-dimethylformamide[5].

The formations of the 3,4- (**4**) and the 2,3-*O*-isopropylidene derivative (**3**) from D-ribose are about equally favoured kinetically, but **3** is thermodynamically more stable than **4** and is the acetal obtained in the presence of acid The isomerization **4** → **3** occurs because **3** can exist in the furanose form, and the *O*-isopropylidene derivative involves two *cis*-fused five-membered rings, which is energetically more favourable than *cis*-fused five- and six-membered rings

Anhydrous cupric sulphate in acetone is a useful reagent for the preparation of reducing mono-*O*-isopropylidene derivatives from aldoses, or derivatives thereof, which are soluble in acetone, when relatively short reaction times are applied Products of high purity are obtained since there is no accompanying occurrence of dimethyl acetalation, a phenomenon observed when 2,2-dimethoxypropane is used. Moreover, removal of the reagents and isolation of the products are easily accom-

plished. The 3,4-*O*-isopropylidene derivatives are valuable starting materials for one-step degradation reactions by periodate or silver carbonate on Celite[8], and *O*-alkylation by mild alkylation reagents, with subsequent acid hydrolysis, offers a rapid way to the 2-*O*-alkyl derivatives

EXPERIMENTAL

Thin-layer chromatography (t l c) was performed on Silica Gel G, using *A*, benzene–ethanol (3·1) and *B*, benzene–ethanol (4 1), and detection with diphenylamine–aniline–phosphoric acid[9] and hydroxylamine–ferric chloride[10]. Mass spectra were recorded with an AEI MS-902 mass spectrometer at an ionizing potential of 70 eV.

*3,4-O-Isopropylidene-*D*-fucose* (**1**) — D-Fucose (400 mg) was stirred at room temperature with acetone (200 ml) and anhydrous cupric sulphate (4 g) for 3 h The solution was filtered and concentrated under reduced pressure The residue was extracted with hot benzene (2 × 15 ml), and the extract was filtered and concentrated to ~5 ml Addition of light petroleum (b p 60–80°) gave a gelatinous precipitate, which was collected and crystallised from ethyl acetate–light petroleum (b p 60–80°) to give **1** (200 mg, 40%), m p 110–111°, $[\alpha]_D^{27}$ +86 (5 min) → +71° (*c* 2, water; 24 h), which reduced Fehling's solution (Found C, 52 78, H, 7 81. $C_9H_{16}O_5$ calc C, 52 94, H, 7.84%) Mass-spectral data *m/e* 189 (12%), 131 (5), 129 (6), 101 (9), 100 (23), 99 (12), 85 (16), 73 (47), 71 (38), 59 (100), 43 (99)

*2-O-Methyl-*D*-fucose* — 3,4-*O*-Isopropylidene-D-fucose (**1**, 100 mg) was shaken with methyl iodide (3 ml) and silver oxide (0 5 g) for 6 h More methyl iodide (2 ml) and silver oxide (0 5 g) were then added, and shaking was continued for 48 h The solution was diluted with chloroform, filtered, and concentrated The residue was treated with 0 5M sulphuric acid at 100° for 4 h, then neutralized with Dowex-1(HCO_3^-) resin, and concentrated under reduced pressure The residue was treated with ethyl acetate to give the title compound (47 mg, 52%), m p 150–153°, $[\alpha]_D^{25}$ +79° (*c* 1, water, final), lit [11] m p 155–161°, $[\alpha]_D$ +87°

*Periodate oxidation of 3,4-O-isopropylidene-*D*-fucose* (**1**) — A solution of **1** (90 mg) in water (4 ml) was treated with sodium periodate (200 mg) for 1 h The solution was maintained at pH 6 with sodium hydrogen carbonate Excess of periodate was destroyed with ethylene glycol, and the solution was extracted with chloroform (5 × 2 ml) The extract was dried (Na_2SO_4), filtered, and concentrated under reduced pressure The residue was extracted with light petroleum (b p 60–80°), and concentration of the extract gave a chromatographically homogeneous (t l c, solvent *B*) syrup (55 mg)

The product was oxidised with silver carbonate on Celite (0 5 g) in benzene (10 ml) at reflux temperature for 1 h The mixture was filtered and concentrated under reduced pressure to yield a syrupy residue containing mainly one component (t l c, solvent *B*, hydroxylamine–ferric chloride) Traces of starting material and another compound could be observed The product exhibited strong i r. absorption

at 1780 cm^{-1} (in $CHCl_3$), but no hydroxyl absorption Crystallization from light petroleum (b p 60–80°) gave colourless crystals (21 mg), m p. 76–81°, $[\alpha]_D^{22}$ +92° (*c* 0 3, acetone) (Found. C, 56 41, H, 7 20 $C_8H_{12}O_4$ calc C, 55.82, H, 6.98%), presumably **6**

3,4-O-Isopropylidene-6-O-methyl-D-galactose (**2**). — 6-*O*-Methyl-D-galactose (300 mg) was stirred with acetone (90 ml) and anhydrous cupric sulphate for 4 h at room temperature T l c (solvent *B*) then showed major (R_F 0.42) and minor (R_F 0.90) products, and a small proportion of starting material (R_F 0 04) The solution was filtered and concentrated to ~2 ml, benzene (20 ml) was added, and the solution was treated with carbon, filtered, and concentrated to ~10 ml Addition of light petroleum (b p 60–80°) gave **2** as a gelatinous precipitate which was collected by filtration; yield, 213 g (58%); m p 99–100°, $[\alpha]_D^{25}$ +79° (*c* 1, water, 4 h) (Found C, 50 95, H, 7.81 $C_{10}H_{18}O_6$ calc C, 51 28, H, 7 69%) Compound **2** reduced Fehling's solution

2,6-Di-O-methyl-D-galactose — A solution of **2** (200 mg) in methyl iodide (5 ml) was stirred with silver oxide (1 g) overnight More methyl iodide (1 g) and silver oxide (1 g) were then added, and stirring was continued for 24 h The solution was diluted with chloroform, filtered, and concentrated, and the residue was hydrolyzed in 0 5M sulphuric acid for 3 h at 100° The hydrolysate was neutralized with Dowex-1(HCO_3^-) resin and concentrated under reduced pressure T l c (solvent *A*) showed the presence of some 6-*O*-methyl-D-galactose and, as major component, a faster moving compound Preparative t l c (solvent *A*) gave the title compound (58 mg), m p 114–119° (from ethyl acetate), $[\alpha]_D^{25}$ +80° (*c* 1, water, final), lit [12] m p 119–120°, $[\alpha]_D$ +87°.

Periodate oxidation of 3,4-O-isopropylidene-6-O-methyl-D-galactose (**2**) — A solution of **2** (20 mg) in water (2 ml) was treated with sodium periodate (50 mg), as previously described for **1** The resulting syrupy product, which was homogeneous by t l c (solvent *B*), was further oxidized by silver carbonate on Celite (0 3 g) in benzene (5 ml), as described above, to yield a chromatographically homogeneous (t l c, solvent *B*, hydroxylamine–ferric chloride) syrup which had strong i r absorption at 1785 cm^{-1} ($CHCl_3$), characteristic of a γ-lactone, and no hydroxyl absorption Crystallization from light petroleum (b p 60–80°) gave long needles, m p 63 5–65°, $[\alpha]_D^{22}$ +88° (*c* 0 5, acetone) (Found C, 53 18; H, 6 68 $C_9H_{14}O_5$ calc C, 53.46, H, 6 93%), presumably **7**

3,4-O-Isopropylidene-D-ribose (**4**) — D-Ribose (1 g) was stirred with acetone (250 ml) and freshly prepared anhydrous cupric sulphate (10 g) at room temperature for 30 min T l.c (solvent *B*) showed the presence of unreacted D-ribose (R_F 0 05) and about equal amounts of two products, R_F 0 45 and 0 58; the fastest moving compound was indistinguishable from 2,3-*O*-isopropylidene-D-ribose (**3**) The solution was filtered and concentrated to ~50 ml, light petroleum (b p 60–80°) (75 ml) was added, and the solution was treated with a small amount of carbon, filtered, and concentrated From a solution of the residue in ethyl acetate–light petroleum, **4** crystallized (215 mg, 17%), m p 119–120°, $[\alpha]_D^{27}$ −85° (*c* 2, water, equil) (Found

C, 50.74, H, 7.15. $C_8H_{14}O_5$ calc. C, 50.53; H, 7.37%). Compound **4** reduced Fehling's solution. Mass-spectral data *m/e* 175 $(M-Me)^+$ (5%), 173 (2), 159 (3), 131 (3), 130 (2), 115 (1), 101 (2), 85 (9), 73 (11), 69 (8), 59 (51), 43 (100)

Periodate oxidation of 3,4-O-isopropylidene-D-ribose (**4**) — A solution of **4** (70 mg) in water (5 ml) was treated with sodium periodate (150 mg) at room temperature for 90 min, sodium hydrogen carbonate being added at intervals to keep the pH above 6. 0.5M Barium acetate was then added until precipitation was complete, and the solution was centrifuged and subsequently treated with Dowex-1(HCO_3^-) and Dowex-50W(H^+) resins. The filtered solution was concentrated under reduced pressure and the residue was dissolved in benzene (10 ml). T.l.c. (solvent *B*) showed the presence of a single component, indistinguishable from 2,3-*O*-isopropylidene-D-erythrose (**8**). The solution was boiled and stirred with silver carbonate on Celite (0.5 g) for 1 h, then filtered, and concentrated, and the residue was crystallised from light petroleum (b.p. 60–80°) to give 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone (**9**, 15 mg), m.p. 68–69°, lit.[13] m.p. 65–67.5°. The i.r. spectrum ($CHCl_3$, strong absorption at 1780 cm^{-1}) was identical with that of an authentic sample of the L enantiomer[14].

4,6-O-Isopropylidene-D-glucose (**5**). — A solution of D-glucose (2 g) in *N,N*-dimethylformamide (4 ml) was poured into a stirred suspension of anhydrous cupric sulphate (8 g) in acetone (120 ml), and stirring was continued for 6 h at room temperature. T.l.c. (solvent *A*) showed the presence of unreacted D-glucose and one product with mobility 0.87 relative to that of 1,2-*O*-isopropylidene-α-D-glucofuranose. The solution was filtered and concentrated to ~4 ml, and the residue was subjected to chromatography on a column (45 × 4 cm, i.d.) of Silica Gel H (solvent *A*). The fractions containing the product were collected and concentrated, and the residue was crystallised from ethyl acetate to give **5** (170 mg, 7%). One recrystallization from ethyl acetate gave material having m.p. 164–166°, $[\alpha]_D^{25}$ −4° (*c* 2, water), which reduced Fehling's solution, lit.[6] m.p. 169–170°, $[\alpha]_D$ −7.3°.

Oxidation of **5** *with periodate.* — A solution of **5** (50 mg) in water (5 ml) was treated with sodium periodate (200 mg), as described above for **4**. T.l.c. (solvent *B*) indicated the presence of a single compound with mobility 0.85 relative to that of 2,3-*O*-isopropylidene-D-erythrose (**8**) and giving the same colour with the spray reagent. The product was dissolved in acetone (5 ml) containing conc. sulphuric acid (0.05 ml). After 2 h, the solution was neutralized with solid sodium hydrogen carbonate, filtered, and then concentrated. The residue contained a single compound (t.l.c., solvent *B*), indistinguishable from **8**.

Oxidation of the product in benzene (10 ml) with silver carbonate on Celite (0.5 g), as described above, and crystallization of the product from light petroleum (b.p. 60–80°) gave 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone (**9**), m.p. 65–66.5°, lit.[13] m.p. 65–67.5°. The i.r. spectrum was identical with that of the authentic L enantiomer.

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