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# OXIDATION OF 1,2-*O*-ISOPROPYLIDENEALDOHEXOFURANOSES WITH SILVER CARBONATE ON CELITE*

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## ABSTRACT

1,2-*O*-Isopropylidenealdohexofuranoses are oxidized by silver carbonate–Celite in boiling methanol to methyl 1,2-*O*-isopropylidenepentofuranuronates. 1,2-*O*-Isopropylidenepentodialdo-1,4-furanoses are intermediates, and various amounts of esters of 1,2-*O*-isopropylidenehexofuranuronic acids are formed as side products. The site of initial oxidation depends on the configuration of the 1,2-*O*-isopropylidenehexose. The results are discussed on the basis of adsorption involving HO-3, HO-5, and HO-6 prior to oxidation.

## INTRODUCTION

Methyl 1,2-*O*-isopropylidene-α-D-xylofuranuronate is formed[1] from 1,2-*O*-isopropylidene-α-D-glucofuranose on oxidation in boiling methanol by the Fetizon reagent, silver carbonate–Celite[2]. As several 1,2-*O*-isopropylidenealdohexofuranoses are now available, a more general investigation of the applicability of silver carbonate–Celite in a one-step method of preparation of penturonic acid derivatives therefrom is possible.

## RESULTS AND DISCUSSION

Oxidation of the 1,2-*O*-isopropylidene-α-D-gluco- (**1**), -allo- (**2**)[3], and -galacto- (**3**)[4] -furanoses, gave, as the main products, methyl 1,2-*O*-isopropylidene-α-D-xylo- (**4**), -α-D-ribo- (**5**), and -β-L-arabino- (**6**) -furanuronates, respectively. Also formed from **2** and **3** were substantial proportions of compounds which chromatographic and mass-spectrometric evidence indicated to be methyl 1,2-*O*-isopropylidenehexofuranuronates, presumably the D-*allo* (**8**) and D-*galacto* (**9**) isomers. Oxidation of **1** also gave a very small proportion of a compound identified by g.l.c.–m.s. as 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (**7**). Prolonged reaction decreased the amount of **7** and explained the earlier finding[1] that methyl 1,2-*O*-isopropylidene-α-D-xylofuranuronate (**4**) was the only detectable product from **1**.

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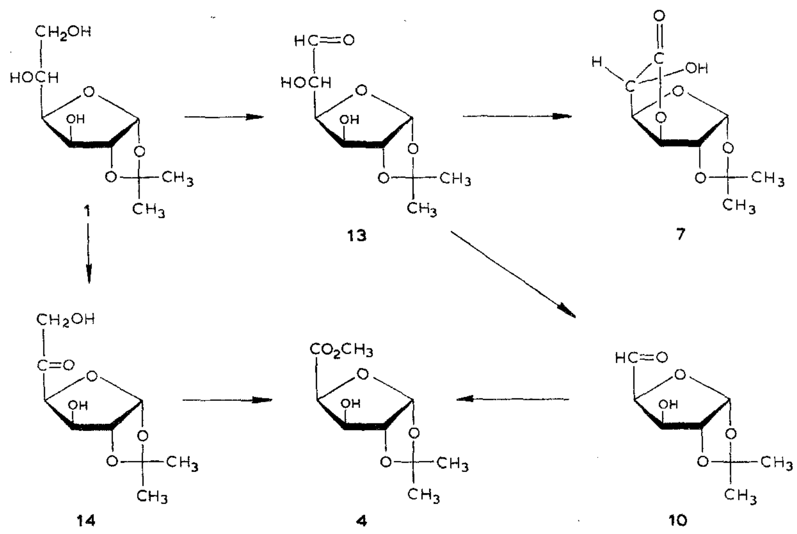
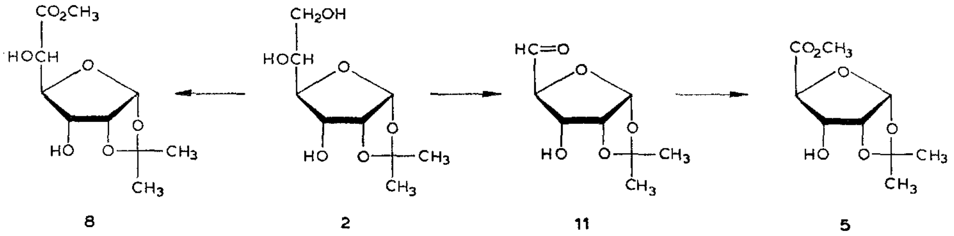
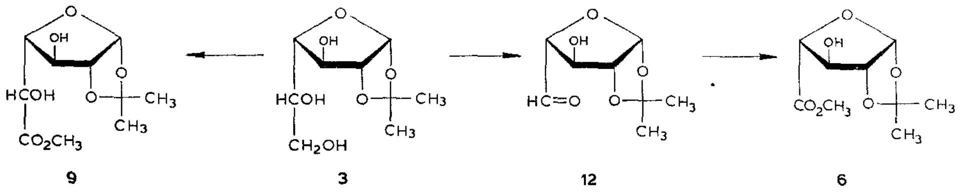
*Oxidation of Carbohydrate Derivatives with Silver Carbonate on Celite: Part XII.







An intermediate detected in the oxidation of 1,2-*O*-isopropylidene-α-D-allofuranose (**2**) was a 1,2-*O*-isopropylidenepentodialdo-1,4-furanose which was chromatographically indistinguishable from the product obtained by periodate oxidation of **2** and thus possessed the D-*ribo* configuration (**11**). 1,2-*O*-Isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**10**) was detected (t.l.c. and g.l.c.–m.s.) in small amounts as an intermediate during the oxidation of **1**, and a compound which was chromatographically indistinguishable from the product obtained by periodate oxidation of 1,2-*O*-isopropylidene-α-D-galactofuranose (**3**) was observed during the oxidation of **3** by silver carbonate–Celite, and is, presumably, 1,2-*O*-isopropylidene-β-L-*arabino*-pentodialdo-1,4-furanose (**12**).

Methyl 1,2-*O*-isopropylidene-α-D-ribofuranuronate (**5**) was obtained as a syrup, although it has been reported[5] crystalline, and the D enantiomer of methyl 1,2-*O*-isopropylidene-β-L-arabinofuranuronate (**6**) is known[6]. Evidence for the identity of **5** and **6** was obtained by borohydride reduction and subsequent acid hydrolysis to give products which were indistinguishable (chromatography and electrophoresis) from the corresponding pentoses. The i.r. and mass spectra of **5** and **6** were similar to those of methyl 1,2-*O*-isopropylidene-α-D-xylofuranuronate (**4**).

The mass spectra (Table I) show fragments of *m/e* 203 ($M^+ - Me$), 159 (cleavage between C-4 and C-5), and 143 ($M^+ - Me - AcOH$) in the higher mass region, and 85, 59 (protonated acetone), and 43 ($Ac^+$) in the lower mass region, in accordance with the known fragmentation patterns of *O*-isopropylidene derivatives[7].

TABLE I

MASS-SPECTRAL DATA FOR 1,2-*O*-ISOPROPYLIDENE DERIVATIVES

*Methyl 1,2-*O*-isopropylidenepentofuranuronates*[a]

*m/e* 203 (22, 17, 17), 160 (1, 5, 0), 159 (10, 15, 9), 143 (14, 15, 12), 141 (2, 2, 2), 129 (3, 2, 0), 115 (4, 2, 2), 103 (3, 4, 3), 102 (13, 12, 5), 101 (8, 11, 6), 100 (5, 3, 2), 99 (4, 4, 4), 85 (8, 5, 5), 73 (14, 16, 2), 71 (17, 22, 13), 60 (5, 4, 4), 59 (84, 90, 64), 58 (5, 4, 5), 55 (15, 12, 14), 45 (5, 5, 6), 44 (10, 9, 40), and 43 (100, 100, 100).

*1,2-*O*-Isopropylidenepentodialdo-1,4-furanoses*[b]

*m/e* 173 (21, 14), 160 (4, 5), 159 (52, 42), 141 (3, 12), 129 (5, 5), 113 (16, 6), 101 (12, 19), 85 (40, 30), 83 (12, 19), 73 (30, 24), 71 (26, 25), 59 (100, 79), 55 (26, 20), and 43 (75, 100).

*Methyl 1,2-*O*-isopropylidenehexofuranuronates*[c]

*m/e* 233 (13, 23), 197 (4, 6), 173 (1, 3), 160 (4, 3), 159 (39, 32), 155 (10. 10), 131 (4, 5), 129 (3, 6), 127 (11, 13), 119 (3, 4), 113 (3, 4), 101 (13, 12), 90 (7, 8), 85 (28, 33), 73 (64, 56), 71 (18, 22), 60 (6, 6), 59 (79, 100), 55 (8, 8), 45 (7, 11), and 43 (100, 61).

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[a] The figures in parentheses are the relative intensities (%) for the α-D-*xylo* (**4**), α-D-*ribo* (**5**), and β-L-*arabino* (**6**) derivatives. [b] The figures in parentheses are the relative intensities (%) for the α-D-*xylo* (**10**) and α-D-*ribo* (**11**) compounds. [c] The figures in parentheses are the relative intensities (%) for the compounds tentatively assigned the α-D-*allo* (**8**) and α-D-*galacto* (**9**) configurations.

The mass spectra (Table I) of two of the 1,2-*O*-isopropylidenepentodialdo-1,4-furanoses (**10** and **11**) are also similar. Each spectrum showed fragments of *m/e* 173 ($M^+ - Me$) and 113 ($M^+ - Me - AcOH$), and peaks of high abundance are found at *m/e* 159, 85, 59, and 43, due to the same type of fragmentation as that for the methyl 1,2-*O*-isopropylidenepentofuranuronates, and the same fragments are also seen in the mass spectra (Table I) of the two methyl 1,2-*O*-isopropylidenehexofuranuronates (**8** and **9**), the ($M^+ - Me$) ion being found at *m/e* 233. The spectra of these compounds also show an intense peak at *m/e* 73.

The formation of hexuronic ester derivatives in the oxidation reaction, though in small amounts only from the *gluco* isomer **1**, shows that the first oxidation step, at least in part, must be the formation of hexodialdose derivatives. As hemiacetals with methanol, or possibly for **1**, with HO-3, these compounds then may be dehydrogenated to give hexuronic esters, or degraded to pentodialdoses as found[8] for aldoses.

Hexodialdose derivatives have not been detected as intermediates in the oxidation of the 1,2-*O*-isopropylidenehexoses. They may be too reactive, and this view is verified by the fact that 1,2-*O*-isopropylidene-α-D-*gluco*-hexodialdo-1,4-furanose (**13**) was completely oxidized within 5 min with the oxidant in boiling methanol. The products were **4**, **7**, and **10**, with the last compound being further oxidized to **4** on prolonged reaction. The amounts of **7** and **10** were considerably greater than those obtained on oxidation of **1**, the ratio of hexuronic to penturonic ester being similar to those from the two other 1,2-*O*-isopropylidenehexoses.

The 1,2-*O*-isopropylidenepentodialdoses, detected during the oxidation of the 1,2-*O*-isopropylidenehexofuranoses, were separately prepared by oxidation of the 1,2-*O*-isopropylidenehexoses with periodate and, when treated with silver carbonate–Celite in boiling methanol, gave methyl 1,2-*O*-isopropylidenepentofuranuronates as the only detectable products. The reactivities of **1–3** did not differ very much from those of **10–12** (see below).

The foregoing data are consistent with the initial formation of hexodialdose derivatives in the oxidation of 1,2-*O*-isopropylidenealdohexofuranoses as one route to the methyl 1,2-*O*-isopropylidenepentofuranuronates. Simultaneous oxidation at C-5 to give hexos-5-ulose derivatives as intermediates could not be completely excluded, and seems likely for **1**. The resulting 1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**14**) would be too reactive to be detectable, and cleavage between C-5 and C-6 would be expected[9] to occur rapidly to give the methyl xylofuranuronate derivative **4**.

For 1,2-*O*-isopropylidene-α-D-allofuranose (**2**), monitoring of the reaction by g.l.c. indicated that the final product must have the pentodialdose derivative **11** as the main precursor. The possibility that the pentodialdose derivatives are formed from the 1,2-*O*-isopropylidenehexoses by glycol cleavage between C-5 and C-6, and not from the hexodialdose derivatives, is not very likely in the light of results of Fetizon and co-workers[10]. Only a few glycols with one tertiary hydroxyl group, and where dehydrogenation is sterically unfavourable, undergo glycol cleavage by silver carbonate–Celite.

Fetizon and co-workers[10,11] have oxidised some steroid diols and triols, and some model compounds, with silver carbonate–Celite. An initial adsorption of the substrate, involving the hydroxyl groups, was suggested[11], followed by oxidation at the HCOH group that is oriented against the surface. Cleavage of the C–H bond was found to be rate determining after an initial induction period.

This theory can explain the difference in the ratios of hexuronic to penturonic ester obtained from the *allo* (**2**) and *galacto* (**3**) isomers compared to that for the *gluco* isomer (**1**). Inspection of models shows that simultaneous contact of HO-3, HO-5, and HO-6 with the oxidant surface is possible in a relatively favourable conformation of the *allo* isomer (**2**). Fig. 1A shows that one H-6 is also in contact with the surface, whereas H-5 is not. Oxidation at C-6 is therefore preferred. Similar considerations apply to the *galacto* isomer (**3**) (Fig. 1B), but the conformation needed is less favourable than for **2** as the C-3–C-4 and C-5–C-6 bonds are nearly eclipsed, and this, presumably, accounts for the somewhat lower reactivity. The times (min) for complete oxidation are as follows: **1** 80–100, **2** 30–40, and **3** 130–140.

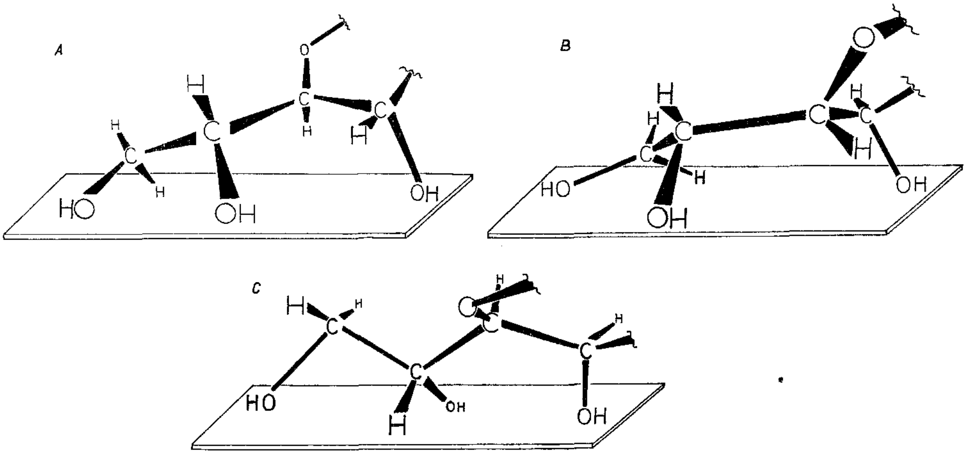

Fig. 1. Proposed, adsorbed states prior to oxidation: *A*, 1,2-*O*-isopropylidene-α-D-allofuranose (**2**); *B*, 1,2-*O*-isopropylidene-α-D-galactofuranose (**3**); and *C*, 1,2-*O*-isopropylidene-α-D-glucofuranose (**1**).

For the *gluco* isomer **1** (Fig. 1C), H-5 is oriented against the surface in the conformation which allows all three hydroxyl groups to participate in the adsorption. A less favourable conformation involves one H-6 in the required orientation, and probably explains the relatively low yield of hexuronic ester derivative, with oxidation occurring mainly at C-5.

The times (min) for complete oxidation of the 1,2-*O*-isopropylidenepentodialdo-1,4-furanoses in the hemiacetal form [*xylo* (**10**) 70–80, *ribo* (**11**) 90–100, and *arabino* (**12**) 140–150] are too small to justify any speculations about a relation between the ease of adsorption and the reactivity.

In oxidations with silver carbonate–Celite, it is difficult to establish exactly reproducible reaction conditions for comparison of reactivities. The oxidation of mixtures of substrates, suggested as a means of overcoming this problem[11], may be complicated by competitive adsorption. This factor can be minimised only by using a very large excess of reagent and solvent. An observed decrease in the reactivity of the *allo* compound **2** in the presence of the *gluco* isomer **1** presumably reflects the more favoured adsorption of the latter.

The foregoing results show the applicability of silver carbonate–Celite–methanol for small-scale, one-step preparations of penturonic acid derivatives from 1,2-*O*-isopropylidenehexofuranoses. The dependence on orientation of the potentially reactive groups in the adsorbed states suggests a possible selectivity in oxidation of free hydroxyl groups of non-reducing carbohydrate derivatives. The choice of solvent is important, as the use of a nonparticipating solvent may lead to other types of products and thus increase the scope of this oxidant in carbohydrate chemistry.

## EXPERIMENTAL

T.l.c. was performed on Silica gel G with *A*, benzene–ethanol (4:1); and *B*, chloroform–methanol (7:1). P.c. was performed on Whatman No. 1 paper with *C*, butanol–pyridine–water (5:3:1); paper electrophoresis was performed with borate buffer (pH 10). Detection was effected with *A*, diphenylamine–aniline–phosphoric acid[12]; *B*, aniline oxalate; and (for esters) *C*, hydroxylamine–ferric chloride[13]. G.l.c. was performed on a Perkin–Elmer F-11 gas chromatograph, equipped with a flame-ionization detector and a stainless-steel column (2 m × 2.2 mm) containing 3% of OV-225 on Gaschrom Q, operated with a temperature programme of 3°/min from 150°. A Micromass 12-F mass spectrometer was used in the g.l.c.–m.s. combination, the ion-source temperature was 220–230°, and the ionizing potential 70 eV.

*Methyl 1,2-*O*-isopropylidene-α-*D*-ribofuranuronate* (**5**). — A boiling solution of 1,2-*O*-isopropylidene-α-D-allofuranose (**2**; 100 mg, prepared by borohydride reduction[3] of 1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[14]) in methanol (100 ml) was stirred with silver carbonate–Celite (4 g) until t.l.c. showed the absence of starting material. Three compounds were detected, $R_F$ 0.74, 0.48, and 0.44 (solvent *B*), and the colours with reagent *A* were yellow, purple, and bluish green, respectively. The first two compounds were also detectable with reagent *C*, and the last was indistinguishable from the product obtained by periodate oxidation of 1,2-*O*-isopropylidene-α-D-allofuranose (**2**) as described below. The oxidation was continued until the compound having $R_F$ 0.44 was completely oxidised, and the solution was then filtered and concentrated under diminished pressure. Distillation (short path) of the residue gave **5** (52 mg, 53%), b.p. 110° (bath)/5 mmHg, $[\alpha]_D$ +36° (*c* 1, methanol), $\nu_{max}^{liquid}$ 1745 cm$^{-1}$, contaminated with traces only of the other carboxylic ester formed (Found: C, 49.68; H, 6.64. $C_9H_{14}O_6$ calc.: C, 49.54; H, 6.47%).

The mass-spectral data are shown in Table I.

Treatment of **5** (10 mg) with sodium borohydride (5 mg) in water for 2 h, followed by removal of cations with Dowex 50W ($H^+$) resin, removal of boric acid by repeated codistillation with methanol, and hydrolysis of the product with 0.5M sulphuric acid at 70° for 5 h, gave ribose identified by p.c. and electrophoresis, and by g.l.c. of the isopropylidene derivatives[15].

*Methyl 1,2-*O*-isopropylidene-β-*L*-arabinofuranuronate* (**6**). — 1,2-*O*-Isopropylidene-α-D-galactofuranose[4] (**3**, 100 mg), when oxidized as described above, gave products (t.l.c., solvent *B*) having $R_F$ 0.55, 0.50, and 0.39 (yellow, purple, and bluish green, respectively, with reagent *A*). The first two were detectable with reagent *C*, and the last was indistinguishable (t.l.c., solvents *A* and *B*) from the product obtained by periodate oxidation of 1,2-*O*-isopropylidene-α-D-galactofuranose, as described below. The oxidation was continued until the compound having $R_F$ 0.39 was almost completely oxidized, and the solution was then filtered and concentrated under diminished pressure. The residue was extracted with acetone, and addition of light petroleum (b.p. 60–80°) to the extract gave **6** (38 mg, 39%), m.p. 132–133° (after sublimation *in vacuo*), $[\alpha]_D$ −45° (*c* 1, methanol), $\nu_{max}^{KBr}$ 1740 cm$^{-1}$; lit.[6] for the D form, m.p. 133–134°, $[\alpha]_D$ +67° (ethanol) (Found: C, 49.52; H, 6.69. $C_9H_{14}O_6$ calc.: C, 49.54; H, 6.47%).

The mass-spectral data are shown in Table I.

Borohydride reduction and subsequent hydrolysis, as described above, gave arabinose containing traces of xylose presumably resulting from epimerization at C-4 prior to reduction of **6**.

*Periodate oxidation of the 1,2-*O*-isopropylidenehexofuranoses.* — A solution of each 1,2-*O*-isopropylidenehexofuranose (20 mg) in water (5 ml) was treated with sodium metaperiodate (30 mg) for 2 h. 0.5M Barium acetate was added until precipitation was complete. After centrifugation, the solution was concentrated, the residue was extracted with chloroform, the chloroform was removed, and a solution of the residue in methanol was boiled for 1 h. A single product was indicated by t.l.c. (solvents *A* and *B*); this gave a bluish green colour with reagent *A*. G.l.c. indicated a single product from **2**, and a major component with a shoulder from **1**. The mass-spectral data are shown in Table I. The product from **3** was not amenable to g.l.c.

*Oxidation by silver carbonate–Celite of the periodate-oxidized 1,2-*O*-isopropylidenehexoses.* — Each of the foregoing products was stirred with silver carbonate–Celite (1 g) in boiling methanol (25 ml) until oxidation was complete (t.l.c). The following products were obtained chromatographically homogeneous (g.l.c.; t.l.c., solvents *A* and *B*).

Methyl 1,2-*O*-isopropylidene-α-D-xylofuranuronate (**4**), m.p. 104–106°, $[\alpha]_D$ −32° (*c* 1, methanol); lit.[16] m.p. 103–104°, $[\alpha]_D$ −32.8°.

Methyl 1,2-*O*-isopropylidene-α-D-ribofuranuronate (**5**), $[\alpha]_D$ +34° (*c* 1, methanol), and methyl 1,2-*O*-isopropylidene-β-L-arabinofuranuronate (**6**), m.p. 132–134°, $[\alpha]_D$ −44° (*c* 1, methanol).

The products were indistinguishable (g.l.c.; t.l.c., solvents *A* and *B*; and i.r. spectra) from the corresponding authentic compounds.

*Oxidation of 1,2-*O*-isopropylidene-α-D-*gluco*-hexodialdo-1,4-furanose* (**13**). — A boiling solution of **13**[3] (40 mg) in methanol (50 ml) was stirred with silver carbonate–Celite (1.5 g) until oxidation was complete (t.l.c., solvent *B*). Products chromatographically indistinguishable (mobility in solvent *B*, and colour with the spray reagents) from methyl 1,2-*O*-isopropylidene-α-D-xylofuranuronate (**4**, $R_F$ 0.60), 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (**7**, $R_F$ 0.54), and 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**10**, $R_F$ 0.46) were detected, together with a compound having $R_F$ 0.54. The last compound gave the same colours with the spray reagents as 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (**7**), and is presumably the methyl ester of 1,2-*O*-isopropylidene-α-D-glucofuranuronic acid.

The oxidation was continued until **10** could not be detected in the reaction mixture, which was then filtered and concentrated. Crystallisation of the residue from ethyl acetate gave **4**, m.p. 103–105°.

When the reaction was monitored by g.l.c.–m.s., the formation of **10**, **4**, and **7** was confirmed.

*Comparison of reactivities of 1,2-*O*-isopropylidene derivatives and identification of side products and intermediates by g.l.c.–m.s.* — A solution of each 1,2-*O*-isopropylidene derivative (5 mg) in boiling methanol (10 ml) was stirred with silver carbonate–Celite (250 mg). The reaction was monitored by t.l.c. (solvent *B*) Immediately after disappearance of the starting material, the reaction mixtures were subjected to g.l.c.–m.s., and the side products and intermediates were thereby identified. The mass-spectral data are given in Table I.

## ACKNOWLEDGMENTS

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