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Note

Synthesis of di-*O*-isopropylidene derivatives of L-fructose

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The di- and mono-isopropylidene acetals of D-fructose and their derivatives have found extensive use in synthetic work to give, for example, otherwise inaccessible isopropylidene derivatives of D-tagatose[1], D-psicose[2–5], and D-*erythro*-pentulose[6,7]. The application of these established synthesis pathways for the preparation of the corresponding enantiomeric products has been hampered by the lack of convenient methods for the synthesis of L-fructose. L-Fructose may be synthesised from L-arabinonic acid in five steps[8] and by isomerisation[9] of L-mannose by an enzyme present in cell-free extracts of *Aerobacter aerogenes* grown on L-rhamnose. A mutant strain of this organism can grow with L-fructose as the sole carbohydrate source[10].

The formation of ketohexoses during the aldol condensation of trioses is long known[11–14]; thus, Schmitz[12] in 1913 reported the isolation of a crystalline mixture of DL-fructose and DL-sorbose, in a combined yield of 33%, after the aldol condensation of DL-glyceraldehyde catalysed by barium hydroxide. From this mixture, DL-fructose could be isolated (yield not given) by fractional crystallisation, and most of the D-fructose was then removed by fermentation. We have found[15] that the hexulose mixture obtained on condensation of DL-glyceraldehyde and 1,3-dihydroxy-2-propanone contained >70% of DL-fructose when catalysed by a strongly basic anion-exchange resin. The utilisation of this observation is now reported for the preparation of di-*O*-isopropylidene acetals of L-fructose.

Since commercial L-glyceraldehyde is usually contaminated with other compounds, it was synthesised from the readily prepared[16] (and also commercially available) L-galactono-1,4-lactone (**1**), *via* the 5,6-*O*-isopropylidene derivative **2**. Periodate oxidation of **2** in the carboxylate form (**3**) and weak-acid hydrolysis of the resulting 2,3-*O*-isopropylidene-L-glyceraldehyde (**4**) gave L-glyceraldehyde (**5**) of high purity.

Condensation of **5** with 1,3-dihydroxy-2-propanone (**6**) for a few minutes at room temperature, catalysed by Dowex 1 (HO^-) resin, gave a hexulose mixture in a yield of >90%. This mixture was treated with acetone–sulphuric acid, and g.l.c.–m.s.[15] of the product mixture showed that it contained 60–65% of 2,3:4,5-di-*O*-

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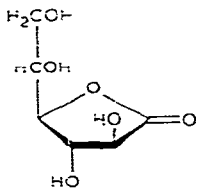

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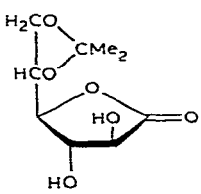

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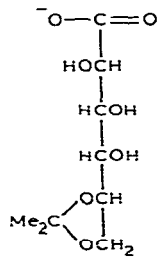

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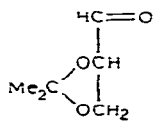

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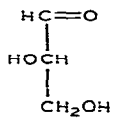

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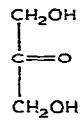

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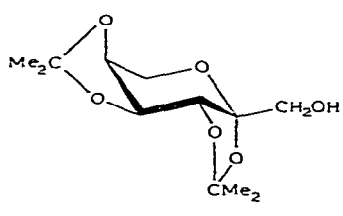
isopropylidene-β-L-fructopyranose (**7**). The isolation of **7** was achieved by taking advantage of its somewhat greater stability towards acid than most of the other di-*O*-isopropylidene acetals present. Thus, appropriate treatment of the mixture with aqueous acetic acid removed at least one of the isopropylidene groups from each of the majority of the other derivatives in the mixture, allowing the isolation of crystalline **7** by partitioning the hydrolysate between chloroform and water.

When the condensation of DL-glyceraldehyde with 1,3-dihydroxy-2-propanone (**6**) was catalysed by Dowex 1 (HO^-) resin, 54% of DL-fructose was obtained by crystallisation from methanol. Treatment of the DL-fructose with bakers' yeast in phosphate buffer gave a product from which 62% of 2,3:4,5-di-*O*-isopropylidene-β-L-fructopyranose (**7**) was isolated after acetonation.



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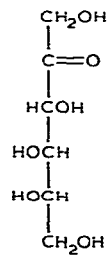

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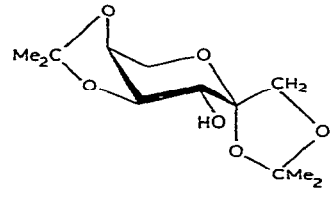

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Hydrolysis of **7** with very dilute sulphuric acid gave syrupy L-fructose (**8**), which was converted into 1,2:4,5-di-*O*-isopropylidene-β-L-fructopyranose (**9**) by treatment with acetone containing 0.2% of sulphuric acid.

EXPERIMENTAL

General. — T.l.c. was performed on silica gel G with chloroform–methanol (*A*, 4:1; *B*, 20:1) and detection with diphenylamine–aniline–phosphoric acid[17] and (for lactones) hydroxylamine–ferric chloride[18]. G.l.c. was performed with a Perkin–Elmer F 11 gas chromatograph, equipped with a flame-ionisation detector and a glass column (6 ft. × 1.5 mm i.d.) filled with 3% of OV-225 on 100/120 Supelcoport, operated with a temperature programme 55°→220° at 6°/min. G.l.c.–m.s. was performed with a Varian Aerograph 2400 gas chromatograph combined with a Micromass 12 F mass spectrometer, operating at 70 eV.

5,6-O-Isopropylidene-L-galactono-1,4-lactone (**2**). — A suspension of L-galactono-1,4-lactone (**1**, 2 g) and anhydrous copper sulphate (4 g) in acetone (100 mL) was stirred for 2 h at room temperature. T.l.c. (solvent *A*) then revealed a product indistinguishable from the D enantiomer of **2**[19], and only traces of **1**. The mixture was filtered, and the solution was stirred for a few min with a small amount of solid sodium hydrogencarbonate, filtered, and concentrated under reduced pressure, to give **2** (2.40 g, 97%) as a syrup, $[\alpha]_D^{25}$ +41° (*c* 2, acetone); lit.[19] $[\alpha]_D^{22}$ −42° for the D enantiomer.

L-*Glyceraldehyde* (**5**). — A solution of **2** (2.40 g) in water (40 mL) was adjusted to pH 8 by the addition, in small portions with external cooling, of 0.5M sodium hydroxide. Sodium metaperiodate (4.5 g) was then added in portions with cooling, and the solution was maintained at pH 8 by the addition of sodium carbonate. After 90 min, more sodium metaperiodate (1 g) was added, and the pH was adjusted as described above. After a further 60 min, 0.5M barium acetate was added until precipitation was complete, the mixture was filtered, and the solution was extracted with chloroform (4 × 50 mL). The aqueous solution was concentrated under diminished pressure to 4–5 mL and extracted with ethyl acetate (40 mL). The combined chloroform and ethyl acetate extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The syrupy residue was chromatographically homogeneous and indistinguishable (t.l.c. and g.l.c.) from authentic 2,3-*O*-isopropylidene-D-glyceraldehyde[19]. Hydrolysis of the syrup in aqueous 40% acetic acid (20 mL) overnight at room temperature, followed by evaporation of the solvents under reduced pressure, gave **5** (620 mg, 63%) as a syrup that was chromatographically (t.l.c., solvent *A*) indistinguishable from D-glyceraldehyde[19]. The dimedon derivative[20] [445 mg (82%) from 140 mg of **5**] had m.p. 195–198°, $[\alpha]_D^{25}$ −200° (*c* 0.5, ethanol); lit.[20] m.p. 195–199°, $[\alpha]_D^{25}$ −210°.

2,3:4,5-Di-O-isopropylidene-β-L-fructopyranose (**7**). — To a mixture of **5** (480 mg) and 1,3-dihydroxy-2-propanone (**6**, 250 mg) in water (15 mL) was added freshly regenerated Dowex 1 (HO^-) resin (20 mL). The mixture was kept at room temperature for 15 min, 50% aqueous acetic acid was added, and the resin was collected and washed with aqueous acetic acid until no more reducing sugar was liberated. The solvents were removed under reduced pressure from the combined filtrate and washings, to give a syrupy mixture (665 mg, 91%) of ketoses, which was

treated with 2.5% sulphuric acid in acetone (20 mL) for 4 h. The solution was neutralised with solid sodium hydrogencarbonate, and g.l.c.–m.s. then showed that the product mixture contained >60% of **7**. The mixture was filtered and concentrated, and a solution of the syrupy residue in aqueous 70% acetic acid (15 mL) was kept at 50–55° for 90 min and then at room temperature overnight. The solvents were removed under reduced pressure, and the residue was partitioned between chloroform (20 mL) and water (20 mL). The aqueous layer was extracted with chloroform (10 mL), and the combined chloroform solutions were dried (Na_2SO_4), filtered, and concentrated under diminished pressure. A solution of the residue in light petroleum (b.p. 40–60°) was concentrated slowly, to give **7** (517 mg, 49%), m.p. 96–97°, $[\alpha]_D^{25}$ +23° (*c* 2, chloroform); lit.[21] m.p. 97°, $[\alpha]_D^{25}$ −24.7° for the D enantiomer.

DL-*Fructose*. — To a solution of DL-glyceraldehyde (4 g) and **6** (3 g) in water (70 mL) was added freshly regenerated Amberlite IRA-400 (HO^-) resin (50 mL), and the mixture was kept at room temperature with occasional shaking for 15 min. Aqueous acetic acid (50%) was then added, the resin was collected and washed as described above, and the solvents were evaporated under reduced pressure from the combined filtrate and washings. A solution of the residue in methanol (20 mL) was kept overnight in a refrigerator, to yield crystalline DL-fructose (2.0 g). More product was obtained by successive additions of ethyl acetate to the mother liquor (total yield, 3.8 g, 54%). The product had m.p. 129–130° (lit.[12] m.p. 129–130°) and was indistinguishable from D-fructose by t.l.c. (solvent *A*) and, after acetonation, by g.l.c.–m.s.[15].

2,3:4,5-Di-O-*isopropylidene-β*-L-*fructopyranose* (**7**) *from* DL-*fructose*. — Bakers' yeast (2 g) was suspended in a solution of D-glucose (0.15 g), potassium dihydrogenphosphate (0.15 g), and disodium hydrogenphosphate (0.15 g) in water (5 mL). When fermentation had started, a solution of DL-fructose (3.6 g) in water (35 mL) was added, and the mixture was kept at 37° for 2 days and then centrifuged. To the supernatant solution was added a fermenting suspension of yeast (2 g) in a solution whose composition was the same as that described above. After another 2 days at 37°, centrifugation was repeated, and the supernatant solution was treated with a mixed bed of Dowex 1 (HCO_3^-) and Dowex 50 W (H^+) resins in the presence of a little activated charcoal, filtered, and concentrated under reduced pressure. The almost colourless, syrupy residue was shaken with acetone (40 mL) containing 2.5% of sulphuric acid, as described above, to give **7** (1.61 g, 62%), m.p. 97°, $[\alpha]_D^{25}$ +24° (*c* 3, chloroform).

1,2:4,5-Di-O-*isopropylidene-β*-L-*fructopyranose* (**9**). — A solution of **7** (2.0 g) in aqueous 70% acetic acid (20 mL) was kept at 90° for 1 h and then concentrated under reduced pressure, and the residue was treated at 97–98° with 0.01M sulphuric acid (20 mL) for 2 h. The cooled solution was neutralised with Dowex 1 (HCO_3^-) resin and filtered, and the resin was washed with water. The combined filtrate and washings were concentrated under reduced pressure, to give **8** as a chromatographically (t.l.c., solvent *A*) homogeneous syrup, indistinguishable from D-fructose. The syrup was stirred with acetone (150 mL) containing 0.2% of sulphuric acid for 3 h,

and the mixture was neutralised with solid sodium hydrogencarbonate, filtered, and concentrated. Extraction of the semi-crystalline residue with hot, light petroleum (b.p. 60–80°, 100 mL) and slow concentration of the extract gave **9** (0.94 g, 47%), m.p. 120°, $[\alpha]_D^{25}$ +150° (*c* 1, acetone); lit.[4] m.p. 119°, $[\alpha]_D^{25}$ −154.8° for the D enantiomer. The compound was indistinguishable from the D enantiomer[4] by t.l.c. (solvent *B*) and by g.l.c.–m.s.[15].

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