632. *Syntheses of Methyl Ethers of Fructose.*

By E. L. Hirst, W. E. A. Mitchell, Elizabeth E. Percival, and (the late) E. G. V. Percival.

3 : 4 : 6-, 1 : 4 : 6-, 1 : 3 : 4-, and 1 : 4 : 5-tri-*O*-methyl-, 3 : 4- and 4 : 5-di-*O*-methyl-, and 4-*O*-methyl-D-fructoses have been synthesised from one of the crystalline compounds 2 : 3-4 : 5- or 1 : 2-4 : 5-di-*O*-*iso*propylidene-D-fructose or from 2 : 3-*O*-*iso*propylidene-1 : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose. The constitutions of these three *iso*propylidene derivatives are well established.

Three crystalline substances whose constitutions have been established previously have been used as starting materials in this work. 1 : 2-4 : 5-, 2 : 3-4 : 5-Di-*O*-*iso*propylidene-D-fructose (D. J. Bell, *J.*, 1947, **1463**) and 2 : 3-*O*-*iso*propylidene-1 : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose (Morgan and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 1023).

Montgomery (*J. Amer. Chem. Soc.*, 1934, **56**, 419) synthesised 3 : 4 : 6-tri-*O*-methylfructose from crystalline 2 : 3-4 : 5-di-*O*-*iso*propylidenefructose by the formation of the 1-benzoyl derivative. In the present synthesis treatment of 2 : 3-4 : 5-di-*O*-*iso*propylidene-D-fructose with toluene-*p*-sulphonyl chloride gave crystalline 2 : 3-4 : 5-di-*O*-*iso*propylidene-1-*O*-toluene-*p*-sulphonyl-D-fructose. Removal of the *iso*propylidene residue followed by conversion into the fructofuranoside led to the isolation of a non-reducing syrup which partly crystallised. Methylation, removal of the toluene-*p*-sulphonyl residue, and hydrolysis gave 3 : 4 : 6-tri-*O*-methylfructose which was characterised by conversion into the crystalline methyl 3 : 4 : 6-tri-*O*-methyl-D-fructuronamide and also by oxidation to crystalline 2 : 3 : 5-tri-*O*-methyl-D-arabonolactone.

1 : 4 : 6-Tri-*O*-methylfructose was synthesised by Montgomery (*loc. cit.*), but only the rotation in chloroform was recorded. In the present work this trimethyl ether has been

synthesised from 1 : 2-4 : 5-di-*O*-*iso*propylidenefructose by blocking position 3 with a toluene-*p*-sulphonyl residue. Removal of the *iso*propylidene group and subsequent glycoside formation and methylation followed by reductive fission of the toluene-*p*-sulphonyl group and hydrolysis gave 1 : 4 : 6-tri-*O*-methylfructose as a chromatographically pure syrup.

An alternative synthesis was achieved from crystalline 2 : 3-*O*-*iso*propylidenefructose, obtained by the removal of the toluene-*p*-sulphonyl residues from 2 : 3-*O*-*iso*propylidene-1 : 6-di-*O*-toluene-*p*-sulphonylfructose. Methylation and hydrolysis gave 1 : 4 : 6-tri-*O*-methyl-D-fructose as a chromatographically pure, mobile syrup, identical with the 1 : 4 : 6-tri-*O*-methylfructose obtained from the former synthesis. 4 : 6-Di-*O*-methylfructuronic acid was obtained on oxidation.

Synthesis of 1 : 3 : 4-tri-*O*-methylfructose was achieved by the conversion of methyl 1-*O*-toluene-*p*-sulphonyl-D-fructofuranoside into the 6-*O*-trityl derivative. Removal of the toluene-*p*-sulphonyl residue followed by methylation gave methyl 1 : 3 : 4-tri-*O*-methyl-6-*O*-tritylfructoside. Hydrolysis of the trityl and glycosidic methoxyl groups gave 1 : 3 : 4-tri-*O*-methylfructose as a syrup which partly crystallised. The mother liquors were freed from 1 : 3 : 4 : 6-tetra-*O*-methylfructose by passage through silica gel (Bell and Palmer, *J.*, 1949, 2522).

Neither the isolation nor the synthesis of 1 : 4 : 5-trimethylfructose has been reported previously. Preferential hydrolysis of 2 : 3-4 : 5-di-*O*-*iso*propylidene-D-fructose gave crude 2 : 3-*O*-*iso*propylidene-D-fructopyranose. This was purified by conversion into the crystalline 1 : 4 : 5-tri-*O*-acetyl-2 : 3-*O*-*iso*propylidene-D-fructose. Hydrolysis of the acetyl groups followed by methylation and removal of the *iso*propylidene residue gave 1 : 4 : 5-tri-*O*-methyl-D-fructose, as a mobile syrup.

Macdonald and Jackson (*J. Res. Nat. Bur. Stand.*, 1940, **24**, 181) prepared syrupy 3 : 4-dimethylfructose from di-D-fructofuranose 2 : 1′-2′ : 1-di-anhydride and reported the isolation of a difficultly crystallisable osazone, m. p. 126°, but no other data or constants were recorded. In the present work methyl 1-*O*-toluene-*p*-sulphonyl-6-*O*-trityl-D-fructoside was methylated and the product on reduction, detritylation, and hydrolysis gave a mixture of 3 : 4-di-*O*-methyl- and 3 : 4 : 6-tri-*O*-methyl-D-fructose, which was separated on cellulose.

3 : 4-Di-*O*-methylfructose has also been synthesised by the removal of the *iso*propylidene residue from 2 : 3-*O*-*iso*propylidene-1 : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose with methanolic hydrogen chloride followed by methylation of the derived glycoside. Reduction and hydrolysis gave 3 : 4-di-*O*-methyl-D-fructose which was again purified from traces of trimethylfructose by separation on cellulose. The constants of the 3 : 4-di-*O*-methylfructose from the two syntheses were in good agreement and the two syrups were chromatographically identical. 3 : 4-Di-*O*-methylfructose was characterised by oxidation and conversion of the product into crystalline (−)-dimethoxysuccinamide and the bismethylamide.

No previous record of the synthesis of 4 : 5-di-*O*-methylfructose could be found. Crystalline 1 : 2-*O*-*iso*propylidene-3-*O*-toluene-*p*-sulphonyl-D-fructose was prepared from the 1 : 2-4 : 5-di-*O*-*iso*propylidene-3-*O*-toluene-*p*-sulphonyl derivative by preferential hydrolysis of the *iso*propylidene residue (Ohle and Just, *Ber.*, 1935, **68**, 601). Methylation followed by reduction gave crystalline 4 : 5-di-*O*-methyl-1 : 2-*O*-*iso*propylidenefructose, and subsequent hydrolysis gave crystalline 4 : 5-di-*O*-methylfructose. A crystalline 2 : 5-dichlorophenylhydrazone and a phenylosazone were prepared.

4-*O*-Methylfructose has been isolated previously from di-D-fructofuranose 2 : 3′-2′ : 1-dianhydride (Macdonald and Jackson, *loc. cit.*) and was identified by the formation of a crystalline osazone, m. p. 156°. In the present work methylation of crystalline 2 : 3-*O*-*iso*propylidene-1 : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose gave crystalline 4-*O*-methyl-2 : 3-*O*-*iso*propylidene-1 : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose. Reduction and hydrolysis led to the isolation of chromatographically pure syrupy 4-*O*-methylfructose. A crystalline osazone, m. p. 158°, identical with 4-*O*-methylglucosazone, was prepared. 4-*O*-Methylfructose was characterised by the same method as for 3 : 4-di-*O*-methylfructose; crystalline-D$_g$-*threo*-2-hydroxy-3-methoxysuccinamide and the bismethylamide were isolated.

Experimental

All solvents were removed under reduced pressure and below 50°. The solvents used for elution, unless otherwise stated, were (I) *n*-butanol–ethanol–water (4 : 1 : 5) and (II) benzene–ethanol–water (167 : 47 : 15). Amberlite resins were used throughout.

3 : 4 : 6-*Tri*-O-*methylfructose*.—2 : 3-4 : 5-Di-*O*-*iso*propylidene-D-fructose, prepared from D-fructose (100 g.) according to the conditions used by Bell (*loc. cit.*), formed transparent needles (105 g., 73%) [from light petroleum (b. p. 60—80°)], m. p. 96—97°, $[\alpha]_D^{16}$ −34·1° (*c*, 5·6 in $CHCl_3$). To a solution of the crystals (82 g.) in dry pyridine (500 c.c.) finely powdered toluene-*p*-sulphonyl chloride (140 g.) was added during 2 hr. The 2 : 3-4 : 5-di-*O*-*iso*propylidene-1-*O*-toluene-*p*-sulphonyl-D-fructose (*A*) (115 g., 88%), isolated in the usual way (Percival and Zobrist, *J.*, 1952, 4306), had m. p. 82°, $[\alpha]_D^{16}$ −26° (*c*, 1·8 in MeOH) (cf. Ohle and Koller, *Ber.*, 1924, **57**, 1566, who record m. p. 83°, $[\alpha]_D^{19}$ −27° in EtOH) (Found: C, 54·7; H, 6·1; S, 7·5. Calc. for $C_{19}H_{26}O_8S$: C, 55·05; H, 6·3; S, 7·8%).

The crystals (*A*) (30 g.) were dissolved in ethanol (50 c.c.), and water (50 c.c.) was added until the solution became slightly turbid. Cation-exchange resin (40 g.) (1R-100 H) was added and the mixture refluxed with vigorous stirring (Glen, Myers, and Grant, *J.*, 1951, 2570) to complete dissolution (20 hr.). Filtration and neutralisation of the filtrate by shaking it with anion-exchange resin (IR-4B) (5 g.) for 2 hr. and removing the solvent gave 1-O-*toluene*-p-*sulphonyl*-D-*fructose* (*B*) (22·6 g., 93%), $[\alpha]_D^{17}$ −23° (*c*, 0·8 in MeOH) (Found: S, 9·1. $C_{13}H_{18}O_8S$ requires S, 9·5%). The syrup (*B*) (13·8 g.), dissolved in methanolic hydrogen chloride (1%; 500 c.c.), was kept at 25° for 100 hr., the maximum rotation ($[\alpha]_D$ +3°) having then been attained. (Further treatment led to a decrease in rotation and the formation of the pyranoside.) Isolation in the usual manner gave *methyl* 1-O-*toluene*-p-*sulphonylfructoside*, a syrup (*C*) (9·0 g., 63%), $[\alpha]_D^{18}$ +16° (*c*, 1·5 in MeOH) (Found: S, 8·6. $C_{14}H_{20}O_8S$ requires S, 9·2%). When kept this syrup partly crystallised; the crystals had m. p. 79—81°, $[\alpha]_D^{18}$ +15·2° (*c*, 1·0 in MeOH) (Found: C, 48·8; H, 5·6; S, 8·7. $C_{14}H_{20}O_8S$ requires C, 48·3; H, 5·8; S, 9·2%). Fivefold methylation of this derivative (9·0 g.) with methyl iodide and silver oxide gave *methyl* 3 : 4 : 6-*tri*-O-*methyl*-1-O-*toluene*-p-*sulphonylfructoside* (8·3 g., 82%), $[\alpha]_D^{18}$ +32° (*c*, 1·2 in MeOH) (Found: OMe, 31·8; S, 8·4. $C_{17}H_{26}O_8S$ requires OMe, 32·8; S, 8·5%). This syrup (8·3 g.), dissolved in methanol (140 c.c.), and water (75 c.c.) added to cause slight turbidity, was treated with sodium amalgam (4%; 200 g.) at 40—45° with vigorous stirring for 17 hr. The filtered solution was extracted with chloroform, and the chloroform extract dried (Na_2SO_4), saturated with carbon dioxide (to pH 7), and filtered. Evaporation and distillation at 120°/0·03 mm. gave methyl 3 : 4 : 6-tri-*O*-methyl-D-fructoside as a mobile syrup (4·55 g.), $[\alpha]_D^{19}$ +67·6° (*c*, 1·05 in MeOH) (Found: OMe, 51·8. Calc. for $C_{10}H_{20}O_6$: OMe, 52·8%). This furanoside (4·45 g.) was hydrolysed to 3 : 4 : 6-tri-*O*-methylfructose by 0·1N-sulphuric acid (250 c.c.) at 95° for 2·5 hr. (whereafter the rotation remained constant). A syrup (*D*) (3·91 g.) was obtained having n_D^{18} 1·4661, $[\alpha]_D^{18}$ +27° (initial); +29° (24 hr.) (*c*, 1·4 in H_2O) (Found: C, 47·9; H, 8·1; OMe, 41·1. Calc. for $C_9H_{18}O_6$: C, 48·6; H, 8·2; OMe, 41·9%). Chromatographic analysis produced a single spot, R_G 0·89 in solvent (I) and 0·75 in solvent (II).

Characterisation of 3 : 4 : 6-*Trimethyl*-D-*fructose*.—(a) *Oxidation with nitric acid followed by barium permanganate*. The syrup (*D*) (0·201 g.) was oxidised with nitric acid (2·5 c.c.; *d* 1·42) (Mullan and Percival, *J.*, 1940, 1505). The syrup (*E*) finally obtained was dried with anhydrous methanol and esterified with boiling methanolic hydrogen chloride (4%; 7 c.c.) for 17 hr. The derived amide (0·048 g.) had m. p. 98—100° (from ether) and showed no depression on admixture with authentic methyl 3 : 4 : 6-tri-*O*-methyl-D-fructuronamide (Found: C, 47·8; H, 7·4; N, 5·5. Calc. for $C_{10}H_{19}O_6N$: C, 48·2; H, 7·7; N, 5·6%).

3 : 4 : 6-Tri-*O*-methyl-D-fructuronic acid (*E*) (0·182 g.) was oxidised with barium permanganate according to the conditions described by Avery, Haworth, and Hirst (*J.*, 1927, 2317). The light petroleum extracts yielded a syrup which after distillation at 90°/0·003 mm. gave crystals (0·052 g.), m. p. 30—31°, $[\alpha]_D^{18}$ +44·8° ⟶ 24·0° (24 days) (*c*, 0·96 in H_2O) (Avery, Haworth, and Hirst, *loc. cit.*, record m. p. 32—33°, $[\alpha]_D$ +44·5° ⟶ 25·5°, for 2 : 3 : 5-tri-*O*-methylarabonolactone).

(b) *Oxidation with periodate*. To a solution of 3 : 4 : 6-tri-*O*-methylfructose (*D*) (0·19 g.) in water (10 c.c.), sodium metaperiodate solution (0·3M; 15 c.c.) was added and the solution set aside in the dark at room temperature for 72 hr. The excess of periodate was destroyed by the addition of ethylene glycol (5 c.c.), and the solution extracted thrice with chloroform (80 c.c.). The chloroform extracts were evaporated and the residue extracted with acetone, which gave a syrup that was repeatedly extracted with hot light petroleum (b. p. 60—80°). Removal

of the light petroleum and distillation of the syrup gave material (0·096 g., 60%), m. p. 30—31° undepressed on admixture with 2 : 3 : 5-tri-*O*-methylarabonolactone, isolated from the previous oxidation with permanganate.

1 : 4 : 6-*Tri*-O-*methyl*-D-*fructose*.—(*a*) Fructose (60 g.) was condensed with acetone (600 c.c.) in the presence of sulphuric acid (0·3%) (cf. Bell, *loc. cit.*), giving 1 : 2-4 : 5-di-*O*-*iso*propylidene-fructose (67·5 g., 78%), m. p. 118—119°, $[\alpha]_D^{16}$ −147° (*c*, 1·5 in $CHCl_3$). This product (58 g.) was converted into the 3-*O*-toluene-*p*-sulphonyl derivative as described above for the 1-*O*-tosyl derivative. The product (*F*) (68 g., 74%) crystallised from aqueous methanol and then from light petroleum (b. p. 60—80°) had m. p. 97—98°, $[\alpha]_D^{17}$ −161° (*c*, 1·0 in MeOH) (Found : C, 54·3; H, 6·0; S, 7·3. Calc. for $C_{19}H_{26}O_8$: C, 55·1; H, 6·3; S, 7·8%). The *iso*propylidene residues were removed and the glycoside formed by refluxing it (60 g.) with methanolic hydrogen chloride (1·5% ; 500 c.c.). The rotation changed : −70·9° (10 min.); +9·1° (1 hr.); +10·5° (2 hr.). The hydrochloric acid concentration was adjusted to 0·5N, and the glycoside was then completely hydrolysed at 85° during 3 hr. Amorphous 3-O-*toluene*-p-*sulphonyl*-D-*fructose* (*G*) (42 g., 87%), $[\alpha]_D^{18}$ −36·5° (*c*, 1·7 in MeOH), was obtained (Found : C, 46·1; H, 5·6; S, 8·6. $C_{13}H_{18}O_8S$ requires C, 46·7; H, 5·4; S, 9·6%).

This compound (*G*) (10·5 g.) in methanolic hydrogen chloride was set aside at 35° for 17 hr., maximum rotation then being attained ($[\alpha]_D$ +1·7°). The mixture was neutralised with diazomethane, the solvent removed, and the residual syrup extracted with ether. Removal of solvent then gave the *furanoside* as a syrup (8·0 g., 73%), $[\alpha]_D^{19}$ +14° (*c*, 2·0 in MeOH) (Found : S, 8·8. $C_{14}H_{20}O_8S$ requires S, 9·2%).

The glycoside (8 g.), dissolved in the minimum quantity of methanol (10 c.c.), was methylated four times with methyl iodide and silver oxide; *methyl* 1 : 4 : 6-*tri*-O-*methyl*-3-O-*toluene*-p-*sulphonyl*-D-*fructoside*, formed a syrup (6·3 g., 70%), $[\alpha]_D^{18}$ +28° (*c*, 1·5 in MeOH) (Found : OMe, 32·1; S, 8·3. $C_{17}H_{26}O_8S$ requires OMe, 32·8; S, 8·5%). Treatment of this product (6·3 g.) with sodium amalgam as described above for (*C*) gave methyl 1 : 4 : 6-tri-*O*-methyl-D-fructoside (3·7 g., 97%) which after distillation at 100°/0·007 mm. had $[\alpha]_D^{18}$ +47° (*c*, 1·0 in MeOH) (Found : OMe, 47·2. Calc. for $C_{10}H_{20}O_6$: OMe, 52·8%). The lesser methylated derivatives were removed by dissolving the syrup (3·03 g.) in water (150 c.c.) and extracting with chloroform (5 × 150 c.c.) (Macdonald, *J. Amer. Chem. Soc.*, 1935, **57**, 772). The combined chloroform extracts were dried (Na_2SO_4) and evaporated. A straw-coloured syrup (*H*) (2·8 g.), $[\alpha]_D^{17}$ +44° (*c*, 1·0 in MeOH), was obtained (Found : OMe, 51·0%).

Attempts to detect any methyl 1 : 4 : 5-tri-*O*-methylfructopyranoside in syrup (*H*) by graded hydrolysis of a portion with hydrobromic acid (0·04N) at 100° (Ford and Peat, *J.*, 1941, 856) were unsuccessful. Preferential formation of the furanoside from the hydrolysed syrup was also attempted. The hydrolysed syrup (0·1 g.) dissolved in methanolic hydrogen chloride (0·5%) was set aside at 18°; the rotation changed from +19·2° (3 min.) to +38·3° (4·5 hr., constant). Since, under these conditions pyranoside formation is unlikely, extraction of an aqueous solution of this fructoside with chloroform should separate any unchanged 1 : 4 : 5-tri-*O*-methylfructose. No difference in rotation was observed in the extracts, from which it was concluded that the sample was pure 1 : 4 : 6-tri-*O*-methylfructose.

The main bulk of (*H*) (2·42 g.) was hydrolysed with sulphuric acid (150 c.c.; 0·1N) at 95° for 2 hr. After purification with charcoal and Filter Cel there was obtained a syrup (1·82 g., 80%), n_D^{18} 1·4643, $[\alpha]_D^{18}$ +19° (*c*, 1·6 in $CHCl_3$), +30° (*c*, 1·13 in H_2O) (Found : C, 47·9; H, 8·1; OMe, 40·9. Calc. for $C_9H_{18}O_6$: C, 48·6; H, 8·2; OMe, 41·9%). Chromatographic analysis gave a single spot R_G 0·91 in solvent (I) and 0·79 in solvent (II) compared with tetramethylglucose R_G 1·0 as control. Attempts to prepare a crystalline phenylosazone were unsuccessful.

(*b*) Crystalline 2 : 3-*O*-*iso*propylidene-D-fructofuranose (7·7 g.) prepared according to Morgan and Reichstein's method (*loc. cit.*) was subjected to four Purdie methylations; 1 : 4 : 6-*tri*-O-*methyl*-2 : 3-O-iso*propylidenefructose* (*J*) was obtained as a chromatographically pure (naphtharesorcinol spray), mobile syrup (8·2 g., 90%), $[\alpha]_D^{18}$ +10° (*c*, 1·3 in EtOH) (Found : OMe, 35·1. $C_{12}H_{22}O_6$ requires OMe, 35·5%). Removal of the *iso*propylidene group with 0·1N-sulphuric acid gave chromatographically pure 1 : 4 : 6-tri-*O*-methylfructose as a mobile syrup (6·0 g. from 8·0 g.; 89%), n_D^{18} 1·4638, $[\alpha]_D^{19}$ +24° (initial) ⟶ +27° (2·5 hr.) (*c*, 1·2 in H_2O).

Characterisation of 1 : 4 : 6-*Tri*-O-*methyl*-D-*fructose*.—Syrupy 1 : 4 : 6-tri-*O*-methyl-D-fructose (1·2 g.) synthesised by both methods was oxidised with nitric acid, under the conditions described for 3 : 4 : 6-tri-*O*-methyl-D-fructose, and 4 : 6-di-*O*-methylfructuronic acid (0·5 g.) was obtained as needles, m. p. 107—109°, $[\alpha]_D$ +18·4° (*c*, 0·9 in H_2O).

1 : 3 : 4-*Tri*-O-*methyl*-D-*fructose*.—Methyl 1-*O*-toluene-*p*-sulphonyl-D-fructofuranoside (*C*) (30 g.) in pyridine (450 c.c.) mixed with triphenylmethyl chloride (60 g.) was kept at room

temperature for 4 days. After removal of crystalline triphenylmethanol the mixture was poured into ice–water (750 c.c.) with vigorous stirring. *Methyl* 1-O-*toluene*-p-*sulphonyl*-6-O-*trityl*-D-*fructoside* separated as a sticky gum which hardened to an amorphous solid when washed continuously with water for 2 weeks. An ethereal solution of the solid was washed with dilute acetic acid (pH 4) (4 times), saturated sodium hydrogen carbonate solution (3 times), and water (4 times), then dried (Na_2SO_4), and the solvent removed, giving an amorphous solid *product* (*K*) (55·2 g., 108%), $[\alpha]_D^{18}$ +7·5° (*c*, 2·40 in MeOH) (Found: S, 4·2. $C_{33}H_{34}O_8S$ requires S, 5·8%).

The amorphous solid (*K*) (28·8 g.) in methanol (260 c.c.) and water (50 c.c.) was treated with sodium amalgam (4%) for 60 hr. at 45° and the solid product (19·1 g., 90%), $[\alpha]_D^{18}$ +12° (*c*, 1·9 in MeOH), isolated as before. Methylation thrice with methyl iodide and silver oxide gave a viscous syrup, n_D^{18} 1·5695 (17·5 g. from 18·9 g., 95%), $[\alpha]_D^{19}$ +9·2° (*c*, 1·1 in MeOH) (Found: OMe, 16·7; trityl, 57·6. Calc. for $C_{29}H_{34}O_6$: OMe, 25·9; trityl, 50·8. Calc. for $C_{29}H_{34}O_6,CPh_3{\cdot}OH$: OMe, 16·8; trityl, 65·8%). All attempts to remove contaminating triphenylmethanol were unsuccessful.

A cooled saturated solution of hydrobromic acid in glacial acetic acid (10 c.c.) was added to crude methyl 1 : 3 : 4-tri-*O*-methyl-6-*O*-trityl-D-fructoside (16 g.) dissolved in glacial acetic acid (30 c.c.) cooled to 0°. After 2 min. the mixture was poured into 0·1N-sulphuric acid (100 c.c.), and the product filtered. The filtrate was heated at 95° for 1 hr. to ensure complete removal of the glycosidic methoxyl group. Extraction with chloroform thrice, and removal of the chloroform, gave 1 : 3 : 4-tri-*O*-methylfructose (4·2 g., 57%) which partly crystallised. The crystals (1·5 g.) after recrystallisation from carbon tetrachloride–light petroleum (b. p. 40—60°) had m. p. 75°, $[\alpha]_D^{20}$ −56·2° (*c*, 1·05 in H_2O) (Found: C, 48·65; H, 8·2; OMe, 41·7. Calc. for $C_9H_{18}O_6$: C, 49·1; H, 8·35; OMe, 41·9%). Chromatographic analysis of the mother liquors (2·74 g.) revealed the presence of tetra-*O*-methylfructose contaminating the 1 : 3 : 4-tri-*O*-methylfructose. Separation was effected on silica (Bell and Palmer, *loc. cit.*). The trimethyl sugar was isolated as a pale yellow syrup (1·31 g.) which slowly crystallised; the solid had m. p. 75°.

1 : 4 : 5-*Tri*-O-*methyl*-D-*fructose*.—2 : 3-4 : 5-Di-*O*-*iso*propylidene-D-fructose (36 g.) dissolved in N-sulphuric acid (1000 c.c.) was kept at 25° for 10 hr. and the solution then neutralised by passage through anion-exchange resin (IR-4B). The eluate (reduced to 250 c.c. by evaporation) was then extracted thrice with chloroform (500 c.c.); evaporation of the aqueous solution gave a syrup which on chromatographic analysis showed only the presence of 2 : 3-*O*-*iso*propylidene-fructose and fructose. Attempted separation of these two sugars with boiling acetone–ethyl acetate was reasonably successful, and after removal of the acetone–ethyl acetate the residual syrup was distilled twice at 200°/0·04 mm. The crude 2 : 3-*O*-*iso*propylidene-D-fructopyranose (7 g.) was acetylated with acetic anhydride and anhydrous sodium acetate; 1 : 4 : 5-tri-*O*-acetyl-2 : 3-*O*-*iso*propylidene-D-fructose formed prisms (7·38 g.), m. p. 55—56° (from aqueous ethanol), $[\alpha]_D^{18}$ +18° (*c*, 1·1 in ethanol) (Found: C, 51·8; H, 6·35. Calc. for $C_{15}H_{22}O_9$: C, 52·0; H, 6·4%). The acetyl groups were removed with cold N-sodium hydroxide, and syrupy, chromatographically pure, 2 : 3-*O*-*iso*propylidene-D-fructopyranose (5·1 g.), $[\alpha]_D^{19}$ +29° (*c*, 1·1 in EtOH), was obtained (Wolfrom, Shilling, and Binkley, *J. Amer. Chem. Soc.*, 1950, **72**, 4544, record $[\alpha]_D^{24}$ +28·2° in EtOH, for this compound).

This syrup was methylated five times with methyl iodide and silver oxide and gave after distillation a chromatographically pure syrup (4·51 g., 74%), b. p. 100°/0·09 mm., n_D^{17} 1·4512, $[\alpha]_D^{17}$ +35° (*c*, 1·34 in EtOH). Hydrolysis with sulphuric acid (100 c.c.; 0·1N) at 95° for 2 hr. gave a syrupy *ether* (3·07 g. from 4·4 g., 82%), n_D^{17} 1·4772, $[\alpha]_D^{18}$ −143° (*c*, 1·0 in H_2O) (Found: OMe, 41·0. $C_9H_{18}O_6$ requires OMe, 41·9%), R_G 0·76 and 0·61 solvents I and II as eluant, respectively. The crystalline phenylosazone had m. p. 66—67°, alone or on admixture with the phenylosazone obtained from 4 : 5-dimethylfructose.

3 : 4-*Di*-O-*methyl*-D-*fructose*.—(*a*) Methyl 1-*O*-toluene-*p*-sulphonyl-6-*O*-trityl-D-fructoside (*K*) (25 g.) was methylated with methyl iodide and silver oxide thrice and gave a viscous syrupy *ether* (23·7 g., 91%), n_D^{18} 1·5608, $[\alpha]_D$ +14° (*c*, 1·5 in MeOH) (Found: OMe, 14·9. $C_{35}H_{38}O_8S$ requires OMe, 15·1%). The toluene-*p*-sulphonyl group was more resistant to fission with sodium amalgam in methanol than that of methyl 3 : 4 : 6-tri-*O*-methyl-1-*O*-toluene-*p*-sulphonyl-fructoside, and treatment had to be continued for 30 hr. A viscous *product* (14·5 g. from 22·5 g., 86%), $[\alpha]_D$ +24° (*c*, 1·3 in MeOH), was obtained (Found: OMe, 20·1. $C_{28}H_{32}O_6$ requires OMe, 20·0%). The trityl residue was removed as in the previous synthesis, the sugar being left in contact with hydrobromic acid for a longer period (10 min.). The syrup obtained after hydrolysis with sulphuric acid was purified by successive solution in acetone, ethanol, and chloroform, followed by agitation of an ethanolic solution with anion exchange resin (IR-4B) for 2 hr. An

amber-coloured syrup was isolated (4·18 g. from 13·7 g.; 68%) which showed, on chromatographic analysis, the presence of tetra- and tri-*O*-methyl- in addition to di-*O*-methyl-fructose. Separation was effected by elution on powdered cellulose with *n*-butanol–light petroleum (b. p. 100—120°) (3 : 7) as eluant. After the complete removal of the tetra- and tri-*O*-methyl fractions (2·3 g.) the solvent proportions were changed to 1 : 1, and 3 : 4-di-*O*-methylfructose (1·22 g.), n_D^{18} 1·4809, $[\alpha]_D^{14}$ −62° (constant value) (*c*, 3·6 in H_2O), was obtained (Found: OMe, 28·0. Calc. for $C_8H_{16}O_6$: OMe, 29·8%), R_G 0·66 and 0·22 in solvents (I) and (II), respectively.

(*b*) 2 : 3-*O*-*iso*Propylidene-1 : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose (*L*) (33·9 g., 23%) was prepared from D-fructose (50 g.) by Morgan and Reichstein's method (*loc. cit.*), the yield being improved by the addition of acetaldehyde (0·1 c.c.) during the condensation with acetone; the compound had m. p. 132—133°, $[\alpha]_D^{16}$ +15·0° (*c*, 1·3 in EtOH) (Found: C, 52·5; H, 5·3; S, 11·7. Calc. for $C_{23}H_{26}O_{10}S_2$: C, 52·3; H, 5·3; S, 11·8%). The *iso*propylidene group was removed and the glycoside formed by treatment with 1% methanolic hydrogen chloride; *methyl* 1 : 6-*di*-O-*toluene*-p-*sulphonyl*-D-*fructoside* (*M*) was isolated as a non-reducing glass in 85% yield; it had $[\alpha]_D$ +14·7° (*c*, 1·36 in MeOH) (Found: S, 13·3; OMe, 6·1. $C_{21}H_{26}O_{10}S_2$ requires S, 13·6; OMe, 6·6%). The product (*M*) (13·3 g.) was methylated twice with methyl iodide and silver oxide, and *methyl* 3 : 4-*di*-O-*methyl*-1 : 6-*di*-O-*toluene*-p-*sulphonyl*-D-*fructoside* (*N*) isolated as a viscous syrup (12·5 g., 90%), $[\alpha]_D^{20}$ +20° (*c*, 1·0 in MeOH) (Found: S, 12·0; OMe, 18·7. $C_{23}H_{30}O_{10}S_2$ requires S, 12·1; OMe, 17·6%). Treatment of (*N*) (12·1 g.) with sodium amalgam as above gave a syrup (3·9 g., 77%) which on chromatographic analysis (acid naphtharesorcinol spray) showed slight contamination with methyl tri-*O*-methylfructoside. Attempted purification by fractional distillation was unsuccessful; the main fraction (2·10 g.) distilled at 150°/0·06 mm. as a pale syrup, $[\alpha]_D^{18}$ +31·6° (*c*, 1·1 in MeOH) (Found: OMe, 43·8. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). This (1·8 g.) was hydrolysed to 3 : 4-di-*O*-methylfructose (1·1 g.) with 0·1N-sulphuric acid and purified from tri-*O*-methylfructoses by separation on powdered cellulose as in the previous synthesis of this derivative. A viscous syrup (1·04 g.) was obtained which had n_D^{18} 1·4817, $[\alpha]_D^{16}$ −19·6° (initial), −35° (17 hr.), −39° (40 hr., const.) (*c*, 1·1 in MeOH), −63° (constant value; *c*, 1·1 in H_2O) (Found: OMe, 28·6. Calc. for $C_8H_{16}O_6$: OMe, 29·8%).

Characterisation of 3 : 4-*Di*-O-*methyl*-D-*fructose*.—3 : 4-Di-*O*-methyl-D-fructose (0·74 g.) was oxidised with sodium metaperiodate (40 c.c.) (0·6M) and then with bromine water according to the conditions described by Arni and Percival (*loc. cit.*). Conversion into the methyl ester gave a syrup (0·25 g.) which distilled at 140°/0·03 mm.; the distillate had n_D^{20} 1·4441, $[\alpha]_D^{20}$ −55·1° (*c*, 2·1 in MeOH).

The distilled (−)-dimethoxysuccinate (0·075 g.) on treatment with methanolic ammonia gave (−)-dimethoxysuccinamide (0·05 g.), m. p. 275—276°, $[\alpha]_D^{21}$ −90·3° (*c*, 0·6 in H_2O). The corresponding *NN'*-dimethyl-(−)-dimethoxysuccinamide was obtained in good yield; it had m. p. 204—205°, unchanged on admixture with an authentic specimen, $[\alpha]_D^{20}$ −132° (*c*, 0·85 in H_2O) (Found: C, 47·1; H, 8·1; N, 13·3. Calc. for $C_8H_{16}O_4N_2$: C, 47·0; H, 7·9; N, 13·7%).

4 : 5-*Di*-O-*methyl*-D-*fructose*.—1 : 2-4 : 5-Di-*O*-*iso*propylidene-3-*O*-toluene-*p*-sulphonyl-D-fructose (*F*) (15·9 g.), dissolved in acetic acid (80%; 80 c.c.), was kept at 60° for 3·5 hr. (Ohle and Just, *loc. cit.*). The acetic acid was removed by distillation and the residue dissolved in ether; the ethereal solution was washed with sodium hydrogen carbonate solution (thrice) and with water, and light petroleum (b. p. 60—80°) added to turbidity. Long needles were deposited of 1 : 2-*O*-*iso*propylidene-3-*O*-toluene-*p*-sulphonyl-D-fructose (13 g., 91%), m. p. 124—125°; $[\alpha]_D^{20}$ −112° (*c*, 1·2 in $CHCl_3$), −128° (*c*, 1·2 in MeOH) (Found: C, 51·1; H, 6·1; S, 8·4. Calc. for $C_{16}H_{22}O_8S$: C, 51·3; H, 5·9; S, 8·6%). Methylation thrice with methyl iodide and silver oxide gave a *dimethyl ether* (92%), prisms (from aqueous methanol), m. p. 84—85°, $[\alpha]_D^{17}$ −121° (*c*, 1·0 in MeOH) (Found: C, 53·9; H, 6·4; OMe, 16·5; S, 7·8. $C_{18}H_{26}O_8S$ requires C, 53·7; H, 6·5; OMe, 15·5; S, 8·0%).

The toluene-*p*-sulphonyl group was removed by treatment with 4% sodium amalgam for 48 hr. at 45°. The product, 4 : 5-*di*-O-*methyl*-1 : 2-*O*-iso*propylidene*-D-*fructose*, after distillation at 130°/0·10 mm. and recrystallisation from light petroleum (b. p. 60—80°) formed hygroscopic needles (4·34 g., 94%), m. p. 64—65°, $[\alpha]_D^{18}$ −169° (*c*, 1·0 in MeOH) (Found: C, 53·2; H, 7·9; OMe, 24·0. $C_{11}H_{20}O_6$ requires C, 53·2; H, 8·1; OMe, 25·0%).

4 : 5-Di-*O*-methyl-1 : 2-*O*-*iso*propylidene-D-fructose (4·0 g.) dissolved in sulphuric acid (0·1N; 100 c.c.) was heated at 95° for 3 hr. Neutralisation by passage through anion-exchange resin (IR-4B) and evaporation gave a syrup (3·27 g., 95%) which crystallised completely. The crystals were dissolved in hot ethanol (2 c.c.) and warm carbon tetrachloride (50 c.c.) was added;

needles of 4 : 5-*di*-O-*methyl*-D-*fructose* were deposited, m. p. 104—105°, $[\alpha]_D^{15}$ −167° (*c*, 1·3 in H_2O) (Found: C, 46·2; H, 7·9; OMe, 28·3. $C_8H_{16}O_6$ requires C, 46·15; H, 7·7; OMe, 29·8%). These gave on chromatographic analysis a single spot, R_G 0·49 in solvent (I), 0·14 in solvent (II). The crystalline phenylosazone had m. p. 67—68° (from aqueous ethanol), $[\alpha]_D^{19}$ −27·5° ⟶ −8·2°) (*c*, 1·1 in ethanol). Orange needles of 4 : 5-*dimethylfructose* 2 : 5-*dichlorophenylhydrazone*, m. p. 102°, $[\alpha]_D^{17}$ −45° (*c*, 0·2 in H_2O), were obtained on refluxing an alcoholic solution of this dimethyl ether with 2 : 5-dichlorophenylhydrazine (Found: C, 45·0; H, 5·3; N, 7·85. $C_{14}H_{20}O_5N_2Cl_2$ requires C, 45·8; H, 5·4; N, 7·6%).

4-O-*Methyl*-D-*fructose*.—Three methylations with Purdie reagents of 2 : 3-*O*-*iso*propylidene-1 : 6-di-*O*-toluene-*p*-sulphonyl-D-fructose (*L*) (11·4 g.) gave crystalline 4-O-*methyl*-2 : 3-O-iso-*propylidene*-1 : 6-*di*-O-*toluene*-p-*sulphonyl*-D-*fructose* (11·6 g., 91%), m. p. 112—113°, $[\alpha]_D^{19}$ +23° (*c*, 1·5 in EtOH) (Found: C, 52·8; H, 5·4; OMe, 5·95. $C_{24}H_{30}O_{10}S_2$ requires C, 53·1; H, 5·6; OMe, 5·7%). Removal of the toluenesulphonyl groups and distillation gave a 4-O-*methyl*-2 : 3-O-iso*propylidene*-D-*fructose* (4·2 g.), b. p. 150°/0·05 mm., $[\alpha]_D$ +6·5° (*c*, 1·5 in EtOH) (Found: OMe, 13·0. $C_{10}H_{18}O_6$ requires OMe, 13·25%).

Hydrolysis of this syrup (3·48 g.) with sulphuric acid (0·1N; 150 c.c.) at 95° for 3 hr. gave 4-*O*-methylfructose (2·91 g., 100%), n_D^{18} 1·4905, $[\alpha]_D^{18}$ −43° ⟶ −61° (72 hr., const.) (*c*, 1·3 in MeOH), −93° ⟶ −97° (4 days, const.) (*c*, 1·0 in H_2O) (McDonald and Jackson, *loc. cit.*, record $[\alpha]_D$ −87·5 in H_2O) (Found: OMe, 16·3. Calc. for $C_7H_{14}O_6$: OMe, 16·0%). Chromatographic analysis of this syrup showed a single spot, R_G 0·37, in solvent (I). The phenylosazone had m. p. 157—158° (from aqueous acetone), undepressed on admixture with authentic 4-*O*-methylglucosazone, $[\alpha]_D^{17}$ −35° ⟶ −14° (*c*, 0·3 in H_2O) (cf. Knauf, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 1447, who record m. p. 158—159°, $[\alpha]_D$ −36·0 ⟶ −14·4° for 4-*O*-methylglucosazone).

Characterisation of 4-O-*Methyl*-D-*fructose*.—Oxidation of the above syrup (0·50 g.) was carried out as for the 3 : 4-di-*O*-methylfructose. The dimethyl (−)-hydroxymonomethoxy-succinate (0·128 g.) had n_D^{17} 1·4510, $[\alpha]_D^{17}$ −41° (*c*, 1·3 in MeOH). Crystalline D-*threo*-2-hydroxy-3-methoxysuccinamide had m. p. 198—200°. The *bismethylamide* was also obtained and after recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave long needles, m. p. 137°, $[\alpha]_D$ −103° (*c*, 0·6 in H_2O) (Found: C, 44·2; H, 7·4; N, 13·5. $C_7H_{14}O_4N_2$ requires C, 44·2; H, 7·4; N, 14·7%). These two derivatives have been synthesised from tartaric acid and had melting points and rotation identical with the above.

Thanks are expressed to the Department of Scientific and Industrial Research for a maintenance grant and to the University for the award of a Post-graduate Studentship to one of us (W. E. A. M.), to Imperial Chemical Industries Limited, and to the Distillers Company Ltd. for grants.

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF EDINBURGH. [*Received, June 17th,* 1953.