234. *Acetone Derivatives of Methylglycosides.*

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The geometry of the conformation of the sugar rings is a subject of which little experimental evidence is available. The possibility of the existence of strainless rings has been already explored (Haworth, "The Constitution of Sugars," 1929, p. 90). Interpretations of the

* [*Note, added in proof.*] Brosset (*Nature*, 1935, **135**, 874) has now shown that this complex $W_2Cl_9^{3-}$ persists in the crystals.

X-ray data carried out in these laboratories by E. G. Cox (J., 1931, 2313; 1932, 138; Cox and Goodwin, J., 1932, 1844) have favoured the adoption of one form of strainless rings for various sugars and their glycosides. This form represents the oxygen of a pyranose ring as occupying a plane different from that of the five carbon atoms. The existence of trimethyl 1 : 4-anhydroglucopyranose (I), which has a bridged-ring structure as in camphor, requires the conformation of a boat-shaped or *cis*-type of pyranose ring in which strain is entirely eliminated. On a previous occasion we showed that xylofuranose 1 : 2-3 : 5-diacetone has a completely strainless structure (II) inasmuch as the union of the acetone residue at positions 3 and 5 is possible without deflexion of any valency direction, despite the fact that the hydroxyl groups involved in the union of the acetone residue are not attached at contiguous carbon atoms (Fig. 1*a*) (Haworth and Porter, J., 1928, 611). Recently we have examined other examples of this type. It has already been shown that when mannose condenses with acetone the pyranose ring is ruptured and the acetone groups attach themselves at what seem the most convenient *cis*-hydroxyl positions of a mannofuranose structure, namely, at the positions 2 : 3 and 5 : 6 (III). We now record the isolation of the crystalline α-methylglycoside of (III). In these furanose forms, however, no question of ring conformation arises, inasmuch as it is highly probable that all the atoms in a furanose ring are co-planar. This condition need not obtain in a pyranose form of mannose and accordingly we attempted to prepare a diacetone derivative of α-methylmannoside. It was found that in the presence of copper sulphate or hydrogen chloride as catalyst acetone containing no methyl alcohol condensed with α-methylmannopyranoside to give the 2 : 3-4 : 6-*diacetone* derivative (IV). If a model of

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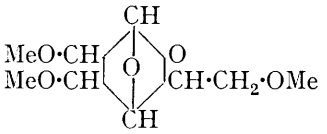
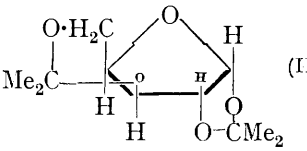
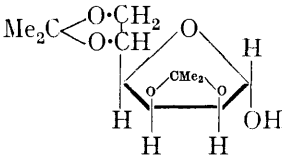


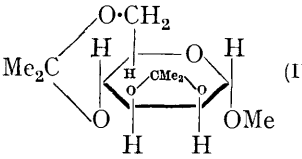
(II.)



(III.)

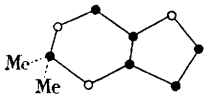


(IV.)

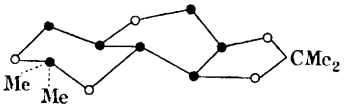


the pyranose form of α-methylmannoside be constructed, it will be seen that the hydroxyls at positions 4 and 6 are somewhat remote in the model built up as a flat ring in which all

FIG. 1.



(a) *Skeleton of* 3 : 5-*acetone linking in xylofuranose diacetone.*



(b) *Skeleton of* 2 : 3-4 : 6-*acetone linkings in* α-*methylmannopyranoside diacetone.*

the atoms constituting it are co-planar. In several forms, however, of both *cis*- and *trans*-conformations the hydroxyl groups at these two positions are brought in such spatial proximity as to be equivalent to a pair of *cis*-hydroxyl groups attached at contiguous carbon atoms (Fig. 1*b*). In these cases the attachment of an acetone residue at positions 4 and 6 may occur without strain or deflexion of the valency bonds. The above α-methylmannopyranoside 2 : 3-4 : 6-diacetone is a well-defined crystalline substance and we have also prepared the corresponding 2 : 3-monoacetone, which is similarly crystalline (compare Ault, Haworth, and Hirst, this vol., p. 517). The latter on methylation gives rise to 4 : 6-*dimethyl* α-*methylmannopyranoside* 2 : 3-*diacetone* and this passes on hydrolysis to 4 : 6-*dimethyl* α-*methylmannopyranoside* and to 4 : 6-*dimethyl mannopyranose*. By condensing the last compound with acetone, the crystalline 4 : 6-*dimethyl* α-*mannopyranose* 2 : 3-

monoacetone was prepared. The reducing hydroxyl position 1 in this substance is unsubstituted, as is shown by its vigorous reducing action towards Fehling's solution.

The above experiments enabled us to proceed with the preparation of substances which may be of importance as reference compounds. In this respect 4 : 6-*dimethyl* δ-*mannonolactone* is of interest. It is a crystalline substance which displays a change of rotation comparable in velocity with that of tetramethyl δ-mannonolactone and it yields a crystalline *phenylhydrazide*. When shaken with acetone in the presence of anhydrous copper sulphate, it gave 4 : 6-*dimethyl* δ-*mannonolactone* 2 : 3-*monoacetone*, which also is crystalline, and attention is directed to the interesting mutarotation phenomena of this substance in alcohol. Methylation of 4 : 6-dimethyl δ-mannonolactone gave the already known 2 : 3 : 4 : 6-tetramethyl δ-mannonolactone and its crystalline phenylhydrazide.

The allocation of a structure to α-methylmannopyranoside diacetone is based upon the following argument. Both acetone residues can be eliminated with ease to give a quantitative yield of α-methylmannopyranoside. The 4 : 6-dimethyl mannonolactone behaves entirely as a δ-lactone and no trace of a γ-lactone was found. This lactone yields an amide which gives a positive Weerman reaction and consequently the 2-position is occupied by a free hydroxyl group. It is highly probable that there is also a hydroxyl group at position 3. The only alternative for this second hydroxyl is at position 4, but in this case we should expect to be able to isolate a γ-lactone as well as a δ-lactone; this, however, is not the case. The properties of α-methylmannoside 2 : 3-monoacetone have been described by Ault, Haworth, Hirst (*loc. cit.*), who show that this readily gives rise on oxidation, followed by elimination of the acetone residue, to α-methylmannuronide. It is therefore clear that in the monoacetone compound the 6-position is free for oxidation to a carboxyl group. We have therefore allocated the 2 : 3-position to the monoacetone and the 2 : 3-4 : 6-positions to the α-methylmannoside diacetone, and this is in agreement with all the facts.

We have extended our experiments also to prepare similar derivatives from β-methylmannopyranoside, which is less accessible than the α-form (Bott, Haworth, and Hirst, J., 1930, 2656). When shaken with acetone in the presence of anhydrous copper sulphate during a period of five months, this gave rise in good yield to the crystalline β-*methylmannopyranoside* 2 : 3-4 : 6-*diacetone*. It is curious that this isomeride has the same melting point (76—77°) as the foregoing α-form, but a mixture of the two depresses the melting point. Removal of the acetone group gives rise to the original β-methylmannopyranoside, but, even after this purification of the latter by passing through the crystalline diacetone derivative, the β-methylmannopyranoside was not crystalline, nor has it ever been obtained crystalline. Accompanying the formation of this diacetone derivative there occurred also the β-*methylmannopyranoside* 2 : 3-*monoacetone*, although this has not yet been obtained quite free from the diacetone compound.

In an attempt to prepare the above substances by condensation of β-methylmannopyranoside with acetone in the presence of 1% hydrogen chloride we found that the glucosidic methyl group was hydrolysed and the product isolated was the mannofuranose 2 : 3-5 : 6-diacetone (Haworth and Porter, J., 1930, 649). It is therefore evident that, although the use of copper sulphate as a catalyst preserved both the β-methylglycosidic group and the pyranose structure, yet the use of hydrogen chloride (which was successful in the α-series) alters the structure in the β-series. This is undoubtedly due to the accumulation of water molecules from the condensation with acetone. In presence of hydrogen chloride the hydrogen-ion concentration is sufficient to hydrolyse completely the glycosidic group, leaving a free reducing group in this position and thus permitting of ring change to the furanose form.

In this connexion it is important to observe that if acetone containing methyl alcohol as impurity be employed, the use of hydrogen chloride as catalyst is equally inapplicable to both α- and β-methylmannopyranosides. Under these conditions an equilibrium is established between the α- and β-forms of the mannopyranosides and mannofuranosides and the resulting acetone condensation products are mixtures containing methylmannofuranoside 2 : 3-5 : 6-diacetone. It was doubtless under these conditions that Levene and Meyer (*J. Biol. Chem.*, 1928, **78**, 363) isolated the latter substance and suggested that

acetonisation of α-methylmannopyranoside led to a change of ring structure from pyranoside to furanoside. Had this been the correct explanation of the formation of Levene and Meyer's products, it would have been indeed a unique example of ring change. We have been able to imitate all Levene and Meyer's results by introducing methyl alcohol deliberately into the acetone employed in the condensation. The facts are, as we have shown above, that no such ring shift occurs when α-methylmannopyranoside is condensed with acetone either with hydrogen chloride or with copper sulphate as catalyst unless methyl alcohol is present as impurity. In the latter case, all the conditions which are well recognised as establishing ring change are present, inasmuch as the general method of introducing ring shift is to mix a sugar or its glycoside with methyl alcohol in the presence of hydrogen chloride. Under these conditions an equilibrium mixture of α- and β-forms of pyranoside and furanoside is produced.

We have also prepared *α-methylgalactopyranoside monoacetone* and inspection of the atom-model suggests that in this substance the acetone grouping is at the *cis*-position 3 : 4. Oxidation with alkaline permanganate gave rise to the potassium salt of α-methylgalacturonide monoacetone. Of considerable interest is the observation that, under the conditions we employed, β-methylfructopyranoside loses its glycosidic residue during the condensation with acetone. Using 1% hydrogen chloride as catalyst, we isolated in good yield fructose β-diacetone, and employing copper sulphate as catalyst we were able to isolate fructose α-diacetone. A quantitative yield of the latter was also obtained by shaking ethyl fructofuranoside during a period of six months with acetone containing anhydrous copper sulphate.

Experimental.

4 : 6-*Dimethyl α-Methylmannopyranoside* 2 : 3-*Monoacetone.*—α-Methylmannopyranoside 2 : 3-monoacetone (8 g.), dissolved in methyl iodide containing a little acetone, was boiled with silver oxide in the usual way. The methylation was thrice repeated, the use of acetone in the later methylations being unnecessary. The product was extracted from the silver residues with ether and after removal of the solvent was purified by distillation. 4 : 6-*Dimethyl α-methylmannopyranoside* 2 : 3-*monoacetone* (yield 8·2 g.) had b. p. 95°/0·01 mm. (bath temp.), $n_D^{16°}$ 1·4505, $[\alpha]_{5780}^{20°}$ + 51° in methyl alcohol (*c*, 1·0), + 40° in chloroform (*c*, 1·0). It was a colourless mobile syrup readily soluble in all the usual organic solvents (Found : C, 54·95; H, 8·3; OMe, 34·6. $C_{12}H_{22}O_6$ requires C, 54·95; H, 8·5; OMe, 35·5%).

4 : 6-*Dimethyl α-Methylmannopyranoside.*—The acetone group in the above compound was slowly removed at room temperature by *N*/50-hydrochloric acid (made up in 70% aqueous methyl alcohol). The reaction, which was followed polarimetrically, was complete in about 72 hours ($[\alpha]_{5780}^{20°}$ + 87°, final constant value, concentration calc. for 4 : 6-dimethyl α-methylmannoside). No hydrolysis of the glycosidic group took place under these conditions. For the preparation of the dimethyl methylmannoside it was advantageous to carry out the hydrolysis at 60°. The reaction was then complete in about 4 hours. The solution was neutralised with silver carbonate, filtered, and concentrated to a non-reducing syrup, which was distilled under diminished pressure, giving 4 : 6-*dimethyl α-methylmannopyranoside* as a colourless syrup, b. p. 130°/0·01 mm. (bath temp.), $n_D^{16°}$ 1·4660, $[\alpha]_{5780}^{20°}$ + 80·5° in water (*c*, 1·2); + 99° in methyl alcohol (*c*, 2·0). Yield, 85% of the theoretical (Found : C, 48·7; H, 8·4; OMe, 42·0. $C_9H_{18}O_6$ requires C, 48·65; H, 8·2; OMe, 41·9%).

4 : 6-*Dimethyl Mannose.*—The above dimethyl α-methylmannoside was hydrolysed by boiling with 4% hydrochloric acid (6 hours), the strongly reducing product being isolated in the usual way and purified by solution in chloroform to eliminate inorganic impurities. 4 : 6-*Dimethyl mannose* was a glass, soluble in water, alcohol, chloroform and acetone, almost insoluble in ether and light petroleum. $[\alpha]_{5780}^{22°}$ + 25° in water (*c*, 4·3) (Found : C, 45·95; H, 7·5; OMe, 29·5. $C_8H_{16}O_6$ requires C, 46·15; H, 7·7; OMe, 29·8%).

4 : 6-Dimethyl mannose reacted readily with aniline in boiling benzene, giving a syrupy anilide (isolated by the usual method), which was soluble in light petroleum and in benzene. The dimethyl mannose combined also with phenylhydrazine, giving an oil which was insoluble in water (probably the osazone).

4 : 6-*Dimethyl α-Mannopyranose* 2 : 3-*Monoacetone.*—4 : 6-Dimethyl mannose (2 g.) in dry acetone (300 c.c.) was shaken for 6 days at room temperature in the presence of anhydrous copper sulphate (30 g.). After filtration the solution was concentrated to a syrup, which was

distilled, giving 4 : 6-*dimethyl mannose* 2 : 3-*monoacetone* (yield, 85% of the theoretical), b. p. 128°/0·01 mm. (bath temp.). This crystallised on cooling and after recrystallisation from light petroleum (b. p. 40—60°) had m. p. 76—77°, $[\alpha]_{5780}^{21°}$ + 11° in dry methyl alcohol (*c*, 1·0); in water (*c*, 1·0), $[\alpha]_{5780}^{20°}$ ± 0° (initial value); − 3° (30 mins.); − 5° (60 mins.); − 7° (2 hrs.); − 8° (3 hrs.); − 9° (4 hrs.); − 9·5° (6 hrs., final equilibrium value). This dimethyl mannose monoacetone was strongly reducing in character (Found: C, 53·0; H, 8·1; OMe, 26·1. $C_{11}H_{20}O_6$ requires C, 53·2; H, 8·1; OMe, 25·0%).

4 : 6-*Dimethyl* δ-*Mannonolactone.*—4 : 6-Dimethyl mannose (1·0 g.) was oxidised by bromine water in the usual way at 25°. The oxidation was complete in about 48 hours. The excess of bromine was removed by aeration, and the solution neutralised with silver carbonate. The silver bromide was filtered off, and the organic acid liberated from the silver salt by titration with hydrochloric acid. Concentration of the aqueous solution under diminished pressure left a viscid syrup, which was dissolved in chloroform. After filtration to remove inorganic impurities and evaporation of the chloroform, the viscid syrup obtained was lactonised by heating at 100°/0·01 mm. for 6 hours (Found: C, 46·0; H, 7·3; OMe, 30·4. $C_8H_{14}O_6$ requires C, 46·6; H, 6·9; OMe, 30·1%). This syrupy lactone was contaminated by free acid which resisted lactonisation. The pure lactone was obtained in the following way. The above syrup (1 g.) was boiled for 6 hours with 2% methyl-alcoholic hydrogen chloride (100 c.c.). After neutralisation of the mineral acid (silver carbonate) the solution was evaporated to a syrup under diminished pressure. This syrup was mainly the methyl ester of 4 : 6-dimethylmannonic acid. When heated in a high vacuum at 165°, it was converted with loss of methyl alcohol into pure 4 : 6-*dimethyl* δ-*mannonolactone*, which distilled forward as a colourless liquid and crystallised slowly when kept. After recrystallisation from ether–absolute alcohol it had m. p. 55°, $[\alpha]_{5780}^{18°}$ + 145° in alcohol (*c*, 1·0), + 165° in water (*c*, 1·0) (Found: C, 46·5; H, 7·0; OMe, 29·4%).

In aqueous solution the rate of mutarotation was $[\alpha]_{5780}^{20°}$ + 165° (initial value; *c*, 1·1); + 118° (24 hrs.); + 93° (48 hrs.); + 81° (72 hrs.); + 75° (96 hrs.); + 70° (150 hrs.). This is comparable with that of tetramethyl δ-mannonolactone. For the acid (calculated as lactone) $[\alpha]_{5780}^{20°}$ + 20° (in water containing 1 mol. of sodium sulphate), rising during 150 hours to + 68°. In both cases the mutarotation was nearly complete in 100 hours. The proportions of lactone and acid at equilibrium were approximately 34% and 66% respectively.

The crystalline lactone cannot be isolated by evaporation of an aqueous solution to dryness. It is necessary to convert the syrupy product so obtained into the ester, followed by distillation as described above. On treatment with methyl-alcoholic ammonia in the usual manner the crystalline lactone gave rise to the corresponding crystalline *amide*, m. p. 119° (after recrystallisation from ethyl alcohol–ether), $[\alpha]_{5780}^{18°}$ − 3° in methyl alcohol (*c*, 0·9); + 15° in water (*c*, 1·0) (Found: C, 43·1; H, 7·8; N, 6·3; OMe, 27·6. $C_8H_{17}O_6N$ requires C, 43·1; H, 7·6; N, 6·3; OMe, 27·8%). This amide (100 mg.) gave a very strong positive Weerman reaction, the yield of hydrazodicarbonamide being 60% of the theoretical and the reaction with the hypochlorite solution being complete in 15 minutes. With α-methoxy-amides, on the other hand, free hypochlorite remains even after several hours, and no hydrazodicarbonamide is obtained (compare Ault, Haworth, and Hirst, J., 1934, 1722).

On treatment with phenylhydrazine at 100° the lactone gave almost quantitatively the *phenylhydrazide* of 4 : 6-dimethylmannonic acid. This was recrystallised from alcohol–light petroleum; m. p. 151°, $[\alpha]_{5780}^{19°}$ − 3·5° in alcohol (*c*, 0·9), $[\alpha]_{5780}^{19°}$ + 14° in water (*c*, 0·9) (Found: C, 53·6; H, 7·3; N, 8·7; OMe, 19·8. $C_{14}H_{22}O_6N_2$ requires C, 53·5; H, 7·1; N, 8·9; OMe, 19·7%).

When shaken with acetone in the presence of anhydrous copper sulphate, the above lactone gave 4 : 6-*dimethyl* δ-*mannonolactone* 2 : 3-*monoacetone*, which crystallised after distillation, b. p. 130°/0·01 mm. (bath temperature), m. p. 112—113° (recrystallised from alcohol–ether) (Found: C, 53·7; H, 7·3; OMe, 26·2. $C_{11}H_{18}O_6$ requires C, 53·7; H, 7·3; OMe, 25·2%), $[\alpha]_{5780}^{19°}$ + 128° in absolute alcohol (*c*, 0·9), $[\alpha]_{5780}^{22°}$ + 121° in 50% aqueous methyl alcohol (initial value; *c*, 0·8). The rotation in this medium diminished slowly for 9 days until the value + 52° was attained. At this stage, evaporation of the solution under diminished pressure yielded the original dimethylmannonolactone monoacetone unchanged. After 9 days, however, the rotation began to increase and hydrolysis of the acetone residue took place. In absolute alcohol (dried by Lund and Bjerrum's method, *Ber.*, 1931, **64**, 210) the rotation of the lactone remains constant, but in ethyl alcohol dried by barium oxide and in all samples of methyl alcohol we have examined, rapid mutarotation is observed. For instance, in one sample of dry methyl alcohol the initial value $[\alpha]_{5780}^{19°}$ + 125° decreased in 7 hours to the constant value

+ 66°. On evaporation of the solution at this stage the original lactone was recovered. In other specimens of methyl alcohol even more rapid mutarotation ($[\alpha]_{5780}^{20°}$ + 125° ⟶ + 67°) was observed, but in all cases the crystalline lactone was recovered unaltered on evaporation of the solvent. Further evidence that some impurity in the methyl alcohol was responsible for initiating the mutarotation was provided by the observation that in 50% aqueous methyl alcohol (the alcohol having been dried over barium oxide and distilled) mutarotation to + 75° took place in a few minutes and was followed by a slower change.

Methylation of 4 : 6-dimethyl δ-mannonolactone by Purdie's reagents gave 2 : 3 : 4 : 6-tetramethyl δ-mannonolactone accompanied by some methyl pentamethylmannonate. The mixture was a colourless mobile liquid, b. p. 120—125°/0·03 mm. (bath temp.), $n_D^{20°}$ 1·4492 (Found : OMe, 58·0. Calc. for $C_{10}H_{18}O_6$: OMe, 53·0. Calc. for $C_{12}H_{24}O_7$: OMe, 66·4%). The presence of 2 : 3 : 4 : 6-tetramethyl δ-mannonolactone was demonstrated by the formation of the corresponding phenylhydrazide of 2 : 3 : 4 : 6-tetramethylmannonic acid (yield, 50%), m. p. 186—187° alone or when mixed with an authentic specimen (Found : C, 56·0; H, 7·4; N, 8·3; OMe, 35·9. Calc. for $C_{16}H_{26}O_6N_2$: C, 56·1; H, 7·6; N, 8·2; OMe, 36·2%).

α-Methylmannopyranoside 2 : 3-4 : 6-Diacetone.—(a) α-Methylmannopyranoside (10 g.) was shaken at room temperature with dry acetone (400 c.c.) for 10 days in the presence of anhydrous copper sulphate. The filtered solution was concentrated to a syrup under diminished pressure. Some unchanged α-methylmannoside was eliminated by dissolving the syrup in cold acetone. After removal of the solvent the product was distilled, giving (1) *α-methylmannopyranoside 2 : 3-4 : 6-diacetone* (1·6 g.), b. p. 125—130°/0·03 mm. (bath temp.), $n_D^{20°}$ 1·4605, and (2) α-methylmannopyranoside 2 : 3-monoacetone (0·8 g.), b. p. 165—170°/0·03 mm. (bath temp.). The latter material crystallised completely on inoculation with crystalline α-methylmannoside monoacetone. Its properties have been described (*loc. cit.*). Increased yields of both the diacetone and the monoacetone derivative were obtained when the condensation was carried out at 50°.

α-Methylmannopyranoside 2 : 3-4 : 6-diacetone crystallised slowly in a desiccator. After recrystallisation from aqueous ethyl alcohol it had m. p. 76—77°, $[\alpha]_D^{22°}$ + 3° in methyl alcohol (*c*, 2·4) (Found : C, 56·9; H, 8·2; OMe, 11·9. $C_{13}H_{22}O_6$ requires C, 56·9; H, 8·1; OMe, 11·3%). When it (0·3 g.) was dissolved in methyl alcohol (12 c.c.), and *N*/25-hydrochloric acid (4 c.c.) added, the following rotational changes took place at 20° (*l*, 1 dm.): $\alpha_D^{20°}$ + 0·06° (initial value); + 0·32° (5 hrs.); + 0·65° (26 hrs.); + 0·78° (47 hrs.); + 1·06° (119 hrs.); + 1·20° (216 hrs.); + 1·25° (350 hrs.; constant value). The final reading corresponds to $[\alpha]_D^{20°}$ + 95° (calc. as α-methylmannoside). The solution was neutralised with silver carbonate and on concentration gave quantitatively α-methylmannoside (0·18 g.), m. p. 195° alone or when mixed with an authentic specimen. Control experiments showed that α-methylmannopyranoside was unaffected at 60° by *N*/100-hydrochloric acid in aqueous methyl alcohol.

(b) α-Methylmannopyranoside 2 : 3-4 : 6-diacetone was also prepared by the action of methyl alcohol-free dry acetone containing 1% by weight of hydrogen chloride. The procedure was the same as that already given for the preparation of α-methylmannopyranoside 2 : 3-monoacetone. The crude syrupy product was extracted with boiling light petroleum, which dissolved the diacetone derivative and left behind the monoacetone derivative. The petroleum extract was concentrated and the syrup which remained was heated at 100°/0·01 mm. until auto-condensation products of acetone had been eliminated. The diacetone derivative of α-methylmannoside distilled at 135°/0·02 mm. as a colourless syrup, $n_D^{21°}$ 1·4609, $[\alpha]_D^{20°}$ + 3° in methyl alcohol (*c*, 1·9), which crystallised when kept and was identical with the material described under (a) above; m. p. 76—77° (Found : C, 57·0; H, 8·2; OMe, 11·0; C_3H_6O, 41·0. Calc. for $C_{13}H_{22}O_6$: C, 56·9; H, 8·1; OMe, 11·3; C_3H_6O, 42·0%). Under these conditions no methylmannofuranoside diacetone is produced (see below; contrast Levene and Meyer, *loc. cit.*).

(c) The diacetone derivative, m. p. 76—77°, was obtained quantitatively when α-methylmannopyranoside 2 : 3-monoacetone, m. p. 105°, was shaken with dry acetone and anhydrous copper sulphate for several days at room temperature.

Action of Acetone containing Hydrogen Chloride on β-Methylmannopyranoside.—β-Methylmannopyranoside (3 g., prepared from tetra-acetyl β-methylmannopyranoside by Bott, Haworth, and Hirst's method, J., 1930, 2656) was shaken at room temperature with acetone (600 c.c.) containing 1% of hydrogen chloride. At the end of 24 hours the acid was neutralised with silver carbonate, and the solution evaporated to dryness in the presence of barium carbonate. The product was dissolved in light petroleum (elimination of inorganic impurities) and, after

removal of the solvent, was distilled, giving mannose 2 : 3-5 : 6-diacetone (2 g.), b. p. 150—155°/0·03—0·04 mm. (bath temp.). This crystallised immediately and was recrystallised from acetone–light petroleum; m. p. 122—123°, alone or when mixed with an authentic specimen, $[\alpha]_{5780}^{17°}$ + 1° in water (equilibrium value; *c*, 1·1), + 25° in acetone (*c*, 1·0).

β-Methylmannopyranoside 2 : 3-4 : 6-Diacetone.—β-Methylmannopyranoside (6·5 g.) was shaken with acetone (650 c.c.) in the presence of anhydrous copper sulphate (50 g.). The condensation proceeded less rapidly than in the case of α-methylmannoside. After continuous shaking for 5 months the products were isolated in the manner described above. Two fractions were obtained on distillation:

(a) *β-Methylmannopyranoside 2 : 3-4 : 6-diacetone* (4·4 g.), b. p. 105°/0·03 mm. (bath temp. 135°), $n_D^{15°}$ 1·4688. This crystallised slowly in a desiccator and after 6 weeks had set to a solid, which was crystallised from aqueous ethyl alcohol (yield, 4·2 g.); m. p. 76—77°, $[\alpha]_{5780}^{20°}$ — 124° in methyl alcohol (*c*, 1·0) (Found: C, 57·0; H, 8·2; OMe, 12·9. $C_{13}H_{22}O_6$ requires C, 56·9; H, 8·1; OMe, 11·3%). A mixture with α-methylmannopyranoside diacetone (m. p. 76—77°) melted at 65°. Although the syrupy distilled product crystallised slowly, it was not less pure than the above crystalline specimen (Found: C, 57·0; H, 7·9; OMe, 12·5%).

β-Methylmannopyranoside diacetone (0·25 g.) was dissolved in methyl alcohol (16 c.c.), 2 c.c. of *N*/10-hydrochloric acid added, and the volume made up to 20 c.c. with methyl alcohol. The following rotational changes were observed at 20° (*l*, 1 dm.): $\alpha_{5780}^{20°}$ — 1·57° (initial value); — 1·29° (5 hrs.); — 0·95° (22 hrs.); — 0·85° (46 hrs.); 0·79° (94 hrs.); — 0·76° (200 hrs.; constant value). The end value corresponds to $[\alpha]_{5780}^{20°}$ — 85°, calc. as β-methylmannoside. [For β-methylmannopyranoside in aqueous methyl alcohol (strength as above) the value $[\alpha]_{5780}^{20°}$ — 84° was observed.] The hydrochloric acid was neutralised with silver carbonate and the solution, which was non-reducing, was evaporated to a syrup (yield, quantitative); this had $[\alpha]_{5780}^{23°}$ — 84° in methyl alcohol (*c*, 1·7), — 67° in water (*c*, 1·7), and was β-methylmannopyranoside. Control experiments showed that β-methylmannopyranoside was unaffected at 60° by *N*/100-hydrochloric acid in aqueous methyl alcohol.

(b) The second fraction (1·4 g.), b. p. 145°/0·03 mm. (bath temp. 175°), was a hygroscopic viscid mass which consisted mainly of *β-methylmannopyranoside 2 : 3-monoacetone*, soluble in water, alcohol, acetone, ethyl acetate, moderately soluble in ether, and insoluble in light petroleum. $[\alpha]_{5780}^{20°}$ — 80° in methyl alcohol (*c*, 1·4), — 72° in water (*c*, 1·4) (Found: C, 51·9; H, 7·8; OMe, 13·4. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·7; OMe, 13·2%). The analytical figures indicate contamination with some of the corresponding diacetone compound. On treatment with *N*/100-hydrochloric acid in aqueous methyl alcohol at 20° this material was transformed quantitatively into β-methylmannopyranoside ($[\alpha]_{5780}^{18°}$ — 63° in water; *c*, 1·0). (See above: no hydrolysis of the methyl glycosidic group occurred and the product was non-reducing.)

α-Methylmannofuranoside 2 : 3-5 : 6-Diacetone.—α-Methylmannofuranoside (m. p. 120—121°; $[\alpha]_D^{24°}$ + 109° in water, *c*, 1·0; prepared by Haworth, Hirst, and Webb's method, J., 1930, 651) (2 g.) was shaken with dry acetone (50 c.c.) and anhydrous copper sulphate (5 g.) for 10 days at room temperature. The filtered solution was evaporated at 35° under diminished pressure to a syrup, which was distilled, giving *α-methylmannofuranoside 2 : 3-5 : 6-diacetone* (2·6 g.), b. p. 125°/0·04 mm. (bath temp.). The distillate crystallised completely when kept at 0° and was recrystallised from aqueous alcohol at — 10°, giving broad plates, m. p. 24°, $[\alpha]_D^{21°}$ + 68° in methyl alcohol (*c*, 2·8) (Found: C, 57·1; H, 8·1; OMe, 11·9. $C_{13}H_{22}O_6$ requires C, 56·9; H, 8·1; OMe, 11·3%).

When α-methylmannofuranoside 2 : 3-5 : 6-diacetone was dissolved in methyl alcohol (3 vols.), and the solution made acid by addition of *N*/25-hydrochloric acid (1 vol.), the acetone residues were slowly removed (400 hours at room temperature) with quantitative formation of α-methylmannofuranoside. This was isolated in the way described above and had m. p. 119°, alone or when mixed with an authentic specimen. Throughout the hydrolysis the solution remained completely non-reducing and it was shown by control experiments that *N*/100-hydrochloric acid under the above conditions is without action upon α-methylmannofuranoside. At higher temperatures (50—60°) hydrolysis of the glycosidic group takes place with formation of mannose.

α-Methylmannoside (40 g.) was shaken with acetone (1 l.), containing 5% of methyl alcohol and 1% of hydrogen chloride, for 4 days in the manner described above. A residue of unchanged α-methylmannoside remained (20 g.). The acetone solution, after neutralisation, was concentrated to a syrup, which was extracted exhaustively with hot light petroleum (b. p. 40—60°). The residue (12·3 g.) crystallised and was shown to be α-methylmannopyranoside monoacetone, m. p. 105°. The light petroleum extracts, on concentration, gave a syrup

(7·1 g.), b. p. 115—120°/0·05—0·06 mm., $n_D^{21°}$ 1·4560, $[\alpha]_D^{24°}$ + 23° in methyl alcohol (Found: C, 56·95; H, 7·9; OMe, 10·9. Calc. for $C_{13}H_{22}O_6$: C, 56·9; H, 8·1; OMe, 11·3%). The analytical figures indicate that the syrup is a methylmannoside diacetone and its chemical properties show it to be a mixture of α-methylmannopyranoside diacetone and α-methylmannofuranoside diacetone. This can be seen from the following table, which gives the rotation results obtained (i) after hydrolysis with *N*/10-hydrochloric acid under the conditions specified by Levene and Meyer (*loc. cit.*), (ii) after hydrolysis with *N*/100-hydrochloric acid at 100° for 90 minutes.

	(i).			(ii).	
	Syrup.	α-Methylmannopyranoside diacetone (cryst.).	α-Methylmannopyranoside.	Syrup.	α-Methylmannopyranoside diacetone (cryst.).
	A.	B.	C.	D.	E.
Initial rotation	+23°	+ 3°	+79°	+23°	+ 3°
Final rotation (calc. as methylmannoside) ...	+42	+69	+68	+50	+77

The reducing values of the solutions D and E after hydrolysis were determined by titration with Fehling's solution. The value obtained for D indicated the presence initially of 38% of furanoside derivative, whereas the solution E (pyranoside) had a negligible reducing value.

Purification of the syrup by Levene and Meyer's procedure increased the percentage of furanoside derivative, this being shown by an enhanced rotation and an increased reducing value after hydrolysis with *N*/100-hydrochloric acid.

α-Methylgalactopyranoside 3 : 4-Monoacetone.—α-Methylgalactopyranoside is troublesome to prepare directly by heating galactose with methyl-alcoholic hydrogen chloride, owing to the difficulty of separating the α- and the β-form of the glycoside. The separation may be effected conveniently by acetylating (either by pyridine and acetic anhydride at 0° or by boiling acetic anhydride in the presence of fused sodium acetate) the crude mixture of the two forms obtained by the action of methyl-alcoholic hydrogen chloride on galactose (this crude product contained about 70% of the α-isomeride). The solid acetylation product is mainly the α-form and gives pure tetra-acetyl α-methylgalactopyranoside, m. p. 88°, $[\alpha]_{5780}^{17°}$ + 136° in chloroform (*c*, 1·1), on recrystallisation from aqueous alcohol. This substance yields on de-acetylation with methyl-alcoholic dimethylamine pure α-methylgalactoside, m. p. 110°, $[\alpha]_{5780}^{17°}$ + 194° in water (*c*, 1·0), after recrystallisation from alcohol. This is the monohydrate, and gives the anhydrous form, m. p. 116°, $[\alpha]_D^{19°}$ + 195° in water (*c*, 1·0), when heated in a vacuum at 100°.

α-Methylgalactopyranoside (anhydrous form; 4·3 g.) was shaken with acetone (600 c.c.), containing 1% of hydrogen chloride, for 24 hours at room temperature. The product, isolated by the method already described, was distilled under diminished pressure, giving *α-methylgalactopyranoside monoacetone* (4 g.), b. p. 145—150°/0·02 mm. (bath temp.). This crystallised when kept and was recrystallised from alcohol–light petroleum, giving needles, m. p. 101—102°, $[\alpha]_D^{20°}$ + 162° in water (*c*, 0·5) (Found: C, 51·0; H, 7·5; OMe, 13·5. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·7; OMe, 13·2%). Almost identical analytical figures were obtained with the syrup before crystallisation took place. In solution this substance readily loses its acetone residue by hydrolysis and considerable care is necessary during recrystallisation. Dry solvents should be employed, and the period of heating reduced to a minimum. In *N*/100-hydrochloric acid at 20° the substance is quantitatively hydrolysed in less than 6 hours to α-methylgalactopyranoside, isolated as the monohydrate, m. p. 110° alone or when mixed with an authentic sample. No hydrolysis of the glycosidic group occurred under these conditions.

α-Methylgalactoside 3 : 4-monoacetone (1·10 g.) was oxidised in alkaline solution with potassium permanganate (1·5 g.) and potassium hydroxide (0·55 g.). The product, which was extracted as described in the preparation of δ-mannonolactone, consisted largely of the potassium salt of α-methylgalacturonide 3 : 4-monoacetone, obtained as a viscid syrup. An extremely small amount of this compound gave a strong positive Tollens–Neuberg test for uronic acids. On removal of the acetone group by hydrolysis at 45° with *N*/50-hydrochloric acid a hard glass was obtained, which is being further investigated.

Attempts to cause α-methylglucopyranoside to condense with acetone in the presence of hydrogen chloride at room temperature or of anhydrous copper sulphate (at 15° and at 50°) were fruitless. In every case α-methylglucoside was recovered unchanged (compare Levene and Meyer, *J. Biol. Chem.*, 1928, **78**, 357).

Formation of α- and β-Fructose Diacetone from β-Methylfructopyranoside.—(a) β-Methyl-

fructopyranoside, m. p. 121° (Hudson, *J. Amer. Chem. Soc.*, 1916, **38**, 1219) (4 g.), was shaken for 24 hours with acetone (300 c.c.) containing 1% of hydrogen chloride. The acid was neutralised with silver carbonate, and the solution evaporated under diminished pressure in the presence of barium carbonate. The syrup which remained was distilled, giving β-fructose diacetone, b. p. 140—145°/0·03 mm. (bath temp.), m. p. (after recrystallisation from alcohol–light petroleum) 96°, alone or when mixed with an authentic sample. Yield, 3 g.; $[\alpha]_D^{21°}$ — 34° in water (*c*, 0·9) (Found : C, 55·1; H, 7·8; OMe, nil. Calc. for $C_{12}H_{20}O_6$: C, 55·4; H, 7·8%).

(b) β-Methylfructopyranoside (3·5 g.) was shaken with acetone (500 c.c.) in the presence of anhydrous copper sulphate (15 g.) for one month at room temperature. The product was isolated in the usual way and distilled, giving α-fructose diacetone (1·5 g.), b. p. 140—145°/0·05 mm. (bath temp.), m. p. (after recrystallisation from acetone–light petroleum) 120° (alone or in admixture with an authentic sample of similar m. p.), $[\alpha]_{5780}^{20°}$ — 168° in water (*c*, 1·1) (Found : C, 55·4; H, 7·8%; OMe, nil).

Ethyl fructofuranoside (prepared by the method of Allpress, Haworth, and Inkster, J., 1927, 1233), when shaken for 6 months with acetone in the presence of anhydrous copper sulphate, gave quantitatively α-fructose diacetone, m. p. 120°.

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