LXXXVII.—*Crystalline α-Methylmannofuranoside (γ-Methylmannoside). Part II.*

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While the preceding research was in progress, leading to the synthesis of crystalline α-methylmannofuranoside from mannose dicarbonate, we were also engaged on the preparation of the same product by a more direct procedure: the condensation of mannose with methyl alcohol in the presence of 1% hydrogen chloride. The neutralised solution yielded a syrup, which was separated from unchanged mannose by solution in ethyl acetate. During the evaporation of this solvent from the extract a copious crop of crystalline α-methylmannofuranoside separated in a yield of 30%, even though the solution had not been nucleated intentionally with a specimen of the mannofuranoside from the preceding synthetic preparation. This occurrence was repeated as frequently as we performed the mannose–methyl alcohol condensation, and it became evident that, once a nucleus was available, α-methylmannofuranoside could be obtained almost as readily as α-methylmannopyranoside (normal α-methylmannoside). We have therefore been able to isolate considerable quantities of this new substance and have instituted a complete investigation of its properties.

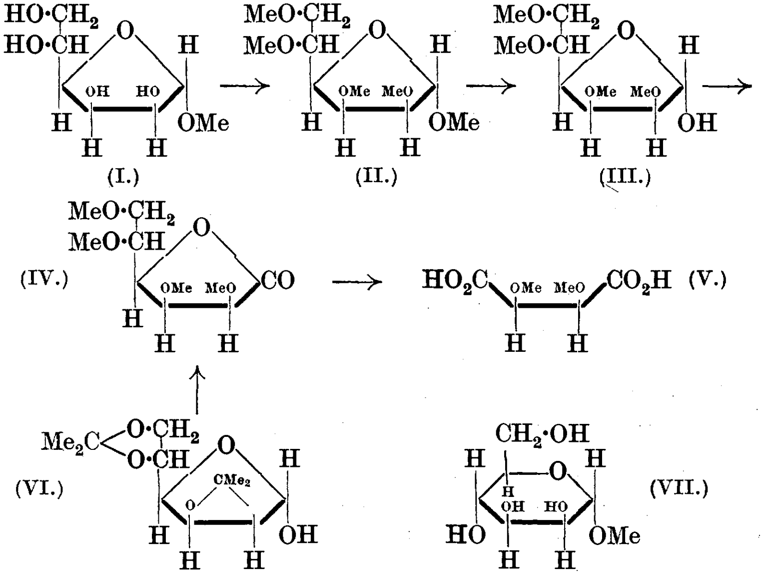
This novel variety of α-methylmannoside is shown to possess the five-atom ring constitution of a furanoside and it therefore falls into line, both in chemical behaviour and in structure, with other γ-sugar derivatives (compare Haworth and Porter, J., 1929, 2796, and earlier papers). It is hydrolysed completely to mannose on being heated at 100° during 2 hours with $N/100$-hydrochloric acid. The velocity coefficient was calculated to be $k = 0{\cdot}015$ (mins. and decimal logarithms), whereas the corresponding six-atom ring form or α-methylmannopyranoside shows a velocity coefficient $k = 0{\cdot}0002$

(Phelps and Hudson, *J. Amer. Chem. Soc.*, 1926, **48**, 503). The pyranoside is, indeed, little affected by heating for this period with acid of this dilution and requires many hours' heating at 100° even with *N*/10-acid for complete hydrolysis.

In contact with 15% alkali at 60° the α-methylmannofuranoside is unaffected during 1½ hours and is quantitatively recovered after this treatment. It may be handled and preserved in the laboratory without its undergoing any change and requires the observance of no special precautions.

α-Methylmannofuranoside (I) undergoes acetylation to give a crystalline *tetra-acetyl* derivative, which may be contrasted with the previously known three forms of tetra-acetyl methylmannoside (compare Dale, *J. Amer. Chem. Soc.*, 1924, **46**, 1050).

Methylation with methyl sulphate and alkali effects a quantitative conversion of (I) into the crystalline *tetramethyl α-methylmannofuranoside* (II). The tetramethyl derivative (II) is very slightly more stable than the initial unmethylated mannoside, and on being heated at 100° during 8 hours with *N*/100-hydrochloric acid it is completely transformed into the free methylated sugar, *tetramethyl mannofuranose* (III). Under identical conditions tetramethyl α-methylmannopyranoside undergoes little, if any, hydrolysis. Oxidation of (III) with bromine water yielded the crystalline



2 : 3 : 5 : 6-tetramethyl γ-mannonolactone (IV). This lactone had already been prepared from mannose-diacetone (VI) by Goodyear

and Haworth (J., 1927, 3136), who determined its structure by oxidative degradation to *i*-dimethoxysuccinic acid (V), identified through its crystalline ester or methylamide.

These experimental results furnish a proof of the constitution of the new α-methylmannofuranoside (I) and demonstrate the presence of a five-atom ring. From a parallel series of transformations the six-atom ring structure of α-methylmannopyranoside (normal α-methylmannoside) has been derived.

These observations are the more significant in view of the work of Irvine and Burt (J., 1924, **125**, 1343), who have recorded the isolation, by the same procedure that we have adopted, of a liquid specimen of γ-methylmannoside. They have ascribed to it exceptional properties. They reported that γ-methylmannoside has only a transient existence and undergoes spontaneous conversion into α-methylmannopyranoside (VII). We have found, on the contrary, that the γ-mannoside can be preserved indefinitely, without suffering any change. They also observed that γ-methylmannoside changes its ring structure during methylation and is partly converted into tetramethyl α-methylmannopyranoside. We differ from this view inasmuch as we have observed a quantitative conversion of the γ-mannoside (I) into its crystalline tetramethyl derivative (II) without ring displacement, either by means of methyl sulphate and alkali or of methyl iodide and silver oxide.

These discrepancies are traceable to the statement by Irvine and Burt that, in the initial condensation of mannose with methyl-alcoholic hydrogen chloride, "almost one-half of the sugar was recovered unchanged, the remainder being converted into the new γ-form of methylmannoside." By making this initial assumption they were led to a mistaken view of the nature of their products. As might have been deduced from general principles, this reaction does not give exclusively γ-methylmannosides. Apart from the unchanged mannose which is obtained, extraction of the neutralised product with ethyl acetate yields a mixture of at least four modifications of methylmannoside which were originally present in the acidified methyl-alcoholic solution before its neutralisation. The proportions of these in the neutralised product are not affected on its being kept, nor do the four under-mentioned mannosides undergo interconversion when they are individually isolated. As indicated in the experimental section, we have recovered from this ethyl acetate extract (*a*) crystalline α-methylmannopyranoside (VII), (*b*) the corresponding β-methylmannopyranoside (as its crystalline tetra-acetate), (*c*) crystalline α-methylmannofuranoside (the γ-mannoside), and have found evidence also of the presence of (*d*) β-methylmannofuranoside. A corresponding mixture is obtainable also by the method originally adopted by Fischer (*Ber.*, 1914, **47**, 1980) for the preparation of γ-methylglucoside, the latter furanoside forms being present along with the α- and β-glucopyranosides.

In view of these facts it is not surprising that preservation of Irvine and Burt's specimen of γ-methylmannoside led to the separation of crystalline α-methylmannopyranoside from the mixture, or that during subsequent conversions into the tetramethyl derivatives evidence of this pyranose form was repeatedly encountered. Their final product, when freed ultimately from this impurity as they suggest, must also have contained β-methylmannopyranoside.

Other discrepancies are : (1) the figures given for the rate of condensation of tetramethyl γ-mannose with acid methyl alcohol are at variance with those that we have recorded. A few of their figures for the earlier part of the reaction can be regarded as approximate, but only if their time intervals are read as *hours* and not as *minutes*. (2) Irvine and Burt record analytical figures for a " tetramethyl dimannose " which they isolated, but these are in agreement neither with the figures required for this compound nor for any closely related alternative.

The above-mentioned misconceptions have led to some confusion in another connexion. For instance, Hudson (*J. Amer. Chem. Soc.*, 1926, **48**, 1434) has been influenced by Irvine and Burt's observations in formulating his views on the ring structure of sugars.

EXPERIMENTAL.

Preparation of α-Methylmannofuranoside.—Mannose (10 g.) was dissolved by shaking in cold dry 1% methyl-alcoholic hydrogen chloride (200 c.c.). After 24 hours at 20°, the acid was neutralised with silver carbonate and the neutral solution was evaporated to dryness under diminished pressure in the presence of barium carbonate. The resultant syrup was extracted ten times with cold ethyl acetate by agitation on a mechanical shaker and the combined ethyl acetate extracts were evaporated under diminished pressure. A syrup remained which crystallised spontaneously once a nucleus of α-methylmannofuranoside (Haworth and Porter, preceding paper) had been introduced into the laboratory. Recrystallisation from methyl alcohol–ether gave pure α-methylmannofuranoside, m. p. 118—119°, $[\alpha]_D^{20^\circ}$ + 113° in water (*c*, 1·0). A mixed m. p. with a sample prepared by Haworth and Porter showed no depression. The yield of pure material (six times crystallised) was 4·5 g. from 15 g. of mannose. The mother-liquors from the crystallisations yielded a small quantity (0·2 g.) of α-methylmannopyranoside, m. p. 190°, $[\alpha]_D^{20^\circ}$ + 79° in water, and it is shown below that they contained also β-methylmannopyranoside.

Control experiments showed that departure from the conditions laid down above resulted in inferior yields of crystalline material. In particular, no advantage could be gained by using heavy concentrations of hydrogen chloride in the initial condensation.

Samples of crystalline α-methylmannofuranoside were kept for several months in an ordinary stoppered bottle in the laboratory. In no case was there any sign of transformation into the pyranose form (contrast Irvine and Burt, *loc. cit.*) and the m. p. and specific rotation remained unaltered.

Hydrolysis of α-Methylmannofuranoside with N/100-*Hydrochloric Acid.*—At 100° in *N*/100-aqueous hydrochloric acid, hydrolysis of α-methylmannofuranoside was complete in about 2 hours. The course of the reaction was followed polarimetrically :

t (mins.) ...	0	15	30	45	60	75	90	120	135
$[\alpha]_D^{20^\circ}$	+113°	72·3°	51·4°	35°	28°	22·6°	18·6°	15·6°	14·8° (constant)

From these figures the velocity coefficient for the unimolecular reaction at 100° was calculated to be $k = 0{\cdot}015$ (mins. and decimal logarithms).

Stability of α-Methylmannofuranoside in the Presence of Alkali.—In 15% aqueous sodium hydroxide solution α-methylmannofuranoside showed $[\alpha]_D^{20^\circ} + 86^\circ$. This value is lower than that observed for aqueous solutions and a similar difference was found in the case of α-methylmannopyranoside, which has $[\alpha]_D^{20^\circ} + 79^\circ$ in water and $[\alpha]_D^{20^\circ} + 69^\circ$ in 15% aqueous sodium hydroxide (c, 1·3).

The alkaline solution of α-methylmannofuranoside remained unaltered in rotation after being heated for 90 minutes at 60°. It was then neutralised by passing carbon dioxide through it and was afterwards evaporated to dryness. The residue was extracted with boiling alcohol, and after removal of the alcohol under diminished pressure the mixture of solid and syrup which remained was treated with boiling ethyl acetate. Evaporation of the latter left crystalline α-methylmannofuranoside (yield, almost quantitative), which after one recrystallisation from methyl alcohol and ether had m. p. 116°. A mixed m. p. with authentic α-methylmannofuranoside showed no depression.

Tetra-acetyl α-Methylmannofuranoside.—A solution of α-methylmannofuranoside (1 g.) in pyridine (8 c.c.) and acetic anhydride (10 c.c.) was kept at 0° for 2 days. It was then poured into water (100 c.c.) and the oil which separated was extracted with chloroform. The chloroform solution was shaken with sodium bicarbonate solution until neutral, washed with water, and evaporated under diminished pressure to a syrup, which still contained pyridine. This was removed by distillation in steam at 40°, after which the residue was dried at 40°/10 mm. for 3 hours, giving a syrup which resisted crystallisation. A small sample left on a watch-glass ultimately solidified and after inoculation with this the main portion crystallised completely (yield, 1·8 g.). Recrystallisation from aqueous alcohol gave *tetra-acetyl α-methylmannofuranoside* as colourless needles, m. p. 63°, $[\alpha]_D^{19^\circ}$ + 107° in chloroform (*c*, 1·0). This substance was non-reducing and was soluble in acetone, ether, alcohol, and chloroform, slightly soluble in water and almost insoluble in light petroleum (b. p. 60—80°) (Found : C, 49·9; H, 6·4; OMe, 8·6; CH_3·CO, 48·0. $C_{15}H_{22}O_{10}$ requires C, 49·7; H, 6·1; OMe, 8·6; CH_3·CO, 47·5%). The m. p. of tetra-acetyl α-methylpyranoside is also 63°, but in admixture with tetra-acetyl α-methylfuranoside the m. p. was depressed to 40—45°.

Acetylation of the Syrupy Residues obtained during the Preparation of α-Methylmannofuranoside.—The mother-liquors from the crystallisation of α-methylmannofuranoside were evaporated to dryness under diminished pressure and the syrup which remained was acetylated with pyridine and acetic anhydride in the manner already described. The product was a syrup from which crystalline material separated on the addition of ether. This solid substance (0·4 g. from 15 g. of mannose) after recrystallisation from absolute alcohol showed m. p. 156°, alone or when mixed with tetra-acetyl β-methylmannopyranoside. It follows, therefore, that the ethyl acetate extract of the syrup obtained by condensing mannose with cold methyl-alcoholic hydrogen chloride contained β-methylmannofuranoside in addition to α-methylmannofuranoside and α-methylmannopyranoside.

After removal of tetra-acetyl β-methylmannopyranoside an uncrystallisable syrup remained which probably consisted mainly of tetra-acetyl β-methylmannofuranoside.

Preparation of Tetramethyl α-Methylmannofuranoside.—(a) *By means of methyl sulphate.* A solution of α-methylmannofuranoside (3 g.) in acetone (30 c.c.) and water (10 c.c.) was rendered slightly alkaline and treated at 50—55° with methyl sulphate (40 c.c.) and 30% aqueous sodium hydroxide (70 c.c.), care being taken to avoid the development of acidity. The product (3·6 g.), after remethylation in acetone solution by methyl sulphate (20 c.c.) and 30% aqueous sodium hydroxide (35 c.c.), was distilled, giving *tetramethyl α-methylfuranoside* (3·2 g.) as a colourless oil, b. p. about 120°/0·23 mm., which solidified completely. $[\alpha]_D^{22^\circ}$ + 97° in water (*c*, 1·0). After recrystallisation from light petroleum (b. p. 40—60°), the substance had m. p. 24°, $[\alpha]_D^{19^\circ}$ + 98·6° in water (*c*, 1·0), $[\alpha]_D^{22^\circ}$ + 65°, equilibrium rotation in 1% methyl-alcoholic hydrogen chloride (Found : C, 53·0; H, 8·9; OMe, 59·5. $C_{11}H_{22}O_6$ requires C, 52·8; H, 8·8; OMe, 62·0%).

(b) *By means of silver oxide and methyl iodide.* A solution of α-methylmannofuranoside (3 g.) in methyl alcohol (15 c.c.) was treated in the usual way with methyl iodide (40 c.c.) and silver oxide (20 g.). The product was soluble in methyl iodide and after three further treatments with methyl iodide and silver oxide the methylation was complete. The final product was a syrup which gave on distillation tetramethyl α-methylmannofuranoside (3·3 g.), b. p. about 90°/0·05 mm., $n_D^{16°}$ 1·4441, $[\alpha]_D^{20°} + 98°$ in water (c, 4·0). This solidified completely when cooled in the ice-chest. Recrystallisation from light petroleum gave needles, m. p. 24° alone or when mixed with the material described above; $[\alpha]_D^{19°} + 99°$ in water.

A mixture of tetramethyl α-methylmannofuranoside, m. p. 24°, and tetramethyl α-methylmannopyranoside, m. p. 37°, had so low a m. p. that it was liquid at 5°. The two substances were further differentiated by comparing their rates of hydrolysis by N/100-hydrochloric acid at 100°. The furanose derivative was completely hydrolysed in about 8 hours, whereas the pyranose derivative was scarcely affected under these conditions. The following polarimetric observations were made during the hydrolysis of tetramethyl α-methylmannofuranoside prepared by method (a):

t (mins.)	0	30	60	120	180	240	330	390	480
$[\alpha]_D^{20°}$	+97·6°	89·2°	82·7°	72·0°	62·0°	55·5°	49·2°	43·6°	42·7° (constant)

A similar experiment was carried out with material made by method (b). Hydrolysis was complete in about 8 hours and the polarimetric observations were in exact agreement with those just given.

Tetramethyl Mannofuranose.—A solution of tetramethyl α-methylfuranoside (2 g.) in N/100-aqueous hydrochloric acid (50 c.c.) was heated on the water-bath until the specific rotation reached the constant value $[\alpha]_D^{20°} + 43°$ (8 hours). After neutralisation with barium carbonate the solution was evaporated to dryness under diminished pressure and the product was extracted with boiling ether. Removal of the ether left a syrup which on distillation gave *tetramethyl mannofuranose* as a colourless liquid (1·3 g.), b. p. 124°/0·1 mm., $n_D^{15°}$ 1·4532, $[\alpha]_D^{21°} + 39°$, initial value in water (c, 0·54). After 10 minutes, mutarotation was complete and the final equilibrium rotation was $[\alpha]_D^{22°} + 43°$; $[\alpha]_D^{22°} + 37°$ in methyl alcohol (c, 0·86) (Found: C, 50·7; H, 8·7; OMe, 51·7. $C_{10}H_{20}O_6$ requires C, 50·8; H, 8·5; OMe, 52·5%).

The still residue (0·2 g.) deposited a minute quantity of crystalline material which will be the subject of further investigation in view of the known tendency of furanose compounds to undergo autocondensation.

Tetramethyl mannofuranose condensed readily with cold methyl alcohol containing 0·25% of hydrogen chloride. The initial specific rotation, $[\alpha]_D^{22°}$ + 35° (c, 0·81) changed to 31° after 2 minutes, 28° (14 mins.), 22° (36 mins.), 13·5° (1 hour), 3·7° (1½ hours), —2·5° (2¼ hours), + 6° (15 hours), + 12° (17 hours), + 20° (21 hours), + 31° (25 hours), 45° (40 hours), 59° (60 hours), 63° (88 hours), 67° (final constant value after 120 hours, calc. as tetramethyl methylmannofuranoside). The final value is in excellent agreement with that given above for the equilibrium mixture of the α- and β-forms of tetramethyl methylmannofuranoside (+ 65°). The observations during the earlier stages of the condensation are in agreement with those of Irvine and Burt only if their times are read in hours instead of in minutes. The slower rate of reaction towards the end of the condensation and the lower value of the final rotation recorded by these authors indicate that their product was impure.

Oxidation of Tetramethyl Mannofuranose.—Tetramethyl mannofuranose (1·1 g.), dissolved in water (20 c.c.), was treated with bromine (1·5 c.c.) for 3 days at 35°. The reducing action had then disappeared. After removal of the bromine by aeration the solution was neutralised with silver oxide. Charcoal was added to remove colloidal silver and the solution was then filtered. The dissolved silver was next removed by titration with $N/2$-aqueous hydrochloric acid and on evaporation of the water under diminished pressure crystalline tetramethyl γ-mannonolactone was obtained (yield, 1·0 g.) which was identical with the lactone previously described by Goodyear and Haworth (*loc. cit.*). After recrystallisation from ether and light petroleum it had m. p. 108°, alone or when mixed with an authentic specimen of tetramethyl γ-mannonolactone, $[\alpha]_D^{20°}$ + 65°, initial value in water (c, 0·87).

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