319. *Crystalline α-Methylglucofuranoside (γ-Methylglucoside) and its Derivatives.*

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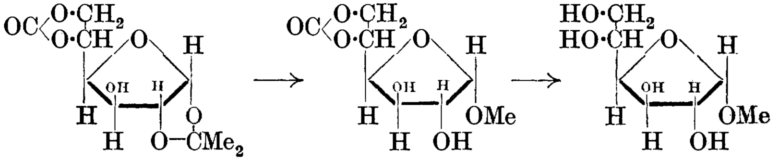
IN continuation of our work on the five-atom ring or γ-forms of sugars, crystalline *α-methylglucofuranoside* (I) has now been isolated. This result has been attained by utilising the reaction of Haworth and Porter (J., 1929, 2796) wherein glucose condenses with carbonyl chloride and acetone to yield glucofuranose-acetone carbonate (III). This, in contact with methyl-alcoholic hydrogen chloride, gives rise to the crystalline *α-methylglucofuranoside* 5 : 6-*carbonate* (II). The subsequent changes are illustrated by the formulæ :



(III.) (II.) (I.)

The corresponding β-methylglucofuranoside has also been obtained but has not yet crystallised. In the original preparation of the γ-methylglucoside as a liquid (E. Fischer, *Ber.*, 1914, **47**, 1980) both of these components were present as a mixture and usually the product is also contaminated with small amounts of the corresponding pyranosides. The β-form of (II) was previously obtained as a crystalline substance by Haworth and Porter, and the success of the present work has followed on the separation of both forms, and also of their diacetates, as crystalline individuals.

The structure of α-methylglucofuranoside is determined by its methylation to the 2 : 3 : 5 : 6-*tetramethyl α-methylglucofuranoside*, which is also crystalline at low temperature. This gave tetramethyl glucofuranose on hydrolysis, and the same sugar has also been obtained from β-ethylglucofuranoside. Its oxidation to crystalline tetramethyl γ-gluconolactone, and the formation of the crystalline phenylhydrazide of the corresponding acid, enabled us definitely to allocate the five-atom ring structure to this series of substances.

It is important to observe the differing rates of hydrolysis of the glucofuranosides as compared with the corresponding pyranosides. The reaction velocities given in the experimental section may be compared with those of other glycosides which have been tabulated (Haworth, *Ber.*, 1932, *A*, 4, 50). α-Methylglucofuranoside does not appear to undergo hydrolysis with either maltase or emulsin. α-Ethylglucofuranoside, β-ethylglucofuranoside, and α-methylmannofuranoside are devoid of action towards these enzyme preparations. Of equal interest is the fact that α-methylglucofuranoside is not acted on by invertase.

With the experience gained in the isolation of homogeneous specimens of crystalline furanosides, opportunity has been taken to prepare in larger quantity those representatives of this group which we have described in earlier publications. These have been submitted to many recrystallisations and the optical values determined in solutions of higher concentration than formerly. The modifications in the specific rotation values are very slight and are tabulated here along with those of the products now described for the first time :

	$[\alpha]_D$ (in water).		$[\alpha]_D$ (in water).
α-Methylglucofuranoside	+118°	α-Methylmannofuranoside	+109°
α-Ethylglucofuranoside	+101	β-Ethylglucofuranoside	− 86

We are engaged upon the attempted isolation of the pure galactofuranosides, since the earlier attempt (Haworth, Ruell, and Westgarth, J., 1924, **125**, 2468) by the use of Fischer's methods led to the formation of a liquid mixture of galactofuranosides which we now regard as not entirely free from pyranosides.

It is important to emphasise that the crystalline furanosides are reasonably stable to neutral aqueous permanganate, and therefore this supposed test for the presence of " γ-glycosides " no longer holds. As formerly employed, this reagent merely oxidised away unsaturated impurities such as derivatives of furfuraldehyde, to which furanosides are prone to give rise.

EXPERIMENTAL.

α-Methylglucofuranoside 5 : 6-Monocarbonate.—The residues from the prep. of β-methylglucofuranoside 5 : 6-monocarbonate (m. p. 145°) (Haworth and Porter, *loc. cit.*) deposited crystals, m. p. 100—105°, $[\alpha]_D + 65°$ (in MeOH). Recrystn. from MeOH and AcOEt alternately gave colourless crystals, m. p. 130°, $[\alpha]_D^{23°} + 130°$ (*c*, 0·6 in MeOH) (Found: C, 43·6; H, 5·7; OMe, 13·2. Calc. for $C_8H_{12}O_7$: C, 43·6; H, 5·6; OMe, 14·1%). The substance was devoid of action with Fehling's solution. On gentle warming with *N*/10-HCl it reduced Fehling's solution actively. It reacted readily with $Ba(OH)_2$ to give $BaCO_3$, and its properties were in agreement with the constitution indicated at the head of this paragraph. An alternative method of prepn. is given below from the diacetate.

2 : 3-*Diacetyl α- and β-Methylglucofuranoside 5 : 6-Monocarbonate.*—Repetitions of the preceding expt. are not always successful unless specially dried MeOH is employed in the original conversion of glucose-acetone carbonate into the methylglucofuranoside monocarbonate. Occasionally a mixture (constant m. p. 106—107°) of α- and β-methylglucofuranoside 5 : 6-monocarbonates is obtained, $[\alpha]_D + 45°$. On acetylation (Ac_2O and pyridine at 60°, 2 hrs.) this gave very readily, after pouring into H_2O, the β-form of the diacetyl compound, m. p. 164° (from Me_2CO–MeOH), prisms 4—5 mm. long, $[\alpha]_D^{18°} - 41°$ (*c*, 1·5 in Me_2CO). From the aq.-pyridine liquors of the original acetylation the α-compound was isolated, m. p. 110—111° (from Me_2CO–MeOH), $[\alpha]_D^{18°} + 148°$ (*c*, 0·5 in Me_2CO) [Found: (for α-form) C, 47·1; H, 5·6; OMe, 9·8: (for β-form) C, 47·1; H, 5·65; OMe, 9·9. Calc. for $C_{12}H_{16}O_9$: C, 47·4; H, 5·3; OMe, 10·2%].

α-Methylglucofuranoside.—Treatment at 60° of the above 2 : 3-diacetyl α-methylglucofuranoside 5 : 6-monocarbonate with a slight excess of *N*/3-$Ba(OH)_2$ eliminated both acetyl groups and the carbonate residue. The excess of $Ba(OH)_2$ was removed by CO_2, and the filtrate, evaporated under diminished press., gave a residue which, extractable with hot AcOEt, furnished cryst. *α-methylglucofuranoside* in almost theo. yield and free from syrup. From AcOEt the purified substance is obtained as rosettes of colourless needles, m. p. 62—63°, $[\alpha]_D^{23°} + 136°$ (*c*, 0·95 in MeOH), $[\alpha]_D^{20°} + 118°$ (*c*, 4·5 in H_2O) (Found: C, 43·1; H, 7·3; OMe, 16·3. $C_7H_{14}O_6$ requires C, 43·2; H, 7·2; OMe, 15·9%). Similarly α-methylglucofuranoside 5 : 6-monocarbonate in contact with a slight excess of $Ba(OH)_2$ gave an immediate ppt. of $BaCO_3$ and after an hr. CO_2 was admitted. The filtrate, evaporated at 50°, gave by extraction with hot AcOEt a quantitative yield of α-methylglucofuranoside which crystallised completely. Its properties were identical with the above. It does not reduce Fehling's solution, but after ½ min. at 20° in contact with *N*-HCl the substance reduces it actively.

α-Methylglucofuranoside did not appear to suffer hydrolysis at 33° after 16 hrs.' contact of 1% aqueous solutions with zymin or emulsin, whilst in control expts. α-methylglucopyranoside was largely hydrolysed by the zymin and β-methylglucopyranoside by the emulsin preps. *Hydrolysis.* With *N*/100-HCl at 95—100°, α-methylglucofuranoside underwent hydrolysis and showed the polarimetric changes: $[\alpha]_D + 104°$ (after 2 mins.), 95° (4 mins.), 86·5° (6 mins.), 82·5° (8 mins.), 78° (11 mins.), 67° (15 mins.), 57° (21 mins.), 51·5° (28 mins.), 50·5° (37 mins.). The figures when plotted give a smooth logarithmic curve; $k_{\text{base }10} \times 10^5 = 4500$. The product is then ordinary glucose.

The rate of hydrolysis of α-methylglucofuranoside by 0·01 N-HCl at 55—60° was observed in a jacketed polarimeter tube and compared with that of α- and of β-ethylglucofuranoside :

	$k_{\text{base } e}$.	$k_{\text{base } 10} \times 10^5$.
α-Methylglucofuranoside	0·0077	335
α-Ethylglucofuranoside	0·0230	1000
β-Ethylglucofuranoside	0·0124	524

β-Methylglucofuranoside.—A highly pure specimen of 2 : 3-diacetyl β-methylglucofuranoside 5 : 6-monocarbonate was submitted to the action of $Ba(OH)_2$ as described in a preceding paragraph for the α-isomeride. This reagent gave rise to β-methylglucofuranoside, isolated as a syrup which, although chemically pure, has not up to the present been crystallised. It showed approximately $[\alpha]_D^{20°}$ − 77° (in H_2O).

2 : 3 : 5 : 6-*Tetramethyl α-Methylglucofuranoside.*—Methylation of α-methylglucofuranoside under the usual conditions gave the cryst. *tetramethyl* derivative, m. p. 11° (recryst. from light petroleum), b. p. 94°/0·04 mm., $n_D^{13°}$ 1·4457; $[\alpha]_D^{18°}$ + 106·5° (c, 1·2 in MeOH), + 102° (c, 1·5 in $CHCl_3$), + 107° (c, 0·7 in H_2O) (Found : C, 53·1; H, 9·0; OMe, 61·2. $C_{11}H_{22}O_6$ requires C, 52·8; H, 8·9; OMe, 62·1%).

Heated with 0·5% methyl-alc. HCl, the substance attained an equilibrium rotation, $[\alpha]_D$ − 33°, representing a mixture of α- and β-forms.

Hydrolysis occurred at 95—100° with N/100-HCl. The polarimetric readings were $[\alpha]_D$ + 101·5° (after 2 mins.), 82·1° (7 mins.), 64·4° (12 mins.), 38° (23 mins.), 22·8° (35 mins.), 2·5° (50 mins.), − 6·2° (70 mins.), − 12·9° (107 mins.). From more complete data the reaction velocity was calculated : $k_{\text{base } 10} \times 10^5 = 1500$.

2 : 3 : 5 : 6-Tetramethyl glucofuranose, isolated from the neutralised aq. solutions, had the same properties as those described in a later paragraph, and was oxidised by Br aq. to give cryst. tetramethyl γ-gluconolactone.

Methylation of β-Ethylglucofuranoside 5 : 6-*Monocarbonate.*—This compound (Haworth and Porter, *loc. cit.*) was methylated, in 50% Me_2CO–H_2O solution, with Me_2SO_4 and alkali under the usual conditions, and finally with Purdie's reagents. The product, 2 : 3 : 5 : 6-*tetramethyl β-ethylglucofuranoside*, distilled at a bath temp. of 118—120°/0·1 mm. as a colourless liquid, n_D 1·4425; $[\alpha]_D^{21°}$ − 71° (c, 0·9 in H_2O), − 69° (c, 1·1 in MeOH), − 76° (c, 0·9 in $CHCl_3$) [Found : C, 54·6; H, 9·4; OR (calc. as OMe), 56·7. $C_{12}H_{24}O_6$ requires C, 54·5; H, 9·1; OR (calc. as OMe), 58·8%].

Its hydrolysis with 0·01N-HCl at 95—100° was complete after 140 mins. and the approximate velocity constant, $k_{\text{base } 10} \times 10^5 = 1900$, was calculated from the polarimetric readings.

2 : 3 : 5 : 6-*Tetramethyl glucofuranose* was isolated (92% yield) from the above reaction as a colourless liquid distilling (bath temp.) at 130°/0·01 mm., $n_D^{16°}$ 1·4564; $[\alpha]_D^{20°}$ − 7·6° (c, 0·9 in H_2O), − 21° (c, 0·8 in MeOH) (Found : C, 50·8; H, 8·7; OMe, 51·1. $C_{10}H_{20}O_6$ requires C, 50·8; H, 8·5; OMe, 52·6%).

Oxidation to tetramethyl γ-gluconolactone was effected in the usual manner with Br and gave almost quantitatively the lactone, m. p. 26° (Drew, Goodyear, and Haworth, J., 1927, 1237), which yielded the characteristic phenylhydrazide, m. p. 135°.

α-Ethylglucofuranoside 5 : 6-*Carbonate.*—The mother-liquors from the prep. of β-ethylglucofuranoside carbonate contained the corresponding α-form, and a syrupy material consisting probably of the dicarbonate of a disaccharide.

The α-ethylglucofuranoside carbonate required considerable purification, as it was the more sol. form. 3·7 G. were fractionally crystallised from AcOEt or EtOH and 0·7 g. was obtained, m. p. 138—140°; $[\alpha]_{5461}^{17^\circ}$ + 133°, $[\alpha]_{5780}^{17^\circ}$ + 120°, $[\alpha]_{D}^{17^\circ}$ + 117° (in EtOH, $c = 1 \cdot 1$). In the last recrystn. a very small head fraction was separated, and this showed the same rotation as the main fraction. The α-glucoside carbonate separated from fairly conc. solutions in EtOH or AcOEt as felted masses, but could be obtained as hard prisms. On treatment with $Ba(OH)_2$ it gave α-ethylglucofuranoside of correct m. p. and rotation (see below).

In order to make certain that the ethylglucoside carbonates were α- and β-forms, each was treated with alc. HCl ($N/20$) on the boiling water-bath and the progress of the change was followed polarimetrically. Exactly the same final equilibrium rotation, $[\alpha]_{D}^{18^\circ}$ − 8°, was obtained from both forms, each of which was afterwards recovered (cryst.) from the equilibrium mixtures.

2 : 3-*Diacetyl α-Ethylglucofuranoside* 5 : 6-*Carbonate.*—This has now been prepared in larger quantity (cf. Haworth and Porter, *loc. cit.*) and recrystallised successsively from aq. EtOH, abs. EtOH, and EtOH–Me_2CO. The m. p. originally given (159—160°) was not altered, but the rotation was enhanced : $[\alpha]_{D}^{23^\circ}$ + 143^2 (*c*, 1·74 in Me_2CO), $[\alpha]_{5780}^{23^\circ}$ + 149°, $[\alpha]_{5461}^{23^\circ}$ + 163°. The substance was sparingly sol. in EtOH. Removal of the acetyl and carbonate groups under the conditions already described gave the cryst. α-ethylglucofuranoside, which was recrystallised seven times from different solvents and the following specific rotations observed: $[\alpha]_{D}^{18^\circ}$ + 101°, $[\alpha]_{5780}^{18^\circ}$ + 107°, $[\alpha]_{5461}^{18^\circ}$ + 119° (*c*, 1·64 in H_2O); $[\alpha]_{D}^{18}$ + 123°, $[\alpha]_{5780}^{18^\circ}$ + 128°, $[\alpha]_{5461}^{18^\circ}$ + 142° (*c*, 1·95 in EtOH).

β-Ethylglucofuranoside was prepared in larger quantity and repeatedly recrystallised from mixtures of four different solvents and the following values are given: $[\alpha]_{D}^{18^\circ}$ − 86°, $[\alpha]_{5780}^{18^\circ}$ − 92°, $[\alpha]_{5461}^{18^\circ}$ − 101° (*c*, 1·9 in H_2O); $[\alpha]_{D}^{18^\circ}$ −96°, $[\alpha]_{5780}^{18^\circ}$ − 100°, $[\alpha]_{5461}^{18^\circ}$ − 110° (*c*, 3·12 in EtOH).

The authors are indebted to the Department of Scientific and Industrial Research for a grant.

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