65. *Furanose and Pyranose Derivatives of Glucurone.*

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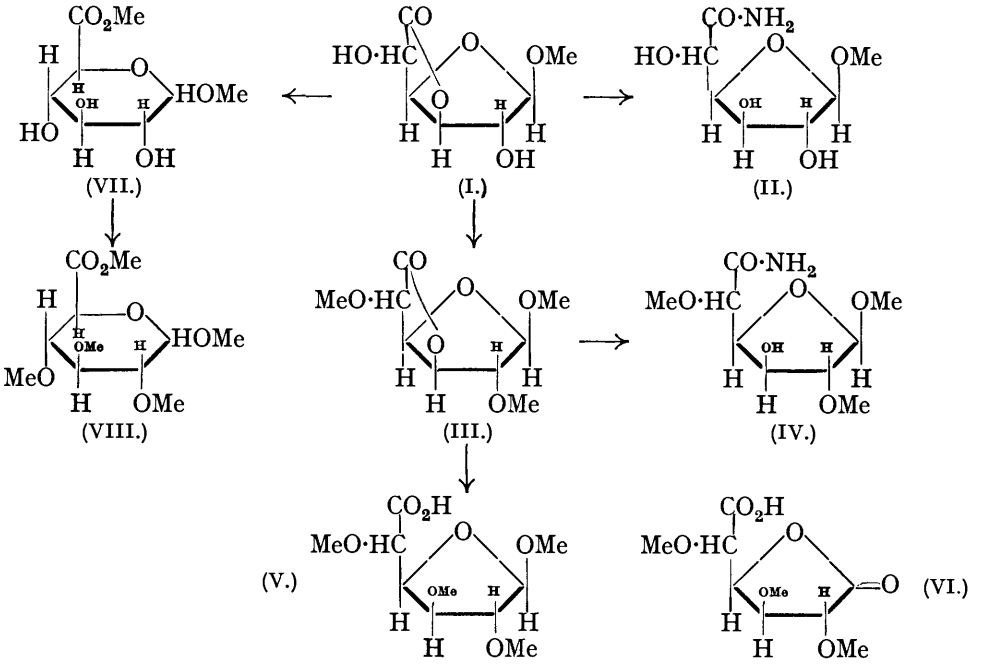
A new derivative of methylglucopyruronoside is described and, in addition, derivatives of glucurone which have a furanose ring have been prepared. Glucurone (glucuronolactone) has been converted into the crystalline *γ-lactone* of β-*methylglucofururonoside* (I), the structure of which is proved by complete methylation, oxidation, and esterification to give the methyl ester of 2 : 3 : 5-trimethyl saccharolactone. From (I) has been prepared the *methyl* ester of *methylglucopyruronoside* (VII), which on complete methylation gives the methyl ester of 2 : 3 : 4-trimethyl methylglucuronoside (VIII). Crystalline 1 : 2-*monoacetone glucofururonolactone* (IX) has been obtained from glucuronolactone and also from 1 : 2-monoacetone glucofururonic acid (X) and it has been converted into the crystalline *amide* (XI); the latter has been prepared also from (X).

The discovery of the presence of uronic acid residues in many polysaccharides of both plant and animal origin has awakened interest in the possibility of preparing derivatives of uronic acids which would be of value as synthetic agents. For this purpose it is sometimes desirable that such derivatives should be of the incompletely substituted type, in order that condensation with other compounds may take place through the remaining hydroxyl groups. Hitherto, all such products have been of the pyranose form; the

present communication is concerned with the formation of derivatives of glucuronolactone (glucurone) in which the sugar ring is of the furanose type.

The action of cold acid methyl alcohol on glucuronolactone led to the formation of a crystalline compound with the empirical formula $C_7H_{10}O_6$, containing one methoxyl group. Under the conditions of the reaction, the introduction of such a residue would be expected to occur only at the reducing carbon atom, C_1, with the formation of a glycoside, or at C_6 with the formation of an ester. Either view is supported by the fact that hydrolysis of the substance with hot dilute acid regenerated glucurone.



A methyl ester formed from glucurone would have the composition represented by the formula $C_7H_{12}O_7$ and it was evident, therefore, that the product was not an ester, a view which was substantiated by the stability of the methoxyl group towards hot alkali. By the following procedure the compound was shown to be the *γ-lactone* of β-*methyl-glucofururonoside* (I).

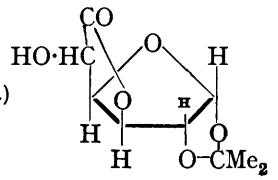
Methylation of (I) with Purdie's reagents gave the *γ-lactone* of 2 : 5-*dimethyl* β-*methyl-glucofururonoside* (III), which was converted with methyl-alcoholic ammonia into the crystalline *amide* (IV). Further methylation of (III) with methyl sulphate yielded 2 : 3 : 5-*trimethyl methylglucofururonoside* (V). Scission of the glycosidic methyl group, followed by oxidation with bromine, resulted in the formation of 2 : 3 : 5-trimethyl saccharolactone (VI), which on esterification gave the crystalline methyl ester of 2 : 3 : 5-trimethyl saccharolactone, identical with a specimen prepared by F. Smith (unpublished work). Furthermore, (I) was converted into a liquid *amide* (II), which gave a positive Weerman reaction for α-hydroxy-amides, thus providing additional evidence of the presence of a hydroxyl group at C_5.

These observations showed clearly that (I) was in the furanose form, and rotational evidence suggested that the β-configuration should be assigned to the compound. In aqueous solution, (I) was neutral to litmus and showed no mutarotation, the behaviour in this respect resembling that of glucuronolactone. Titration with cold alkali followed the usual course for a γ-lactone, but the amount taken up was in excess of one equivalent. Furthermore, a reducing action was apparent when (I) was added to boiling Fehling's solution. An explanation of these anomalies is to be found in the presence of two five-membered rings in the molecule, since it is known that sugars containing double ring

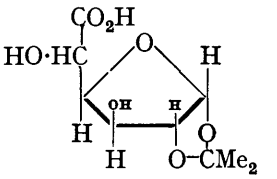
systems readily give rise to unsaturated products which are responsible for the reducing power in alkaline solution (Smith, *Chem. and Ind.*, 1938, **57**, 450). In support of this theory, it was found that, whereas in aqueous solution no absorption band could be detected, in dilute alkali bands were observed at λ 2790 and λ 4160 A.

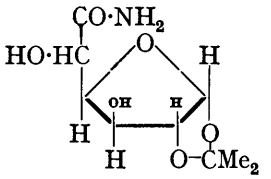
When the crystalline compound (I) was boiled with acid methyl alcohol, there was obtained a liquid dimethyl derivative of glucuronic acid which was non-reducing and behaved as an ester, reacting with one equivalent of alkali and simultaneously losing one methoxyl group. It was shown that the treatment with hot acid methyl alcohol had brought about a ring change from furanose to pyranose and the liquid product was the *methyl* ester of *methylglucopyruronoside* (VII). Methylation with Purdie's reagents yielded the methyl ester of 2 : 3 : 4-trimethyl methylglucuronoside (VIII), which was identified by conversion into the crystalline amide of 2 : 3 : 4-trimethyl α-methylglucuronoside (Smith, J., 1939, 1724).

(IX.)

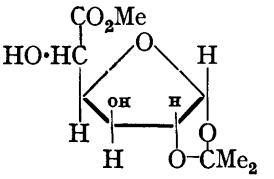


(X.)

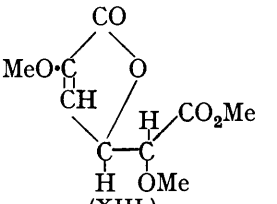




(XI.)



(XII.)



(XIII.)

A derivative analogous to (I) with respect to ring form was prepared when glucuronolactone was condensed with acetone in the presence of sulphuric acid, the crystalline product being 1 : 2-*monoacetone glucofururono-γ-lactone* (IX). The furanose structure of this derivative was indicated in that it was possible to prepare it by the lactonisation in a high vacuum of the 1 : 2-monoacetone glucofururonic acid (X) of Zervas and Sessler (*Ber.*, 1933, **66**, 1326). The latter acid is described as a furanose derivative because it is derived from 1 : 2-monoacetone glucofuranose. Additional proof of the structure of (IX) was afforded by the conversion of both the lactone (IX) and the methyl ester (XII) into crystalline 1 : 2-monoacetone glucofururonamide (XI). This amide gave a positive Weerman test for α-hydroxy-amides, indicating the presence of a hydroxyl group at C_5.

In aqueous solution (IX) was neutral to litmus and exhibited no mutarotation; reaction with cold aqueous alkali was slow, and, as in the case of (I), a stoicheiometric relationship was not observed. Furthermore, iodoform was produced by the action of alkaline hypoiodite on (IX) and a reducing action was observed when the compound was added to boiling Fehling's solution. In aqueous solution, no absorption band could be detected but in dilute alkali bands were present at λ 2790 and λ 4100 A.

Methylation of (IX) with Purdie's reagents gave the methyl ester of 2 : 5-dimethyl 2 : 3-dehydrosaccharolactone (XIII) identical with the trimethyl glucuralone described by Pryde and Williams (*Biochem. J.*, 1933, **27**, 1205; compare Pryde and Griffiths, *Chem. and Ind.*, 1938, **57**, 601), the structure of which has been proved by Schmidt, Dippold, and Zeiser (*Ber.*, 1937, **70**, 2402) and by Smith (*Chem. and Ind.*, 1938, **57**, 450). It is evident, therefore, that the unusual properties of (I) and (IX) are due to reactions involving the formation of unsaturated compounds.

Subsequent to the completion of this work in 1939, there has appeared a paper by R. E. Reeves (*J. Amer. Chem. Soc.*, 1940, **62**, 1616), who has demonstrated that the crystalline trimethyl glucurone of Pryde and Williams (*loc. cit.*) has a furanoside and not a pyranoside structure and is, in fact, the γ-lactone of 2 : 5-dimethyl α-methylgluco-

fururonoside. It is claimed that treatment of this substance with methyl-alcoholic hydrogen chloride in the cold brings about its conversion into the isomeric β-form, which should be identical with our product (III). Reeves' substance is, however, crystalline (m. p. 90—91°), whereas ours is a syrup, giving a crystalline amide, m. p. 95°.

Experimental.

γ-Lactone of β-Methylglucofururonoside (I). —Glucuronolactone (1 g.) was dissolved in ½% methyl-alcoholic hydrogen chloride (50 c.c.) and kept at room temperature for 3 days. After neutralisation with silver carbonate, the solution was filtered and evaporated under reduced pressure, and the product recrystallised from alcohol–ether. The *γ-lactone* of *β-methylglucofururonoside* (I) (yield, 0·4 g.) formed colourless prisms, m. p. 139°, $[\alpha]_D^{18°}$ — 57° (*c*, 0·4 in water, unchanged after 48 hours). It was readily soluble in acetone, alcohol, and water, sparingly soluble in ether, and insoluble in light petroleum (Found: C, 44·4; H, 5·5; OMe, 15·5. $C_7H_{10}O_6$ requires C, 44·2; H, 5·3; OMe, 16·3%). On the addition of a small crystal to boiling Fehling's solution, reduction occurred.

The compound (22·12 mg.) in 0·3N-barium hydroxide (3 c.c.) was kept at 60° for 30 minutes. After neutralisation with carbon dioxide and evaporation to dryness, the residue gave silver iodide (18·73 mg.) when an estimation of methoxyl content was carried out. This figure corresponded to OMe 11·2%, calculated on the weight of (I) taken. Slight decomposition had evidently occurred.

Titration of (I) with 0·1N-sodium hydroxide followed the usual course for a γ-lactone, the neutralisation being slow. The equivalent estimated by this method varied with the time allowed for the reaction (Found: 130—150. $C_7H_{10}O_6$ requires equiv., 190).

In aqueous solution (*c*, 0·02) no absorption band could be detected, but on the addition of dilute alkali solution a yellow colour was developed, and absorption bands were present at λ 2790 (ε, 8300) and λ 4160 A. (ε, 8300). After a short time the colour faded and the solution then exhibited a band only at λ 2790 A. The latter disappeared on acidification, but returned when the solution was again made alkaline.

A solution of (I) (50 mg.) in 0·1N-sulphuric acid (50 c.c.) was heated at 90°, the hydrolysis being followed polarimetrically: $[\alpha]_D^{20°}$ — 56° (initial value); — 15° (1 hour); + 19° (3 hours); + 27° (5 hours); + 30° (9 hours). The cooled solution was neutralised with barium carbonate, filtered, treated with a slight deficiency of dilute sulphuric acid, again filtered, and evaporated to dryness under reduced pressure. Extraction of the residue with boiling ethyl acetate gave, after removal of the solvent, crystalline glucuronolactone (28 mg.), m. p. 173° (Found: OMe, nil; equiv. by titration, 171. Calc. for $C_6H_8O_6$: equiv., 176).

The *amide* of *β-methylglucofururonoside* (II) was prepared from (I) (50 mg.) by treatment at 0° with methyl-alcoholic ammonia. The product, a colourless syrup (Found: OMe, 14·7. $C_7H_{13}O_6N$ requires OMe, 15·0%), gave a positive Weerman reaction, hydrazodicarbonamide, m. p. and mixed m. p. 257°, being isolated in good yield.

γ-Lactone of 2 : 5-Dimethyl β-Methylglucofururonoside (III).—(I) (0·2 g.), dissolved in acetone (5 c.c.), was methylated with silver oxide and methyl iodide; the product, which was soluble in methyl iodide, was submitted to two further methylations and then distilled as a colourless syrup (0·14 g.), b. p. (bath temp.) 130—150°/0·01 mm., $n_D^{18°}$ 1·4685 (Found: OMe, 44·6. $C_9H_{14}O_6$ requires OMe, 42·2%). The distillate thus contained a small proportion of a substance of high methoxyl content, probably the methyl ester of 2 : 3 : 5-trimethyl β-methylglucofururonoside. Purification was accomplished by treating the mixture for 20 minutes with a slight excess of cold 0·3N-barium hydroxide, after which any ester present was removed by three extractions with small quantities of chloroform; the *lactone* (III) was then regenerated from the aqueous solution of the barium salt in the usual way. It distilled as a colourless syrup (80 mg.), b. p. (bath temp.) 150°/0·01 mm., $n_D^{18°}$ 1·4732 (Found: OMe, 42·1%). Treatment with methyl-alcoholic ammonia at 0° for 24 hours gave the *amide* of 2 : 5-*dimethyl* β-*methylglucofururonoside* (IV), which crystallised from acetone–ether–light petroleum in plates, m. p. 95° (Found: N, 6·35; OMe, 39·8. $C_9H_{17}O_6N$ requires N, 6·0; OMe, 39·9%).

Formation of 2 : 3 : 5-Trimethyl Saccharolactone Methyl Ester.—The γ-lactone of 2 : 5-dimethyl β-methylglucofururonoside (0·4 g.) (OMe, 44·6%), containing a small quantity of ester (see above), dissolved in water (10 c.c.) and acetone (10 c.c.), was methylated at 40° with methyl sulphate (15 c.c.) and 30% sodium hydroxide solution (40 c.c.), the reagents being added in tenths during 4 hours. The reaction mixture was then heated at 100° for 30 minutes, cooled in ice, acidified with dilute sulphuric acid, and treated with a large excess of alcohol. Sodium

sulphate was removed by filtration, and the solution made faintly alkaline and evaporated to small volume. It was again acidified with sulphuric acid and extracted several times with chloroform. The extracts were washed with a little water, dried over anhydrous magnesium sulphate, filtered, and evaporated to a brown syrup. The crude 2 : 3 : 5-*trimethyl* β-*methyl-glucuronoside* (V) was acid to litmus and non-reducing to boiling Fehling's solution (Found : OMe, 46·0. $C_{10}H_{18}O_7$ requires OMe, 49·6%). The glycosidic methyl group was removed by heating a solution of the crude material (0·18 g.) in 3% hydrobromic acid at 90° for 8 hours. Bromine (1 c.c.) was then added, and the oxidation allowed to proceed at 50° for 24 hours. The product, isolated in the usual way, was esterified by refluxing for 8 hours with 2% methyl-alcoholic hydrogen chloride (20 c.c.), and yielded a syrup (40 mg.), which crystallised. After two recrystallisations from ether–light petroleum, 2 : 3 : 5-trimethyl saccharolactone methyl ester was obtained in colourless needles, m. p. and mixed m. p. 77—78° (Found : OMe, 50·4. Calc. for $C_{10}H_{16}O_7$: OMe, 50·0%).

Methyl Ester of Methylglucopyruronoside (VII).—A solution of (I) (0·5 g.) in 2% methyl-alcoholic hydrogen chloride (50 c.c.) was refluxed for 6 hours. The cooled solution was neutralised with silver carbonate, filtered, and evaporated under reduced pressure. The *methyl* ester of *methylglucopyruronoside* was obtained as a colourless non-reducing syrup (0·5 g.), $[\alpha]_D^{20°}$ + 88° (*c*, 0·9 in water). It was neutral to litmus and behaved as an ester when warmed with sodium hydroxide solution (Found : OMe, 27·5; equiv. by titration, 224. $C_8H_{14}O_7$ requires OMe, 27·9%; equiv., 222). After treatment for 30 minutes at 60° with 0·3N-barium hydroxide the methoxyl content was 13·3% ($C_8H_{14}O_7$ requires residual OMe, 14·0%).

Formation of the Methyl Ester of 2 : 3 : 4-*Trimethyl Methylglucopyruronoside* (VIII).—The methyl ester of methylglucopyruronoside (0·3 g.) was methylated three times with silver oxide and methyl iodide; the product distilled as a colourless syrup (0·2 g.), b. p. (bath temp.) 120°/0·02 mm., $n_D^{20°}$ 1·4460, $[\alpha]_D^{17°}$ + 84° (*c*, 1·0 in methyl alcohol) (Found : OMe, 57·0; equiv. by titration, 267. Calc. for $C_{11}H_{20}O_7$: OMe, 58·7%; equiv., 264). With methyl-alcoholic ammonia, the ester (27 mg.) was converted into the amide of 2 : 3 : 4-trimethyl α-methyl-glucuronoside, which after recrystallisation from acetone–ether–light petroleum, had m. p. and mixed m. p. 182°.

1 : 2-*Monoacetone Glucofururonolactone* (XII).—(a) *From glucuronolactone.* Glucurono-lactone (1 g.) was dissolved by shaking in dry acetone (50 c.c.) containing concentrated sulphuric acid (0·4 c.c.). The solution was kept for 24 hours, neutralised with barium carbonate, filtered, and evaporated, leaving a solid residue. 1 : 2-*Monoacetone glucofururonolactone* crystallised from ether–light petroleum in colourless needles (0·8 g.), m. p. 120°, $[\alpha]_D^{18°}$ + 70° (*c*, 1·0 in acetone, methyl alcohol and water). It was soluble in water, methyl and ethyl alcohols, acetone, chloroform, ether, and ethyl acetate, insoluble in light petroleum (Found : C, 50·1; H, 5·6. $C_9H_{12}O_6$ requires C, 50·0; H, 5·55%). With aqueous alkali, the substance behaved as a δ-lactone, but estimations of equivalent by titration gave low results [cf. compound (I) above], and with alkaline hypoiodite a precipitate of iodoform was obtained. The compound in aqueous solution (*c*, 0·01) showed no absorption band, but the yellow solution in dilute alkali showed bands at λ 2790 (ε, 7100) and λ 4100 A. (ε, varying with time). On standing, a colourless solution resulted which showed a band only at λ 2790 A.; on acidification this disappeared, but returned when the solution was again made alkaline.

A small quantity of the compound was methylated twice with silver oxide and methyl iodide. The 2 : 5-dimethyl-2 : 3-dehydrosaccharolactone methyl ester (XIII) so obtained, recrystallised first from ether–light petroleum and then from alcohol, had m. p. 89°, $[\alpha]_D$ + 89° and $[\alpha]_{5461}^{17°}$ + 108° (*c*, 1·0 in methyl alcohol) (Found : C, 49·9; H, 5·4; OMe, 42·2. Calc. for $C_9H_{12}O_6$: C, 50·0; H, 5·55; OMe, 43·0%). It gave iodoform on treatment with alkaline hypoiodite and showed an absorption band at λ 2290 A. (ε, 6546) which moved to λ 3010 A. (ε, 3240) when the solution was made alkaline.

(b) *From* 1 : 2-*monoacetone glucofururonic acid.* The acid (X) (30 mg.), prepared by the method of Zervas and Sessler (*loc. cit.*), was heated at 95—100°/0·01 mm. for an hour. On the cooler portion of the vessel was formed a crystalline sublimate, m. p. 119°, not depressed on admixture with (IX) prepared from glucuronolactone. A mixed m. p. with the original acid (X) (m. p. 146°) was 108—110°.

1 : 2-*Monoacetone Glucofururonamide* (XI).—(a) *From* 1 : 2-*monoacetone glucofururonolactone.* The compound (0·1 g.) was dissolved in dry methyl alcohol (5 c.c.) saturated with dry ammonia at 0°, and kept at this temperature for 24 hours. Thereafter the solvent was removed by evaporation in a vacuum and the solid residue was recrystallised from alcohol–ether. 1 : 2-*Monoacetoneglucofururonamide* formed colourless prisms, m. p. 164° (decomp.),

$[\alpha]_D^{18°}$ — 14° (*c*, 0·9 in water) (Found : C, 46·5; H, 6·3; N, 6·2. $C_9H_{15}O_6N$ requires C, 46·4; H, 6·5; N, 6·0%).

A solution of the amide (30 mg.) in water (1 c.c.) was treated with a slight excess of 1·5N-sodium hypochlorite for 30 minutes at 0°; the excess was then removed by the addition of a few drops of sodium thiosulphate solution. On the addition of sodium acetate, followed by semicarbazide hydrochloride, a precipitate of hydrazodicarbonamide was obtained, m. p. and mixed m. p. 258°.

(b) *From* 1 : 2-*monoacetone glucofururonic acid.* The acid (30 mg.), suspended in dry ether (3 c.c.), was treated with a slight excess of an ethereal solution of diazomethane. The liquid ester obtained on evaporation was treated with methyl-alcoholic ammonia at 0° for 36 hours. Removal of the solvent gave a solid residue, which, after recrystallisation from alcohol–ether, had m. p. (with decomposition) 164°, unchanged on admixture with (XI) obtained from 1 : 2-monoacetone glucofururonolactone.

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