

86. *Derivatives of 3 : 4-Monoacetone β -1 : 6-Anhydrogalactose.*

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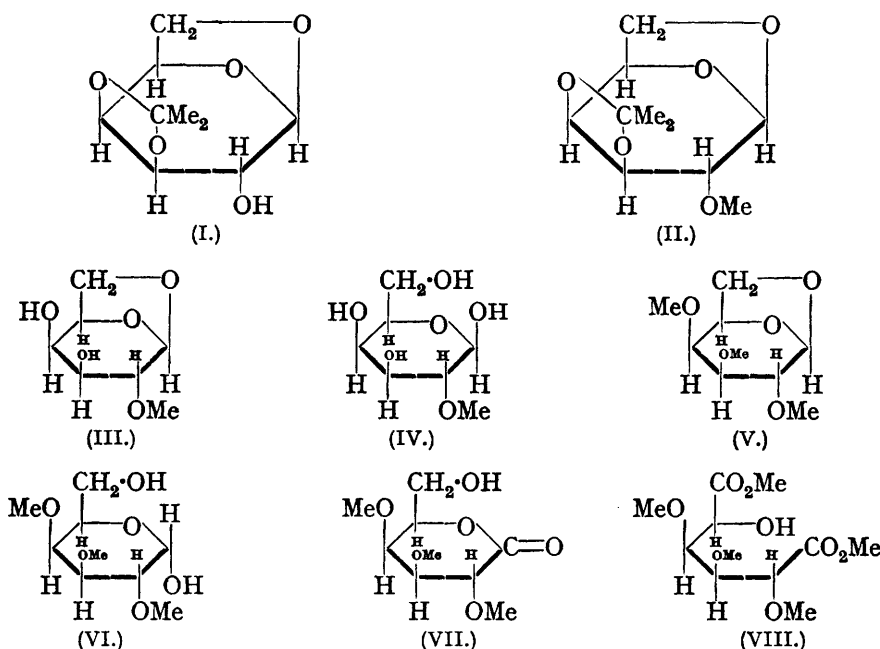
With crystallographic data by E. G. COX and (MISS) A. I. WAGSTAFF.

The isolation of 3 : 4-monoacetone β -1 : 6-anhydrogalactopyranose is described. It has been converted successively into 2-methyl 3 : 4-monoacetone β -1 : 6-anhydrogalactose, 2-methyl β -1 : 6-anhydrogalactose, 2-methyl β -galactose, 2 : 3 : 4-trimethyl β -1 : 6-anhydrogalactose, and 2 : 3 : 4-trimethyl galactose, the structures of which are proved. A crystallographic examination of β -1 : 6-anhydrogalactose and of 3 : 4-monoacetone β -1 : 6-anhydrogalactose has been carried out.

DURING the preparation of 1 : 2-3 : 4-diacetone galactose, required for the synthesis of *l*-ascorbic acid (Haworth, Hirst, *et al.*, J., 1933, 1422), it was found in a few cases that some decomposition occurred during the vacuum distillation of the product and in addition to the syrupy diacetone galactose a crystalline substance of higher boiling point was obtained. This product proved to be identical with a monoacetone anhydrogalactose prepared by Micheel (*Ber.*, 1929, **62**, 687). The formation of anhydrogalactoses (or galactosans) by destructive distillation of galactose is well known (Pictet and Vernet, *Helv. Chim. Acta*,

1922, 5, 44; Pictet and Vogel, *ibid.*, 1928, 11, 209; Micheel, *loc. cit.*) and in this instance the production of monoacetone anhydrogalactose might be ascribed to a failure to maintain the high vacuum. In agreement with this view it was found that the yield of crystalline material was increased when a mercury vapour pump alone was used for the distillation, presumably owing to the fact that such a pump had not the capacity of the combined oil and mercury vapour pump usually employed.

The investigation carried out by Micheel (*loc. cit.*), while strongly suggesting that the monoacetone anhydrogalactose was to be described as 3 : 4-monoacetone β -1 : 6-anhydrogalactose (I), did not provide conclusive evidence in support of this view. This evidence is now provided by the series of transformations detailed below.



Methylation of the monoacetone anhydrogalactose (I) prepared as described yields a *monomethyl monoacetone anhydrogalactose* (II), the hydrolysis of which with mineral acid eliminates the acetone residue with the formation of a *monomethyl anhydrogalactose* (III). This substance is non-reducing and it is clear, therefore, that the reducing group in (I) is protected by the anhydro-ring and not by the acetone residue. Further treatment of the monomethyl anhydrogalactose (III) with methyl sulphate and sodium hydroxide solution gives a trimethyl anhydrogalactose (V) which also is non-reducing. Fission of the anhydro-ring in (V) was achieved by treatment with aqueous mineral acid and a trimethyl galactose was isolated as the monohydrate. This product was identical with the 2 : 3 : 4-trimethyl galactose monohydrate (VI) obtained by the hydrolytic cleavage of methylated degraded arabic acid (Smith, unpublished results). It follows from this result that the anhydro-ring in (V) and therefore in (I) involves the reducing group (C_1) and the primary alcohol group (C_6).

The position of the methyl group in monomethyl anhydrogalactose (III) was determined in the following way. Hydrolysis of (III) by mineral acid gave a crystalline monomethyl β -galactose (IV), which when treated with phenylhydrazine furnished galactose phenylosazone. During this reaction the methyl group was eliminated, an indication that the group occupies position 2. 2-Methyl- β -galactose (IV), which forms a crystalline *anilide*, has been described by Oldham and Bell (*J. Amer. Chem. Soc.*, 1938, 60, 323). The recognition of (III) as 2-methyl 1 : 6-anhydrogalactopyranose clearly shows that the acetone residue in (I) engages C_3 and C_4 . Inspection of the model of (I) indicates that the 1 : 6-

anhydro-ring must engage the hydroxyl group on C_1 in the β -position and therefore (I) is designated 3 : 4-monoacetone β -1 : 6-anhydrogalactopyranose.

The structure of the 2 : 3 : 4-trimethyl galactose (VI) was confirmed by its transformation with bromine into 2 : 3 : 4-trimethyl δ -galactonolactone (VII). The latter was characterised by the formation of a crystalline phenylhydrazide, which was identified by m. p. and by comparison with an authentic specimen (compare Challinor, Haworth, and Hirst, J., 1931, 258). Furthermore, when the 2 : 3 : 4-trimethyl δ -galactonolactone was oxidised with concentrated nitric acid, 2 : 3 : 4-trimethyl mucic acid was produced, which was identified as its crystalline dimethyl ester (VIII), identical with an authentic specimen (Challinor, Haworth, and Hirst, *loc. cit.*).

EXPERIMENTAL.

Isolation of 3 : 4-Monoacetone 1 : 6-Anhydrogalactopyranose (I).—Condensation of galactose with acetone in the presence of sulphuric acid (Freudenberg and Doser, *Ber.*, 1925, 58, 296) yielded a product which on high vacuum distillation furnished mainly diacetone galactose and sometimes, in addition, a small quantity of a higher-boiling distillate which solidified. After recrystallisation from benzene–light petroleum this material had m. p. 151–152°; $[\alpha]_D^{19} - 61.3^\circ$ in water (*c.* 1.42), $[\alpha]_D^{19} - 72.5^\circ$ in chloroform (*c.* 1.7), and $[\alpha]_D^{19} - 66.2^\circ$ in ethyl alcohol (*c.* 1.8) (Found : C, 53.5; H, 6.9. Calc. for $C_6H_{14}O_5$: C, 53.5; H, 7.0%). The substance did not reduce Fehling's solution, but when boiled with 5*N*-hydrochloric acid for a few minutes, the solution, after neutralisation, had reducing properties and gave a positive iodoform test. The properties of the 3 : 4-monoacetone galactosan quoted by Micheel (*loc. cit.*), m. p. 151–152°, $[\alpha]_D^{22} - 61.7^\circ$ in water, $[\alpha]_D^{22} - 73.3^\circ$ in chloroform, are in good agreement with the above figures. The m. p. of a mixture with 3 : 4-monoacetone β -1 : 6-anhydrogalactose prepared by Micheel's method showed no depression.

2-Monomethyl 3 : 4-Monoacetone β -1 : 6-Anhydrogalactopyranose (II).—The monoacetone anhydrogalactose (I) (3.8 g.) was methylated at 50° with methyl sulphate (20 c.c.) and sodium hydroxide (50 c.c. of a 30% aqueous solution) in the presence of acetone, the reagents being added in one-tenth portions during 1½ hours. The methylation was completed by heating the solution at 90° for 10 minutes. The material, a syrup (3 g.) isolated by means of chloroform, had b. p. (bath temp.) 110°/0.12 mm., $n_D^{29} 1.4680$, $[\alpha]_D^{17} - 84.5^\circ$ in ethyl alcohol (*c.* 1.7). It did not reduce Fehling's solution (Found : OMe, 14.6. $C_{10}H_{16}O_3$ requires OMe, 14.35%).

2-Monomethyl β -1 : 6-Anhydrogalactopyranose (III).—2-Monomethyl 3 : 4-monoacetone 1 : 6-anhydrogalactopyranose (2.5 g.) was dissolved in 0.5*N*-sulphuric acid (50 c.c.) and ethyl alcohol (25 c.c.) and heated for 1½ hours on a boiling water-bath; the rotation then became constant. After neutralisation with barium carbonate the solution was filtered and evaporated under reduced pressure, giving a viscous non-reducing syrup (2.0 g.). The acetone residue had been completely eliminated, since after further acid hydrolysis no acetone could be detected in the solution by the iodoform reaction. Without further purification the material was used for the following experiment.

2 : 3 : 4-Trimethyl β -1 : 6-Anhydrogalactopyranose (V).—2-Monomethyl 1 : 6-anhydrogalactose (2 g.) was methylated with methyl sulphate (20 c.c.) and sodium hydroxide (50 c.c. of 30% aqueous solution) in the presence of acetone and the crystalline product (1.7 g.) was isolated by means of chloroform. It crystallised well from acetone–light petroleum, had m. p. 61°, $[\alpha]_D^{19} - 69.2^\circ$ in ethyl alcohol (*c.* 1.32), and did not reduce Fehling's solution even on prolonged boiling (Found : C, 52.9; H, 7.9; OMe, 45.3. $C_9H_{16}O_5$ requires C, 52.9; H, 7.9; OMe, 45.6%).

2 : 3 : 4-Trimethyl Galactopyranose (VI).—2 : 3 : 4-Trimethyl 1 : 6-anhydrogalactopyranose (1.3 g.) was hydrolysed by boiling with 4% hydrochloric acid (40 c.c.) for 14½ hours. The solution was neutralised with barium carbonate, filtered, and evaporated to dryness under diminished pressure. The residue was extracted with boiling chloroform and after removal of the solvent a colourless reducing syrup (1 g.) was obtained which readily crystallised as a monohydrate on exposure to the air. After recrystallisation from acetone–ether–light petroleum the material had m. p. 80° (sintering at 74°); $[\alpha]_D^{20} + 150^\circ$ (initial value in water, *c.* 1.0), changing in 3½ hours to + 114° (constant value). It gave no depression in m. p. when mixed with a pure specimen of 2 : 3 : 4-trimethyl galactose monohydrate. The material was readily soluble in water, methyl alcohol, ethyl alcohol, and acetone but insoluble in ether and light petroleum (Found : C, 45.3; H, 8.0; OMe, 38.5. Calc. for $C_9H_{18}O_6 \cdot H_2O$: C, 45.0; H, 8.4; OMe, 38.8%). After keeping over phosphoric oxide the m. p. rose to 86° (without previous sintering) (Found :

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OMe, 42.9. Calc. for $C_9H_{18}O_6$: OMe, 41.9%). The 2 : 3 : 4-trimethyl galactose (100 mg.), freed from moisture by heating in a vacuum at 100° , was allowed to react with aniline (70 mg.) in boiling absolute alcohol (5 c.c.) for 5 hours. The solvent was removed; the pale yellow syrup crystallised spontaneously, and after recrystallisation from a small volume of absolute alcohol the product (70 mg.) had m. p. 169° . This anilide was sparingly soluble in ether and insoluble in light petroleum but readily dissolved in acetone and in methyl and ethyl alcohols (Found: C, 60.8; H, 7.8; OMe, 32.8; N, 4.8. Calc. for $C_{15}H_{23}O_5N$: C, 60.6; H, 7.8; OMe, 31.4; N, 4.7%).

Formation of 2 : 3 : 4-Trimethyl δ -Galactonolactone (VII).—2 : 3 : 4-Trimethyl galactose (0.9 g.), dissolved in water (10 c.c.), was allowed to react with bromine (1 c.c.) at room temperature for 2 days until a small portion of the solution, after removal of the excess of bromine and neutralisation with sodium hydroxide, no longer reduced Fehling's solution. The solution was then freed from bromine by aeration, neutralised with silver oxide, filtered, and treated with hydrogen sulphide. Silver sulphide was removed, and the clear solution evaporated to dryness under diminished pressure. The syrupy lactone thus produced (0.75 g.) had b. p. (bath temp.) $145^\circ/0.01$ mm., $n_D^{18} 1.4750$, $[\alpha]_D^{18} + 135^\circ$ (initial value in water, c , 1.0), falling in 10 hours to $+25^\circ$ (equilibrium value). On heating with phenylhydrazine (1.1 mols.), the lactone (0.1 g.) readily gave rise to a crystalline phenylhydrazide (60 mg.), which, after recrystallisation from alcohol-ether, had m. p. 175 — 176° alone or in admixture with a pure specimen of the phenylhydrazide of 2 : 3 : 4-trimethyl galactonic acid (Found: C, 54.9; H, 7.3; OMe, 28.4; N, 8.8. Calc. for $C_{15}H_{24}O_6N_2$: C, 54.9; H, 7.4; OMe, 28.4; N, 8.5%).

Formation of Methyl 2 : 3 : 4-Trimethyl Mucate (VIII).—A solution of the lactone (0.6 g.) in nitric acid (10 c.c., d 1.42), was heated for $\frac{1}{2}$ hour at 50° and for 3 hours at 90° . It was then diluted with water and freed from nitric acid by distillation under reduced pressure at 50 — 60° , water, and in the final stages, methyl alcohol, being added to facilitate this process. When free from nitric acid and water, the acidic product was subjected to esterification by boiling with 2% methyl-alcoholic hydrogen chloride (50 c.c.) for 8 hours under reflux. The solution was neutralised with silver carbonate, filtered, and evaporated to a syrup, which readily crystallised. This crystallised well from acetone-ether-light petroleum in plates, m. p. 102 — 103° alone or in admixture with authentic methyl 2 : 3 : 4-trimethyl mucate. It showed $[\alpha]_D^{23} + 36^\circ$ in water (c , 1.7) (Found: C, 47.2; H, 7.2; OMe, 54.8. Calc. for $C_{11}H_{20}O_8$: C, 47.1; H, 7.2; OMe, 55.3%).

2-Methyl Galactopyranose (IV).—A solution of 2-methyl 3 : 4-monoacetone 1 : 6-anhydrogalactopyranose (0.9 g.) in 5% hydrochloric acid (50 c.c.) was heated on a boiling water-bath for 21 hours; the rotation then became constant. The solution, which now reduced Fehling's solution actively, was neutralised with silver carbonate, filtered, and evaporated to dryness under reduced pressure. The syrup was dissolved in ethyl alcohol, filtered, and the solution evaporated to dryness, giving a residue of 2-methyl galactose. After crystallisation from glacial acetic acid or water the product had m. p. 145 — 148° . It showed $[\alpha]_D^{25} + 52^\circ$ (initial value in water, c , 0.5), changing to $+94^\circ$ (equilibrium value) [Oldham and Bell (*loc. cit.*) give $[\alpha]_D + 53^\circ$ (after 5 mins. in water, c , 4.77), changing to $+82.6^\circ$ (equilibrium value)]. Since the 2-methyl galactose exhibits an increase in rotation, it probably has the β -configuration (Found: C, 42.9; H, 7.25; OMe, 16.0. Calc. for $C_7H_{14}O_6$: C, 43.3; H, 7.3; OMe, 16.0%). When the 2-methyl galactose (100 mg.), dissolved in absolute alcohol (2 c.c.), was heated under reflux in the presence of aniline (1.1 mols.) for 6 hours, the anilide was readily formed, and removal of the solvent gave a crystalline product which separated well from acetone-light petroleum. The anilide of 2-methyl galactose had m. p. 165° ; it was soluble in water, methyl and ethyl alcohol, acetone, and ether but insoluble in light petroleum (Found: OMe, 11.3. $C_{13}H_{19}O_5N$ requires OMe, 11.5%).

Formation of Galactose Phenyllosazone.—When the 2-methyl galactose (100 mg.) was heated with phenylhydrazine (4 mols.) in 45% aqueous acetic acid at 75° for $3\frac{1}{2}$ hours, galactose phenyllosazone was produced. After recrystallisation from aqueous alcohol the osazone had m. p. 202° (decomp.) alone or in admixture with an authentic specimen (Found: C, 60.4; H, 6.6; N, 15.6; OMe, nil. Calc. for $C_{18}H_{22}O_4N_4$: C, 60.3; H, 6.2; N, 15.6%).

X-Ray Crystallographic Examination [By E. G. COX and (MISS) A. I. WAGSTAFF].

β -1 : 6-Anhydrogalactose.—The crystals of this substance prepared according to the directions given by Micheel (*loc. cit.*) are orthorhombic, tabular on {100} and with marked cleavage parallel to {001}. The cell dimensions are $a = 28.41$, $b = 11.07$, and $c = 6.30$ Å., and the observed density is 1.613 g./c.c. The space-group is $P2_12_12$ (Q^3), but the molecular arrange-

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ment must approximate closely to that of $P2_12_12_1$, since the reflection from (001) is absent and that from (003) is very weak. There are thus *four* asymmetric units in the cell, and the deduced molecular weight is 484 [Calc. for $(C_6H_{10}O_6)_3$: 486].

3:4-Monoacetone β -1:6-Anhydrogalactose.—This substance is orthorhombic, showing elongated development of the form {210}. The cell dimensions are $a = 17.68$, $b = 9.72$, and $c = 5.45$ Å., and the space-group is $P2_12_12$, in this case also approximating to $P2_12_12_1$. The observed density is 1.422 g./c.c., giving a molecular weight (for four molecules per unit cell) of 203 (calc. for $C_9H_{14}O_5$, 202), so this substance is monomeric in the solid state.

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