386. 3 : 4-*Dimethyl Galactose.*

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Crystalline 3 : 4-*dimethyl galactose* has been prepared and its constitution proved. Seven new crystalline derivatives of galactose are described.

RECENT investigations on galactose-containing polysaccharides have resulted in the isolation of several previously unknown partially methylated galactoses, *e.g.*, the 2 : 4 : 6-trimethyl and 2 : 4-dimethyl derivatives from methylated agar (Percival and Somerville, J., 1937, 1615) and from methylated snail galactogen (Baldwin and Bell, J., 1938, 1461) and degraded arabic acid (Smith, this vol., p. 1724) respectively. In this laboratory we have therefore considered it advantageous to continue our synthetic experiments, with a view to preparing new partially methylated galactoses, which may be of service as reference compounds. The present paper describes the operations leading to the production of crystalline 3 : 4-*dimethyl galactose* and to the proof of its constitution.

It was found practicable to treat 3 : 4-monoacetone β-methylgalactoside with pure nitrogen pentoxide in chloroform solution so that the very labile *iso*propylidene group largely remained *in situ*, with the formation of crystalline 3 : 4-*monoacetone* β-*methylgalactoside* 2 : 6-*dinitrate*. By the action of hot, very dilute acid the *iso*propylidene radical was hydrolysed, leaving crystalline β-*methylgalactoside* 2 : 6-*dinitrate* (the constitutions of this and following substances are afforded by subsequent evidence). This material was methylated by Purdie's reagents to give the crystalline 3 : 4-dimethyl derivative, but great difficulty was experienced in effecting complete methylation, as inseparable mixed crystals of low methoxyl content were repeatedly obtained. Alkaline reduction yielded crystalline 3 : 4-*dimethyl* β-*methylgalactoside*. This substance, on hydrolysis by aqueous acid, gave the free *sugar* in crystalline form, to which the β-configuration was attributed on the ground that in aqueous solution the crystals displayed mutarotation in an upward sense.

That the sugar is a derivative of galactose was shown by boiling a specimen with methyl alcohol containing hydrogen chloride, methylating the resulting glycoside, and removing the glycosidic methyl group by acid hydrolysis. This left 2 : 3 : 4 : 6-tetramethyl galactose, which was identified as the crystalline anilide.

Proof of the position of the two methyl groups rests upon the method of synthesis and upon subsequent reactions, which confirm the presence of a methyl group in position 4 and the presence of free hydroxyl in position 2 : (1) The synthesis involves the substitution of two methyl groups for the *iso*propylidene group known to occupy positions 3 and 4 in the β-methylgalactoside derivative. During this substitution positions 2 and 6 are protected by nitrate groups, which are not known to migrate under the conditions of methylation used.

(2) A specimen of the sugar when dissolved in methyl-alcoholic hydrogen chloride showed little change in optical rotation in the course of two days. This failure to form a furanoside proves that position 4 is methylated (cf. Robertson and Lamb, J., 1934, 1321). This was confirmed by observing the rate of mutarotation of the *lactone*, prepared by oxidising the sugar with bromine in the usual way. It was typical of a δ-galactonolactone (the yield of acid obtained by bromine oxidation was extremely low).

The amide prepared from the lactone reacted with sodium hypochlorite (Weerman reaction) to form cyanate. This indicates that position 2 is free (Ault, Haworth, and Hirst, J., 1934, 1722).

These two findings are confirmed by the fact that 2 : 4-dimethyl galactose (Baldwin and Bell, *loc. cit.*; Smith, *loc. cit.*) has dissimilar properties and since there is no evidence that esterifying radicals ever migrate from position 6 to 4 there is no doubt that the new sugar has the constitution which we have assigned to it.

EXPERIMENTAL.

Solvents were evaporated under reduced pressure; in the instances of the nitrates, below 50°. Polarimetric measurements were made on chloroform solutions (unless stated otherwise) in a 2-dm. tube.

3 : 4-iso*Propylidene* β-*Methylgalactoside* 2 : 6-*Dinitrate* (I).—To each of eight 2 g. lots of 3 : 4-*iso*propylidene β-methylgalactoside (Micheel, *Ber.*, 1929, **62**, 687) dissolved in 40 ml. of dry chloroform, 20 ml. of a solution of 70 g. of nitrogen pentoxide in 250 ml. of dry chloroform were added. The mixture was cooled in ice for 5 minutes then poured into ice and water, and quickly shaken and the chloroform layer was run into potassium bicarbonate solution, to remove any remaining acid, and then dried over anhydrous sodium sulphate. Evaporation of the chloroform left a syrup, which was dissolved in ether and treated with charcoal. On evaporation of the solvent the residual syrup crystallised (14 g.) in plates of the *dinitrate* (I), m. p. 79°, $[\alpha]_D^{23°}$ + 40·0° (c = 10) (Found : C, 38·0; H, 5·4; N, 8·3; OMe, 9·2. $C_{10}H_{16}O_{10}N_2$ requires C, 37·0; H, 4·9; N, 8·6; OMe, 9·6%).

In the course of this preparation β-*methylgalactoside* 2 : 3 : 4 : 6-*tetranitrate* was isolated. A specimen was prepared from β-methylgalactoside for comparison (see below).

β-*Methylgalactoside* 2 : 3 : 4 : 6-*Tetranitrate* (II).—To 2 g. of β-methylgalactoside suspended in 10 ml. of dry chloroform cooled in ice, 30 ml. of a 30% solution of nitrogen pentoxide in dry chloroform were added; the mixture was kept in ice for 20 minutes and then poured into a large volume of ice and water. The chloroform layer was washed with potassium bicarbonate solution, dried over sodium sulphate, and evaporated to dryness. The syrup was dissolved in ether, treated with charcoal, and again evaporated to dryness. It crystallised in a vacuum desiccator in plates, m. p. 114—115°, $[\alpha]_D^{19·5°}$ − 12·4° (c = 4), $[\alpha]_D^{22·5°}$ − 7·1° (c = 3·5, alcohol) (Found: C, 24·4; H, 3·1; N, 13·9; OMe, 8·5. $C_7H_{10}O_{14}N_4$ requires C, 22·5; H, 2·7; N, 15·0; OMe, 8·3%).

β-*Methylgalactoside* 2 : 6-*Dinitrate* (III).—15 G. of (I) were heated on the boiling water-bath with 110 ml. of acetone containing 5 ml. of N-hydrochloric acid, and the hydrolysis was followed polarimetrically. After 4 hours the acid was neutralised with barium carbonate, and the solution filtered. The greater part of the acetone was removed by distillation, and the residual fluid (20 ml.) washed with benzene into a separating funnel. The benzene layer was extracted six times with water, and the combined water fractions once with benzene. The solid remaining on evaporation of the water was dissolved in ether, treated with charcoal plus anhydrous sodium sulphate, and evaporated to dryness. Yield, 10 g. of needles (from chloroform), m. p. 110—111°, $[\alpha]_D^{23°}$ + 15·2° (c = 5, alcohol) (Found : C, 29·1; H, 4·2; N, 8·55. $C_7H_{12}O_{10}N_2$ requires C, 29·6; H, 4·2; N, 9·9%).

3 : 4-*Dimethyl* β-*Methylgalactoside* 2 : 6-*Dinitrate* (IV).—10 G. of (III) were dissolved in 50 ml. of methyl iodide plus a little dry acetone. The solution was heated under reflux at 45° with 15 g. of silver oxide. The operation was repeated three times and yielded a crystalline product at each stage. (Four methylations were sufficient to introduce the necessary two methyl groups in this preparation, but in another eight were needed, and in a third a crystalline substance, m. p. 114—115°, with a methoxyl content corresponding to a monomethyl methylglycoside dinitrate was isolated.) Plates (6·5 g.) were obtained from aqueous methyl alcohol; m. p. 75—76°, $[\alpha]_D^{21°}$ − 13·3° (c = 6·5) (Found : C, 35·6; H, 5·4; N, 9·0; OMe, 28·2. $C_9H_{16}O_{10}N_2$ requires C, 34·6; H, 5·1; N, 9·0; OMe, 29·8%).

3 : 4-*Dimethyl* β-*Methylgalactoside* (V).—6·5 G. of (IV) were dissolved in 100 ml. of alcohol and boiled under reflux for 30 minutes with 35 ml. of a 30% sodium hydroxide solution saturated with hydrogen sulphide. The alcohol was removed by distillation and potassium carbonate was dissolved in the aqueous solution until chloroform just sank in it. Ten extractions with small quantities of chloroform (totalling 500 ml.) which was thereafter dried over anhydrous sodium sulphate and evaporated to dryness yielded 3 g. of a syrup which crystallised on addition of acetone and ether. A further 0·5 g. was obtained by further chloroform extraction. The *substance* crystallised from carbon tetrachloride containing a little chloroform in small needles, m. p. 102—103°, $[\alpha]_D^{20°}$ − 9·1 (c = 6·2) (Found : C, 48·5; H, 7·8; OMe, 40·8. $C_9H_{18}O_6$ requires C, 48·6; H, 8·1; OMe, 41·9).

3 : 4-*Dimethyl* β-*Galactose* (VI).—2·6 G. of (V) were heated on the water-bath under reflux with 85 ml. of N-hydrochloric acid. The hydrolysis was followed polarimetrically and after 4 hours the solution was cooled, neutralised with silver carbonate, filtered through charcoal, and saturated with hydrogen sulphide until the clear (kieselguhr-filtered) solution showed no further sign of silver. After evaporation of the water the residue was dissolved in acetone–ethyl acetate. Solid material was removed, and the *sugar* crystallised from the filtrate. At first hygroscopic, it was crystallised eventually from ethyl acetate, 2 g. of needles being obtained, m. p. 164—166° (Found : C, 48·5; H, 7·8; OMe, 29·8. $C_8H_{16}O_6$ requires C, 46·15; H, 7·7; OMe, 29·8%).

A solution of 0·6546 g. of the sugar in 10 ml. of water displayed the following optical behaviour :

Minutes ...	0	6	30	48	170	260	20 (hours)
$[\alpha]_D^{20^\circ}$	+95·0°	+96·9°	+104·0°	+107·4°	+115·4°	+116·1°	+116·5°

A second specimen (0·2220 g. in 10 ml.) confirmed this :

Minutes ...	0	2	17	30	75	185	290	16 (hours)
$[\alpha]_D^{20^\circ}$	+95·7°	+96·4°	+101·8°	+105·0°	+110·4°	+116·2°	+116·9°	+117·1°

(The two zero values were obtained by extrapolation.)

0·3 G. of the sugar, dissolved in 10 ml. of acid (1%) methyl alcohol, showed an optical rotation rising from + 5·3° to + 9·5° during 2 days at room temperature, afterwards falling extremely slowly. More alcohol and hydrochloric acid were then added to the solution, and the whole boiled under reflux for 3 hours. The mixed galactosides so obtained were twice methylated with Purdie's reagents, the glycosidic methyl group removed by acid hydrolysis (Found : OMe, 51·9. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%), and the tetramethyl sugar heated under reflux for 5 hours with 10 ml. of absolute alcohol and 1 ml. of aniline. Crystals of the anilide, m. p. 192—193°, were obtained which did not depress the m. p. of an authentic specimen of 2 : 3 : 4 : 6-tetramethyl galactose anilide.

3 : 4-*Dimethyl Galactonolactone* (VII).—1·5 G. of (VI) were dissolved in 15 ml. of water, and bromine added in excess of saturated solution. After 5 days at room temperature, as the solution still reduced Fehling's solution, it was kept at 40° for 2 days. No reducing material remained. The bromine was removed by aeration, bromide ion by addition of silver carbonate, and silver was precipitated by saturation with hydrogen sulphide. The clear filtrate (through kieselguhr and charcoal) on evaporation gave a brown residue, partly of a crystalline nature. Attempts to recrystallise it were unsuccessful and it was eventually dried at 100° under diminished pressure. The product was a brown solid which could not be cleaned by any ordinary method [Found : OMe, 28·9. $C_8H_{14}O_6$ requires OMe, 30·1%. Found : equiv. wt. (by titration), 210·6. Dimethyl galactonolactone requires equiv., 206].

A solution in water of the compound exhibited the slow polarimetric equilibration characteristic of a δ-galactonolactone :

Minutes ...	0	7	40	90	186	240	1073	1695	5240
$[\alpha]_D^{21^\circ}$	+89·0°	+83·6°	+74·1°	+58·5°	+37·5°	27·2°	+7·8°	+7·8°	+7·0°

(Zero reading obtained by extrapolation.)

3 : 4-*Dimethyl Galactonamide* (VIII).—2 G. of (VII) were treated with 100 ml. of dry methyl alcohol saturated with dry ammonia. After 2 days a sediment separated; this was removed, and the filtrate evaporated to dryness. The residue when dissolved in alcohol–acetone crystallised overnight in hexagonal prisms, m. p. 172—174°. The yield was poor (0·5 g.) (Found : C, 43·2; H, 7·9; N, 6·2; OMe, 28·2. $C_8H_{17}O_6N$ requires C, 43·05; H, 7·6; N, 6·3; OMe, 27·8%).

About 35 mg. of the *amide* were dissolved in water, and the solution filtered through charcoal. To the filtrate (2 ml.) was added 1 ml. of a sodium hypochlorite solution (as used by Weerman, approx. N × 1·5). After 30 minutes 1 ml. of N-sodium thiosulphate was added (to remove the excess of hypochlorite), followed by a few crystals of sodium acetate (to buffer the solution) and finally a few drops of a saturated solution of semicarbazide hydrochloride. A crystalline precipitate settled out after several hours, m. p. and mixed m. p. with hydrazodicarbonamide 255—256°.

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