223. 2 : 4 : 6-*Trimethyl Galactose and its α- and β-Methylgalactosides.*

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2 : 4 : 6-Trimethyl galactose has been synthesised by two methods which leave no doubt as to its constitution. The sugar has been proved to be identical with that isolated from agar by Percival and Somerville (J., 1937, 1617). Ten new crystalline derivatives of galactose have been characterised.

The recent isolation of 2 : 4 : 6-trimethyl galactose from agar by Percival and Somerville (J., 1937, 1617) and from certain plant gums by Hirst and Jones, at Bristol (private

communication from Professor E. L. Hirst, F.R.S.), has shown that galactose units in these vegetable polysaccharides can be linked through the hydroxyl group of position 3, a mode of glycosidic union so far confined to the sugar in question. That a similar mode of linkage between galactose units is present in the animal polysaccharide, galactogen, secreted by *Helix pomatia*, has recently come to light through researches in this laboratory (Baldwin and Bell, unpublished work). In order to provide material for this and cognate work, and, incidentally, to confirm the structure assigned by Percival and Somerville to their product from agar, we have, by the use of conventional methods, synthesised 2 : 4 : 6-trimethyl galactose by two independent routes which leave no doubt as to the accuracy of the findings of the Edinburgh workers.

The starting point in the first method was the 4 : 6-benzylidene 2-methyl β-methyl-galactoside, the constitution of which is definitely proved (Oldham and Bell, *J. Amer. Chem. Soc.*, 1938, **60**, 323). The steps leading to the synthesis of 2 : 4 : 6-trimethyl galactose are summarised below.

" B " signifies β-methylgalactoside. The compound in parenthesis has not been characterised.

4 : 6-Benzylidene 2-methyl B.
↓
3-p-*Toluenesulphonyl* 4 : 6-*benzylidene* 2-*methyl B.*
↓
(3-*p*-Toluenesulphonyl 2-methyl B.)
↓
3-p-*Toluenesulphonyl* 2 : 4 : 6-*trimethyl B.*
↓
2 : 4 : 6-*Trimethyl B.*
↓
2 : 4 : 6-Trimethyl α-galactose
↙ ↘
4 : 6-Dimethyl galactosazone 2 : 4 : 6-Trimethyl galactonamide

Since the constitution of the starting material is established, and since the *p*-toluene-sulphonyl group does not migrate, there is no doubt that the two new methyl groups have been introduced into positions 4 and 6.

6-*p*-Toluenesulphonyl 3 : 4-*iso*propylidene A.
↓
6-p-*Toluenesulphonyl* 2-*methyl* 3 : 4-iso*propylidene A.*
↙
2-*Methyl* 3 : 4-iso*propylidene A.* ⟶ *2 : 6-*Dimethyl* 3 : 4-iso*propylidene A.*
↓ ↙ ↓
*2-*Methyl A.* 2 : 6-Dimethyl β-galactose 2 : 6-*Dimethyl A.* 3 : 4-*dinitrate*
↓ ↘
2-Methyl β-galactose
↓
4 : 6-*Benzylidene* 2-*methyl A.*
↘
3-p-*Toluenesulphonyl* 4 : 6-*benzylidene* 2-*methyl A.*
↓
(3-*p*-Toluenesulphonyl 2-methyl A.)
↓
3-p-*Toluenesulphonyl* 2 : 4 : 6-*trimethyl A.*
↓
2 : 4 : 6-*Trimethyl* α-*methylgalactoside*
↓
2 : 4 : 6-Trimethyl α-galactose

The second method employed as starting material the easily accessible 6-*p*-toluenesulphonyl 3 : 4-*iso*propylidene α-methylgalactoside described by Ohle and Thiel (*Ber.*, 1933, **66**, 525). In the course of the synthesis outlined on p. 1197 we obtained 4 : 6-*benzylidene 2-methyl α-methylgalactoside*; the position of the benzylidene group follows from the work of Robertson and Lamb (J., 1934, 1321).

"A" signifies α-methylgalactoside. The compound in parenthesis has not been characterised; those marked * could not be crystallised.

Incidental to the work outlined above we have simplified the preparation of our starting materials, and also describe alternative routes to obtaining both 2-methyl and 2 : 6-dimethyl galactose (Oldham and Bell, *loc. cit.*).

It has been postulated by Oldham and Robertson (J., 1935, 685) that when Walden inversion occurs during saponification of a *p*-toluenesulphonyl group in a sugar derivative, there is intermediate formation of an anhydro-ring. They have shown, in the glucose series, that a toluenesulphonyl group can be eliminated by saponification without causing inversion, provided anhydro-formation is inhibited by substituting resistant radicals such as methyl or *iso*propylidene for the remaining hydroxyls of the sugar. The latter finding we have confirmed in the three instances of detoluenesulphonylation now described, and we were further interested to observe the extraordinary difference in stability towards alkali displayed by the toluenesulphonyl radical in the two substances, 6-*p*-toluenesulphonyl α-methylgalactoside and its 2-methyl 3 : 4-*iso*propylidene derivative. Warmed in alcohol with the theoretical amount of N-sodium hydroxide, the former is immediately converted into 3 : 6-anhydro-α-methylgalactoside (Ohle and Thiel, *loc. cit.*), whereas the latter, where anhydro-rings cannot be formed, requires 36 hours' boiling with 50% aqueous-alcoholic 4N-sodium hydroxide to effect complete saponification.

Experimental.

Unless otherwise stated, solvents were evaporated under reduced pressure below 50° and polarimetric measurements were made in chloroform solution, in a 2 dm. tube. Substances were recrystallised to constant m. p.

Simplified Preparation of 2-Methyl β-Methylgalactoside (I).—The original preparation of this substance by Oldham and Bell (*loc. cit.*) necessitated seven distinct stages from β-methylgalactoside. It can now be obtained in four operations, since we have found that 3 : 4-*iso*propylidene β-methylgalactoside can be obtained readily if the reaction between the galactoside and acetone is catalysed by sulphuric acid. Micheel's method (*Ber.*, 1929, **62**, 687) using hydrogen chloride as catalyst gives impractically small yields. 22 G. of β-methylgalactoside were shaken for 24 hours with 2·2 l. of acetone containing 0·5% of sulphuric acid; complete solution resulted. The acid was then neutralised with solid sodium carbonate, and the filtered solution evaporated to a thick syrup at p_H 7·4. 13 G. of crystals, m. p. 134°, $[\alpha]_D^{20°}$ + 21° (water), were deposited from a benzene solution of the crude product. The constants agree with those given by Micheel. The material remaining in the benzene was largely diacetone galactose. 10·6 G. of the above crystals were heated for an hour at 100° with 1·5 mols. of trityl chloride dissolved in 50 ml. of dry pyridine. The whole was poured into water and triturated until solid. The crude material was washed with water, dried, dissolved in benzene, and precipitated by addition of light petroleum. The solid thus obtained was twice methylated by Purdie's reagents, and the crude product subjected to controlled hydrolysis by dissolution in a mixture of 430 ml. of acetone and 200 ml. of N/10-hydrochloric acid, the solution being boiled for 1·5 hours. The acid was then neutralised by silver carbonate, solids filtered off, and the acetone removed by distillation. Trityl derivatives separated and were removed by chloroform extraction. The water solution, on evaporation, yielded a crystalline residue, giving, after crystallisation from ethyl acetate, 5·5 g. of needles, m. p. 131—132°, identical with the 2-methyl β-methylgalactoside of Oldham and Bell.

4 : 6-*Benzylidene 2-Methyl β-Methylgalactoside* (II).—5·5 G. of (I) were shaken for 3 hours with 14 ml. of freshly distilled benzaldehyde and 14 g. of anhydrous zinc chloride. On addition of 50 ml. of water a small quantity of the crystalline product was precipitated, the bulk remaining in solution, from which it was isolated, after precipitation of the zinc by hot sodium carbonate solution and filtration, by evaporation of the filtrate to small volume; crystallisation then ensued. Recrystallised from alcohol, 4·7 g. were obtained, m. p. 160°, $[\alpha]_D^{20°}$ − 32·8°. Oldham

and Bell (*loc. cit.*) erroneously gave m. p. 169° and $[\alpha]_D$ − 59°. By appropriate treatment, 0·66 g. of (I) was recovered from the original mother-liquors; hence the yield of (II) was 64%.

3-p-*Toluenesulphonyl* 4 : 6-*Benzylidene* 2-*Methyl* β-*Methylgalactoside* (III).—4·64 G. of (II) were treated with *p*-toluenesulphonyl chloride in dry pyridine. When the mixture was poured into dilute alkali solution, the product crystallised. Extraction of the alkaline liquors recovered 1·2 g. of (II), which were again treated with toluenesulphonyl chloride. 4·74 G. (66%) of needles (from methyl alcohol) were obtained, m. p. 126°, $[\alpha]_D^{20°}$ + 38·4° (*c* = 2·5) (Found: C, 58·6; H, 5·8; OMe, 13·3; S, 7·5. $C_{22}H_{26}O_8S$ requires C, 58·7; H, 5·8; OMe, 13·7; S, 7·1%).

3-p-*Toluenesulphonyl* 2 : 4 : 6-*Trimethyl* β-*Methylgalactoside* (IV).—4·6 G. of (III) were boiled with a mixture of 100 ml. of acetone and 50 ml. of water containing hydrochloric acid equivalent to N/20, until a constant rotation was observed (4 hours). After neutralisation of the acid with silver carbonate the solvents were distilled off, leaving 3·5 g. of crystals, essentially 3-*p*-toluenesulphonyl 2-methyl β-methylgalactoside, but contaminated with reducing material which proved impossible to eliminate. The crude product was therefore methylated four times with Purdie's reagents, 3·15 g. of non-reducing crystals being obtained. Recrystallised from methyl alcohol, the *substance* (needles) had m. p. 130° and $[\alpha]_D^{22°}$ + 20·4° (Found: C, 51·9; H, 6·9; OMe, 31·0; S, 8·5. $C_{17}H_{26}O_8S$ requires C, 52·3; H, 6·7; OMe, 31·8; S, 8·2%).

2 : 4 : 6-*Trimethyl* β-*Methylgalactoside* (V).—3·15 G. of (IV) were heated at 90° for 14 hours with 82 ml. of 6% sodium methoxide in methyl alcohol; 80 ml. of water were added, and the whole extracted six times with 40 ml. lots of chloroform. Evaporation of the dried chloroform extract left a crystalline residue (sulphur-free). On recrystallisation from light petroleum (b. p. 60—80°), 1·74 g. (91·5%) of extremely long, silky needles were obtained, m. p. 111—112°, $[\alpha]_D^{23°}$ − 40·9° (*c* = 5) (Found: C, 49·95; H, 8·5; OMe, 51·1. $C_{10}H_{20}O_6$ requires C, 50·8; H, 8·5; OMe, 52·5%).

2 : 4 : 6-*Trimethyl* α-*Galactose* (VI).—1·4 G. of (V) were boiled with 50 ml. of N/3-hydrochloric acid until a constant rotation was observed. After the usual treatment, an ethereal solution of the product gave, on evaporation, 1·25 g. (94%) of a colourless syrup, which immediately crystallised. On recrystallisation from dry ether, needles, m. p. 102—105°, were obtained, mixed m. p. with the substance of Percival and Somerville (m. p. 103—105·5°), (1) 103—106°; (2) 102—105°. The sugar showed downward mutarotation in water (*c*, 3·4): $[\alpha]_D^{23°}$ (initial) + 124°; (at equilibrium) + 90·4°. Dr. Percival (private communication) has redetermined the constants of his material and finds $[\alpha]_D$ (initial) + 124°, (at equilibrium) + 89°, instead of + 124° ⟶ + 93° (Found: C, 48·6; H, 8·2; OMe, 41·5. Calc. for $C_9H_{18}O_6$: C, 48·6; H, 8·1; OMe, 41·9%).

Simplified Preparation of 6-p-*Toluenesulphonyl* α-*Methylgalactoside* (VII).—250 G. of 6-*p*-toluenesulphonyl diacetone galactose (Freudenberg and Hixon, *Ber.*, 1923, **56**, 2123) were boiled with 2·5 l. of methyl alcohol containing 2% of hydrogen chloride. After 30 minutes, the solution was cooled; a quantity of the product then crystallised. Further crops were obtained by adding methyl alcohol and concentrating the mother-liquor each time. Yield, 111 g., m. p. 170°, $[\alpha]_D^{20°}$ + 103·5° (pyridine) (cf. Ohle and Thiel, *loc. cit.*).

6-p-*Toluenesulphonyl* 2-*Methyl* 3 : 4-iso*Propylidene* α-*Methylgalactoside* (VIII).—110 G. of (VII) were condensed with acetone (Ohle and Thiel, *loc. cit.*), 75 g. of the *iso*propylidene derivative, m. p. 129—130°, being obtained. This was methylated four times with Purdie's reagents. Yield, 69 g. of needles (from light petroleum, b. p. 60—80°), m. p. 90°, $[\alpha]_D^{20°}$ + 90·9° (*c* = 1·7) (Found: C, 54·6; H, 6·4; OMe, 15·6; S, 8·1. $C_{18}H_{26}O_8S$ requires C, 55·1; H, 6·6; OMe, 15·8; S, 8·1%).

2-*Methyl* 3 : 4-iso*Propylidene* α-*Methylgalactoside* (IX).—68 G. of (VIII) were boiled for 36 hours with a mixture of 400 ml. of alcohol and 400 ml. of 30% aqueous caustic potash. The alcohol was then distilled off, and the watery solution extracted six times with chloroform. The residue obtained on evaporation of the chloroform was dissolved in a small amount of benzene, and this solution extracted repeatedly with water. The aqueous extract was then extracted six times with chloroform; evaporation of the latter solvent from the combined extracts left a residue which crystallised from light petroleum (b. p. 60—80°) in prisms (20 g.), m. p. 77—78°, $[\alpha]_D^{20°}$ + 157·4° (*c* = 1·0) (Found: C, 53·0; H, 8·0; OMe, 25·6. $C_{11}H_{20}O_6$ requires C, 53·2; H, 8·1; OMe, 25·0%).

2 : 6-*Dimethyl* 3 : 4-iso*Propylidene* α-*Methylgalactoside* (X).—Methylation of (IX) by the Purdie reagents yielded a syrup which could not be crystallised, even after distillation at 120°/0·1 mm. It had $n_D^{20°}$ 1·4550 and $[\alpha]_D^{20°}$ + 155° (in water, *c* = 1) (Found: OMe, 34·6. $C_{12}H_{22}O_6$ requires OMe, 35·5%). Hydrolysis by 5% hydrochloric acid gave crystalline 2 : 6-dimethyl β-galactose (Oldham and Bell, *loc. cit.*).

2 : 6-*Dimethyl* α-*Methylgalactoside* 3 : 4-*Dinitrate* (XI).—It was not found possible to obtain a crystalline methylgalactoside from (X) by hydrolytic removal of the acetone residue, but a crystalline *dinitrate* was produced by the following method. 14·6 G. of (X) were treated for 30 minutes at 0° with 100 ml. of a 30% solution of fuming nitric acid in dry chloroform. The solution was washed first with water, then with concentrated potassium bicarbonate solution. The residue remaining after evaporation of the chloroform was dissolved in benzene and extracted several times with water; the benzene layer, on evaporation, left a colourless syrup (yield, almost theoretical), which crystallised on keeping. Recrystallised from light petroleum (b. p. 60—80°), the substance (stout needles) had m. p. 50—51° and $[\alpha]_D^{20°}$ + 160·7° (c = 2) (Found: C, 34·8; H, 5·2; OMe, 29·3; N, 9·2. $C_9H_{16}O_{10}N_2$ requires C, 34·6; H, 5·1; OMe, 29·8; N, 9·0%).

2-*Methyl* α-*Methylgalactoside* (XII).—20 G. of (IX) were boiled with 10% aqueous acetic acid until a constant rotation was observed. The solvent was distilled off, leaving 15·7 g. of a colourless syrup which would not crystallise. $[\alpha]_D^{18°}$ + 180° (in methyl alcohol, c = 3·5) (Found: OMe, 29·5. $C_8H_{16}O_6$ requires OMe, 29·8%). A specimen of this *substance*, hydrolysed in the usual way, yielded crystalline 2-methyl β-galactose (Oldham and Bell, *loc. cit.*).

4 : 6-*Benzylidene* 2-*Methyl* α-*Methylgalactoside* (XIII).—18·5 G. of (XII) were treated as in the preparation of (II), yielding 20 g. (80%) of needles (from alcohol), m. p. 152°, $[\alpha]_D^{20°}$ + 131·6° (c = 2·3) (Found: C, 60·7; H, 6·7; OMe, 21·5. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·75; OMe, 20·9%).

3-p-*Toluenesulphonyl* 4 : 6-*Benzylidene* 2-*Methyl* α-*Methylgalactoside* (XIV).—20 G. of (XIII) were toluenesulphonylated as for the preparation of (III), yielding 27 g. (90%) of needles (from methyl alcohol), m. p. 145°, $[\alpha]_D^{20°}$ + 158·4° (c = 1·3) (Found: C, 58·8; H, 5·6; OMe, 14·2; S, 7·1. $C_{22}H_{26}O_8S$ requires C, 58·7; H, 5·8; OMe, 13·7; S, 7·1%).

3-p-*Toluenesulphonyl* 2 : 4 : 6-*Trimethyl* α-*Methylgalactoside* (XV).—26 G. of (XIV) were treated as for the preparation of (IV). The product was contaminated with reducing material, but crystallisation from 25% aqueous alcohol removed this. Recrystallised from methyl alcohol, the *product* (needles, 12 g.; 66%) had m. p. 112°, $[\alpha]_D^{20°}$ + 150·0° (c = 1·1) (Found: C, 52·1; H, 6·6; OMe, 31·3; S, 8·2. $C_{17}H_{26}O_8S$ requires C, 52·3; H, 6·7; OMe, 31·8; S, 8·2%). About 5 g. of strongly reducing syrup were isolated from the mother-liquors.

2 : 4 : 6-*Trimethyl* α-*Methylgalactoside* (XVI).—10·5 G. of (XV) were saponified as in the preparation of (V); 72 hours' treatment were required in this instance, five times longer than the period necessary to effect complete saponification of the β-compound. 4·8 G. of needles (from light petroleum, b. p. 60—80°) were obtained. Yield, 80%. After rigorous drying at 50° over phosphoric oxide the *substance* melted at 73—74°, but exposure to air rapidly lowered this value to 50°. The galactoside is very hygroscopic. $[\alpha]_D^{20°}$ + 163·9° (in water, c = 0·9) (Found: C, 50·4; H, 8·8; OMe, 51·0. $C_{10}H_{20}O_6$ requires C, 50·8; H, 8·5; OMe, 52·5%). Hydrolysis by dilute hydrochloric acid produced crystalline 2 : 4 : 6-trimethyl α-galactose (VI). The sugar, treated with phenylhydrazine, formed 4 : 6-dimethyl galactosazone, m. p. 159—160° alone and mixed with an authentic specimen provided by Dr. Percival. Further evidence proving the identity of our product with that of Percival and Somerville was afforded by preparation of the 2 : 4 : 6-trimethyl galactonamide of these authors; our amide had m. p. 166° alone or mixed with authentic material.

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