

**211. Use of the Benzyl Radical in Syntheses of Methylated Sugars.
Part II. 4 : 6-Dimethyl Galactose.**

By J. S. D. BACON, D. J. BELL, and J. LORBER.

The synthetic preparation of 4 : 6-*dimethyl galactose* is described. The properties of the new sugar show that the dimethyl galactose isolated from methylated damson gum by Hirst and Jones (J., 1939, 1482) is not the 4 : 6-derivative.

SOME time ago Professor E. L. Hirst informed us privately, in advance of publication, that experiments in his laboratory on the structure of damson gum had led to the isolation of a crystalline dimethyl galactose. From the evidence at that time available this was considered to be the 4 : 6-dimethyl derivative (see Hirst and Jones, J., 1939, 1482). At Professor Hirst's invitation we commenced experiments on the synthesis of this sugar with a view to assisting in its identification, but, despite varied methods of approaching the problem, we failed to obtain a crystalline compound displaying the properties of the substance isolated at Bristol. The reason for this became apparent when Hirst and Jones informed us that, as a result of further examination of their sugar, they had obtained a final proof that it was in fact the 2 : 4-derivative already described by Baldwin and Bell (J., 1938, 1461) and by Smith (J., 1939, 1724) (see Hirst and Jones, forthcoming paper).

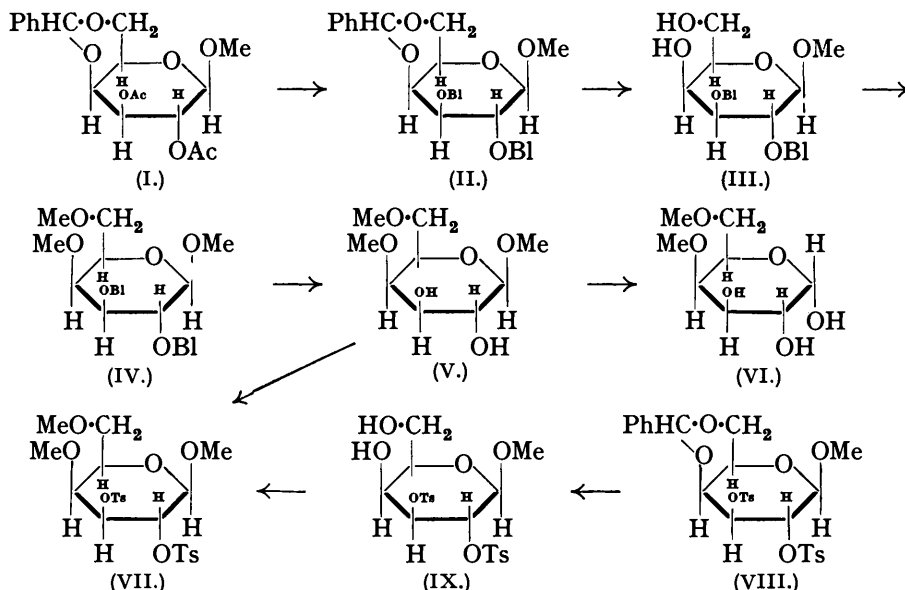
The synthesis of 4 : 6-*dimethyl galactose* about to be detailed follows closely in its development the preparation of the corresponding glucose derivative as described by Bell and Lorber (Part I, this vol., p. 453). 2 : 3-Diacetyl 4 : 6-benzylidene β -methylgalactoside (I) was converted into the 2 : 3-*dibenzyl* derivative (II) by the procedure of Zemplén, Csürös, and Angyal (*Ber.*, 1937, 70, 1848). This substance, on mild acid hydrolysis, yielded 2 : 3-*dibenzyl* β -methylgalactoside (III), which was methylated to give the 4 : 6-*dimethyl* derivative (IV). The action of metallic sodium and alcohol on the last substance eliminated the benzyl radicals, forming 4 : 6-*dimethyl* β -methylgalactoside (V), from which the free, crystalline sugar was obtained after hydrolysis with mineral acid.

In addition to the evidence afforded by the method of synthesis, proof of the constitution of the new sugar was obtained as follows: (1) Methylation of the glycoside (V), followed by acid hydrolysis, yielded 2 : 3 : 4 : 6-tetramethyl galactose, which was identified as the crystalline anilide. The sugar is therefore derived from galactose.

(2) Treatment of the sugar with phenylhydrazine yielded 4 : 6-dimethyl galactosazone identical with that prepared from 2 : 4 : 6-trimethyl galactose (see Percival and Somerville, J., 1937, 1617; Bell and Williamson, J., 1938, 1196; Hirst and Jones, *loc. cit.*). The two methyl groups must occupy positions 4 and 6 and there can of course be no substitution of position 2.

(3) Tosylation of (V) yielded the 2 : 3-*derivative* (VII), which, unexpectedly, could not

be crystallised. Treated with sodium iodide and acetone (Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366), the material was recovered unchanged. From



(Bl = CH_2Ph ; Ts = $\text{SO}_2\cdot\text{C}_6\text{H}_5$. With the exception of VII, all these substances crystallised.)

2:3-ditosyl 4:6-benzylidene β -methylgalactoside (VIII), crystalline 2:3-ditosyl β -methylgalactoside (IX) was obtained. On methylation this yielded a product identical with (VII). Evidence is thus afforded that a methyl group occupies position 6.

(4) When the new sugar was dissolved in cold methyl alcohol containing hydrogen chloride, a pronounced rise in the specific rotation was observed, indicating that furanoside formation was not taking place and that a methyl group must occupy position 4.

EXPERIMENTAL.

Solvents were evaporated under reduced pressure. Rotations were measured in chloroform solution in a 2 dm. tube, unless otherwise stated.

2:3-Dibenzyl 4:6-Benzylidene β -Methylgalactoside (II).—10.5 G. of 2:3-diacetyl 4:6-benzylidene β -methylgalactoside (Müller, Móricz, and Verner, *Ber.*, 1939, **72**, 745) were treated with 100 ml. of benzyl chloride, as described by Bell and Lorber (*loc. cit.*); 125 ml. of xylene were used, and the heating continued for 3 hours. The greater part of the aromatic constituents were removed by steam-distillation and the solid that separated was filtered off (14.5 g.) and recrystallised from aqueous alcohol; m. p. 132.5–133.5°, $[\alpha]_D^{20.5} + 50.2^\circ$ ($c = 7$) (Found: C, 73.1; H, 6.7; OMe, 6.8. $\text{C}_{28}\text{H}_{30}\text{O}_6$ requires C, 72.7; H, 6.5; OMe, 6.7%).

2:3-Dibenzyl β -Methylgalactoside (III).—14.5 G. of (II) were dissolved in 85 ml. of *n*-hydrochloric acid-acetone (1:20) and refluxed for 3 hours until a constant polarimetric measurement was attained. Water and potassium bicarbonate were added and the benzaldehyde was removed by steam-distillation. The aqueous suspension was then extracted five times with chloroform. The chloroform extract dried over anhydrous sodium sulphate and evaporated to dryness, yielded 6.5 g. of a syrup. This later crystallised and was recrystallised from light petroleum (b. p. 60–80°)-ether; m. p. 70–71°, $[\alpha]_D^{18} + 10.6^\circ$ ($c = 4$) (Found: C, 67.9; H, 6.9; OMe, 8.7. $\text{C}_{21}\text{H}_{22}\text{O}_6$ requires C, 67.4; H, 6.95; OMe, 8.3%).

2:3-Dibenzyl 4:6-Dimethyl β -Methylgalactoside (IV).—12 G. of (III) were methylated with Purdie's reagents. After the third methylation the syrup obtained was distilled (230–235°/0.05 mm.) in two fractions. The first crystallised after a day at -10° and was recrystallised from light petroleum (b. p. below 40°); needles separated at -10° (Found: OMe, 20%). The second fraction had OMe, 17%.

The whole of the material was methylated again, giving a mixture of crystals and syrup. By successive crystallisations from light petroleum (b. p. below 40°) a substance of constant

m. p. was obtained. 9.0 G. of (IV) were used for the next operation, but less than a gram was carefully purified. M. p. 68—69°, $[\alpha]_D^{17.5} + 3.05^\circ$ ($c = 6.5$) (Found: C, 69.1; H, 7.4; OMe, 24.05. $C_{23}H_{30}O_6$ requires C, 68.7; H, 7.5; OMe, 23.1%).

4 : 6-Dimethyl β -Methylgalactoside (V).—9.0 G. of (IV) were dissolved in 50 ml. of alcohol and 15 g. of sodium were added down a wide air-condenser, more alcohol being needed later to keep the contents of the flask mobile. When most of the sodium had been converted into ethoxide the last traces were removed by heating on the water-bath, water was added, and carbon dioxide passed in. Solid that separated was filtered off, and the filtrate concentrated. Addition of acetone and further distillation enabled most of the inorganic solid to be removed by filtration, and the final filtrate, taken to dryness, was partitioned between water and benzene. The aqueous layer, five times extracted with benzene, was taken to dryness. The benzene layer, after extraction with an equal volume of water, was dried over anhydrous sodium sulphate and also evaporated to dryness. It yielded 2 g. of a syrup, which was again treated with sodium in alcohol, and isolated as above. The material from the aqueous layers crystallised (2.5 g.). Difficulty was experienced in the purification of the crystals, but after fractional distillation in a high vacuum a homogeneous product was obtained. It crystallised from dry ether in needles, m. p. 140°, $[\alpha]_D^{20} - 41.5^\circ$ ($c = 4$) (Found: C, 48.2; H, 8.2; OMe, 41.0. $C_9H_{16}O_6$ requires C, 48.6; H, 8.1; OMe, 41.9%).

2 : 3-Ditosyl 4 : 6-Benzylidene β -Methylgalactoside (VIII).—3 G. of 4 : 6-benzylidene β -methylgalactoside were dissolved in the minimum quantity of pyridine, 6 g. of *p*-toluenesulphonyl chloride added, and the mixture left at 38° for 2 days. After addition of water the solid crystallised and was filtered off and washed with water and alcohol. Yield, 5 g., recrystallised from alcohol-acetone; m. p. 168—170°, $[\alpha]_D^{20} + 29.5^\circ$ ($c = 3$) (Found: C, 57.05; H, 5.04; S, 11.15; OMe, 5.3. $C_{28}H_{30}O_{10}S_2$ requires C, 59.6; H, 5.1; S, 10.8; OMe, 5.25%).

2 : 3-Ditosyl β -Methylgalactoside (IX).—5 G. of (VIII) were refluxed with 165 ml. of acetone, 50 ml. of water, and 10 ml. of *N*-hydrochloric acid until there was no further polarimetric change. Barium carbonate was added to neutralise the acid, solid material filtered off, and the filtrate concentrated. Chloroform was added to the concentrate and after separation was washed several times with potassium bicarbonate solution and water. When dried over anhydrous sodium sulphate and evaporated to dryness, it yielded a gelatinous mass. This was soluble in alcohol, benzene, acetone, chloroform and ethyl acetate, sparingly soluble in ether, light petroleum, and water. Crystallisation from alcohol resulted in the recovery of 1.3 g. of (V), m. p. 168—169°, and from the mother-liquors the substance itself was obtained. Yield, 1.7 g. of needles, recrystallised from acetone-light petroleum (b. p. 60—80°), m. p. 149—150°, $[\alpha]_D^{19} + 18.4^\circ$ ($c = 2.4$) (Found: C, 49.95; H, 5.1; S, 13.3; OMe, 6.2. $C_{21}H_{26}O_{10}S_2$ requires C, 50.2; H, 5.2; S, 12.75; OMe, 6.2%).

2 : 3-Ditosyl 4 : 6-Dimethyl β -Methylgalactoside (VII).—1.6 G. of (IX) were methylated three times with Purdie's reagents. The product failed to crystallise. It was treated with charcoal in ethereal solution and dried (Found: OMe, 17.12. $C_{23}H_{30}O_{10}S_2$ requires OMe, 17.5%).

The properties of this substance was compared with that prepared by tosylation of (V) (see below).

Tosylation of (V).—0.22 G. of (V) was dissolved in the minimum quantity of pyridine, and 0.8 g. of tosyl chloride added. After 40 hours at 38° water was added, and the substance extracted with benzene. The benzene solution was washed with acid and alkali and dried before evaporation to dryness. The product failed to crystallise. The syrup was again treated with fresh reagents, but no crystalline material was obtained (Found: OMe, 17.0. $C_{23}H_{30}O_{10}S_2$ requires OMe, 17.5%).

The rotations of the two substances were $+5^\circ$ ($c = 1.76$) from (V) and $+6^\circ$ ($c = 2.34$) from (IX).

Neither substance, when treated with sodium iodide in acetone at 100° under the usual conditions, gave any evidence of replacement of tosyl by iodine.

4 : 6-Dimethyl α -Galactose (VI).—1.25 G. of (V) were hydrolysed with 50 ml. of *N*-hydrochloric acid. The solution was heated in a water-bath and hydrolysis was complete after 2 hours. The acid was neutralised with lead carbonate, acetone (2 vols.) added, and the solid filtered off. The filtrate, when evaporated to dryness (below 70°), gave a residue, which was exhaustively extracted with ethyl acetate containing a little alcohol. When this was concentrated the sugar began to crystallise (0.6 g.); recrystallised from ethyl acetate containing alcohol, it had m. p. 131—133° (Found: C, 45.6; H, 7.6; OMe, 29.4. $C_8H_{16}O_6$ requires C, 46.15; H, 7.7; OMe, 29.8%).

A solution of 0.2445 g. of the sugar in 10 ml. of water displayed the following optical behaviour :

Mins.	0.0	2.5	6.0	10	15	22	30	895	1135
$[\alpha]_D^{19}$	+133°	+131.7°	+130.1°	+129.0°	+127.0°	+124.2°	+121.9°	+76.9°	+76.9°

(The zero value was obtained by extrapolation.)

0.12 G. of the sugar, dissolved in 10 ml. of acid (1%) methyl alcohol, showed $[\alpha]_D^{20}$ rising from +58° to +87.5° in 30 hours. The solution was then boiled under reflux for 3 hours and neutralised with silver carbonate, and the residue after removal of the solvents methylated twice with Purdie's reagents (n_D^{20} 1.4481). The glycosidic methyl group was removed by hydrolysis with *N*-hydrochloric acid, and 0.08 g. of the sugar so obtained refluxed with absolute alcohol and 0.2 ml. of aniline for an hour. Crystals of the anilide separated on cooling, m. p. 196—197°, mixed m. p. with authentic 2 : 3 : 4 : 6-tetramethyl galactose anilide, 196—197°.

The osazone of the sugar was prepared in the usual way and obtained in good yield. After two recrystallisations it had m. p. 160—162°, mixed m. p. with authentic 4 : 6-dimethyl galactosazone 160—161°. The mutarotation of the compound confirms its identity :

Time	8 mins.	28 mins.	3 hrs.	23	29	47	71	95	119	143
$[\alpha]_D^{20}$	+51.0°	+40.0°	+35.5°	+19.0°	+16.5°	+0.5°	-10.5°	-16.3°	-21.3°	-21.0°

Attempts were made to prepare an anilide by the usual methods, but in all three cases the product was not crystalline and, in fact, appeared to contain no aniline. It was not found possible to recover the sugar from the reaction mixture.

THE BIOCHEMICAL LABORATORY, CAMBRIDGE.

[Received, July 9th, 1940.]