263. *Acyl Migration in a Derivative of Galactose.*

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Crystalline 2 : 3 : 6-*tribenzoyl* β-*methylgalactoside* on methylation with Purdie's reagents yielded an amorphous methyl ether, from which, after appropriate treatment, some 2-methyl β-methylgalactoside was isolated. This is believed to be the first example of acyl migration observed in the galactose series.

In order to attempt certain substitution reactions in position 4 of the galactose molecule, we first prepared 2 : 3 : 6-*tribenzoyl* β-*methylgalactoside* by a method essentially similar to those employed in the syntheses of the 2 : 3 : 6-tribenzoates of α- and β-methylglucosides (Bell, J., 1934, 1177; Levene and Raymond, *J. Biol. Chem.*, 1932, **97**, 763). The essential steps may be summarised as follows: 4 : 6-benzylidene β-methylgalactoside (A) ⟶ 2 : 3-*dibenzoyl* 4 : 6-*benzylidene* β-*methylgalactoside* (B) ⟶ 2 : 3-*dibenzoyl* β-*methylgalactoside* (C) ⟶ 2 : 3 : 6-tribenzoyl β-methylgalactoside (D). The final stage depended on preferential benzoylation of the primary alcoholic group of (C). Proof of the positions occupied by the benzoyl groups in the new tribenzoate may be adduced as follows: (1) Controlled acid hydrolysis of (B) yielded a crystalline dibenzoyl methylhexoside, (C). Since (B) was regenerated in 90% yield on treatment of (C) with benzaldehyde and zinc chloride, there seems to be no question that (C) has the constitution assigned above, *i.e.*, the acyl groups occupy positions 2 and 3. (2) We have no grounds for suspecting that acyl migration takes place during acylation in pyridine solution. (3) The only tribenzoyl β-methylgalactoside isomeric with (D), and having positions 2 and 3 benzoylated, is the 2 : 3 : 4-derivative. This is known only as a syrup, but its 6-*p*-toluenesulphonate is described by Müller (*Ber.*, 1931, **64**, 1820) as having m. p. 194° and $[\alpha]_D$ in chloroform, + 148·7°; he has also shown that the substance reacts quantitatively with sodium iodide in acetone, with formation of the 6-iodohydrin. On the other hand, (D) yielded a p-*toluenesulphonyl* derivative of m. p. 175° and $[\alpha]_D$ in chloroform + 58·9°; it did not react with sodium iodide and therefore was not sulphonylated in position 6.

In an attempt to prepare the unknown 4-methyl galactose (cf. Munro and Percival, J., 1936, 640), we treated (D) with Purdie's reagents after the manner in which Levene and Raymond (*loc. cit.*) prepared 4-methyl glucose from 2 : 3 : 6-tribenzoyl β-methylglucoside, and obtained an amorphous product having the composition of a tribenzoyl dimethyl hexose; on debenzoylation this gave (*a*) an amorphous portion (OMe, 27%), and (*b*) crystalline 2-methyl β-methylgalactoside (Oldham and Bell, *J. Amer. Chem. Soc.*, 1938, **60**, 323).

Since the above results pointed to acyl migration having taken place, we carried out a further experiment to confirm that (D) did not, in fact, possess a free hydroxyl group in position 2, and thus make certain that a benzoyl radical had indeed moved from there. We prepared crystalline 2-p-*toluenesulphonyl* β-*methylgalactoside* by a method which ensured substitution in the 2-position (Bell and Williamson, J., 1938, 1196), and benzoylation of this yielded 3 : 4 : 6-*tribenzoyl* 2-p-*toluenesulphonyl* β-*methylgalactoside*, m. p. 143—144°, $[\alpha]_D$ in chloroform, + 45·5°. The difference in properties between this substance and the derivative of (D) renders it certain that we have here to deal with a genuine instance of acyl migration.

The behaviour of (D) towards Purdie's reagents falls into line with similar observations in the glucose series (cf. Haworth, Hirst, and Teece, J., 1931, 2858; Robertson, J., 1933, 737). As far as we are aware, no other instance of acyl migration in a galactose derivative has hitherto been recorded.

Experimental.

Solvents were evaporated under diminished pressure. Polarimetric measurements were made on chloroform solutions (unless stated otherwise), using a 2-dm. tube.

4 : 6-*Benzylidene* β-*Methylgalactoside* (I) (cf. Oldham and Bell, *loc. cit.*).—The yield of this substance, which is rather soluble in cold water, has been considerably improved by modifying Freudenberg, Toepffer, and Andersen's method (*Ber.*, 1928, **61**, 1750): 30 g. of β-methylgalactoside were shaken for 20 hours with 80 ml. of freshly distilled benzaldehyde and 25 g. of powdered,

anhydrous zinc chloride. An excess of hot saturated sodium carbonate solution was then added, and the whole heated at 100° to precipitate the zinc. The filtered, zinc-free solution was evaporated to dryness after adding sufficient water to steam-distil the excess benzaldehyde. An alcoholic extract of the residue thus obtained yielded several crops of needles; on recrystallisation from alcohol, 27 g. were finally obtained, m. p. 198—201°.

2 : 3-*Dibenzoyl* 4 : 6-*Benzylidene* β-*Methylgalactoside* (II).—To 21 g. of (I), dissolved in 25 ml. of dry pyridine and kept cold, a mixture of 20 ml. each of dry benzene and benzoyl chloride was added; the whole was then kept at 38° for 24 hours. On adding 20 ml. of water, a mass of crystals formed. These were washed with water and light petroleum, and recrystallised from alcohol containing some acetone. 28 G. of needles were thus obtained, m. p. 195—196°, $[\alpha]_D^{17°}$ + 156·1° (c = 3·4) (Found : C, 68·5; H, 5·2; OCH_3, 6·4; $CO{\cdot}C_6H_5$, 42·6. $C_{28}H_{26}O_8$ requires C, 68·5; H, 5·3; OCH_3, 6·3; $CO{\cdot}C_6H_5$, 42·8%).

2 : 3-*Dibenzoyl* β-*Methylgalactoside* (III).—43 G. of (II) were boiled for 5 hours with a mixture of 774 ml. of acetone and 86 ml. of 0·25N-hydrochloric acid. After the acid had been neutralised with solid barium carbonate, the acetone was distilled off, and the crude product dissolved in 300 ml. of warm benzene. The benzene extract was rapidly washed with sodium bisulphite solution and finally with water; on cooling, it deposited 38 g. of needles which contained solvent of crystallisation. On recrystallisation of these from ethyl acetate–light petroleum (b. p. 60—80°), 24·5 g. of fine needles were obtained. These had m. p. 136·5—138·5°, $[\alpha]_D$ + 101·9° (c = 2·8) (Found : C, 62·1; H, 5·81; OCH_3, 8·0; $CO{\cdot}C_6H_5$, 53·5. $C_{21}H_{22}O_8$ requires C, 62·7; H, 5·47; OCH_3, 7·7; $CO{\cdot}C_6H_5$, 52·2%). The substance also crystallises from chloroform (with 1 mol. $CHCl_3$), m. p. 80°, $[\alpha]_D$ + 80·6°. Drying at 70—75° for 30 minutes yields material identical with that crystallised from ethyl acetate–light petroleum.

Regeneration of (II) *from* (III). 2 G. of (III) were shaken for 5 hours with 10 ml. of freshly distilled benzaldehyde and 1 g. of anhydrous zinc chloride. Benzene was added, the bulk of the excess benzaldehyde washed out with bisulphite solution, and any acid remaining neutralised with sodium hydroxide. On evaporating the dehydrated benzene solution to dryness, and crystallising the residue from alcohol–acetone (2 : 1), 2·2 g. of needles were obtained (90% yield) having m. p. 198° and $[\alpha]_D$ + 155° (c = 4). The m. p. was not depressed on mixing with an authentic specimen of (II).

2 : 3 : 6-*Tribenzoyl* β-*Methylgalactoside* (IV).—To 8·75 g. of (III), dissolved in 54 ml. of dry pyridine, a solution of 2·8 g. (1·1 mols.) of benzoyl chloride in 14 ml. of benzene was added drop by drop during 30 minutes, the reaction mixture being cooled in running water. After it had stood at room temperature for 4 hours, 6 ml. of water were added, followed 30 min. later by 150 ml. of benzene and much ice-water. The benzene layer was washed first with ice-cold N-sulphuric acid till acid to Congo-red, then with water. The dehydrated benzene layer was evaporated to dryness, and the resulting syrup crystallised from 75% alcohol. 5·2 G. (47%) of stout needles were obtained; m. p. 143—144°, $[\alpha]_D^{18°}$ + 56·1° (c = 8) (Found : C, 66·0; H, 5·05; OCH_3, 6·2; $CO{\cdot}C_6H_5$, 61·9. $C_{28}H_{26}O_9$ requires C, 66·4; H, 5·1; OCH_3, 6·1; $CO{\cdot}C_6H_5$, 62·2%).

4-p-*Toluenesulphonyl* 2 : 3 : 6-*Tribenzoyl* β-*Methylgalactoside* (V).—1·1 G. of (IV) were treated with a 50% excess of the sulphonyl chloride in dry pyridine for 48 hours at 38°. On addition of water to the reaction mixture, the product crystallised. By recrystallisation from alcohol–acetone (1 : 1), 1·2 g. of needles were obtained; m. p. 175°, $[\alpha]_D^{20°}$ + 58·9° (c = 1·8) (Found : C, 63·1; H, 5·2; OCH_3, 4·9; S, 4·6. $C_{35}H_{32}O_{11}S$ requires C, 63·6; H, 4·8; OCH_3, 4·7; S, 4·8%). The substance was unaffected by treatment with sodium iodide in acetone at 100°.

Methylation of (IV).—5 G. of material were twice methylated with Purdie's reagents, 4 g. of an uncrystallisable glass being finally obtained. This approximated in composition to a tribenzoyl dimethyl hexose (Found : OCH_3, 11·4; $CO{\cdot}C_6H_5$, 58·9%). On debenzoylation by Zemplén's procedure, a syrup was obtained which partly crystallised. The crystals (Found : OCH_3, 29·8. Calc. for $C_8H_{16}O_6$: OCH_3, 29·6%), on recrystallisation from ethyl acetate, had m. p. 132—133°, not depressed on admixture with an authentic specimen of 2-methyl β-methylgalactoside (m. p. 131—132°). In water, $[\alpha]_D^{18°}$ was + 1·2° (c = 1·5); Oldham and Bell found $[\alpha]_D$ + 1·69°.

The syrupy residue could not be shown to contain any isomeric methyl methylgalactosides. Treatment with acid–acetone yielded a small amount of crystalline 3 : 4-monoacetone 2-methyl β-methylgalactoside (Oldham and Bell), and the residues from this gave some galactosazone after appropriate hydrolytic treatment.

2-p-*Toluenesulphonyl* 3 : 4-iso*Propylidene* 6-*Trityl* β-*Methylgalactoside* (VI).—10·5 G. of monoacetone β-methylgalactoside were treated with trityl chloride in pyridine according to Bell and Williamson (*loc. cit.*). The crude product (25 g.) was dissolved in 100 ml. of dry pyridine, 12 g. of *p*-toluenesulphonyl chloride added, and the whole kept at 38° for 48 hrs. The reaction mixture was then poured into dilute sodium hydroxide, and the gum which separated was stirred until solid. The crude product was dissolved in acetone and precipitated with dilute ammonia. The precipitate was crystallised from alcohol containing a little acetone. Yield, 26 g. of needles, m. p. 163—164°, $[\alpha]_D^{21°}$ − 8·4° (c = 2·6) (Found : C, 68·4 : H, 5·9; OCH_3, 5·3; S, 5·3. $C_{36}H_{38}O_8S$ requires C, 68·5; H, 6·0; OCH_3, 5·0; S, 5·1%).

2-p-*Toluenesulphonyl* β-*Methylgalactoside* (VII).—3·5 G. of (V) were dissolved in a mixture of 100 ml. of acetone, 22 ml. of water, and 3·3 ml. of N-hydrochloric acid, the whole heated to 100° and the course of the reaction followed polarimetrically. The observed change in α was very small; after 220 minutes (α constant) the acid was neutralised with barium carbonate and the solution filtered. On washing the residue with acetone, some barium chloride separated from the filtrate; this was filtered off. Water was added to the filtrate to make the total volume up to about 80 ml., and the trityl carbinol which separated was removed by filtration through charcoal. The residue from evaporation of the filtrate was extracted with hot ethyl acetate; on concentration of the solution thus obtained, 1·2 g. of crystals separated. After recrystallisation from ethyl acetate–light petroleum (b. p. 60°), 1·1 g. of prisms were obtained, m. p. 143—144°, $[\alpha]_D^{21°}$ (in alcohol) − 23·7° (c = 4·8) (Found : C, 48·4; H, 5·7; S, 8·9; OCH_3, 9·4. $C_{14}H_{20}O_8S$ requires C, 48·3; H, 5·8; S, 9·2; OCH_3, 8·9%).

3 : 4 : 6-*Tribenzoyl* 2-p-*Toluenesulphonyl* β-*Methylgalactoside* (VIII).—1·2 G. of (VII) were dissolved in the minimum of dry pyridine, cooled, and 3 ml. of benzoyl chloride added. After being kept at 38° for 72 hours the product was isolated from a washed benzene solution in the usual way and crystallised from alcohol. 2·5 G. of needles were obtained, m. p. 143—144°, $[\alpha]_D^{18°}$ + 45·5° (c = 5) (Found : C, 63·4; H, 5·0; S, 4·8; OCH_3, 4·9. $C_{35}H_{32}O_{11}S$ requires C, 63·6; H, 4·8; S, 4·8; OCH_3, 4·7%).

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