58. 3 : 6-*Anhydrogalactose. Part II. 2-Methyl and 4-Methyl* 3 : 6-*Anhydro-α-methylgalactopyranoside.*

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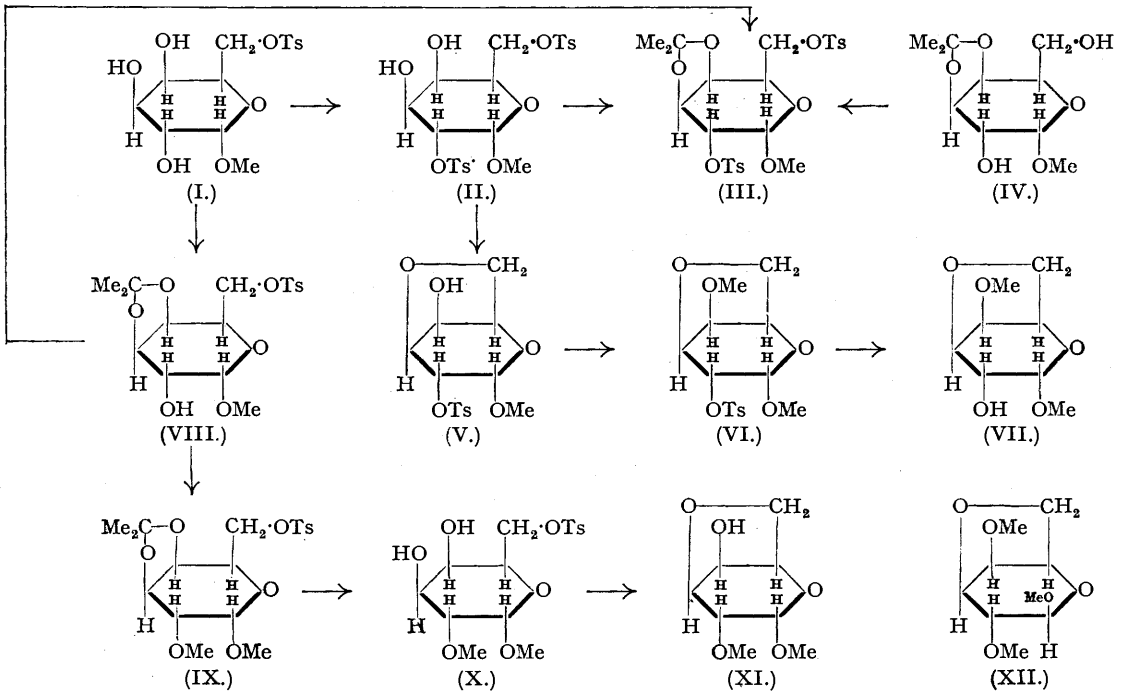
The ditosyl α-methylgalactopyranoside obtained by the action of *p*-toluenesulphonyl chloride upon α-methylgalactopyranoside (Haworth, Jackson, and Smith, J., 1940, 620) has been shown to be the 2 : 6-*ditosyl* derivative (II). Mild treatment of (II) with dilute alkali yielded 2-*tosyl* 3 : 6-*anhydro-α-methylgalactopyranoside* (V), which upon methylation with silver oxide and methyl iodide afforded 2-*tosyl* 4-*methyl* 3 : 6-*anhydro-α-methylgalactopyranoside* (VI). More drastic treatment of (VI) with sodium hydroxide gave crystalline 4-*methyl* 3 : 6-*anhydro-α-methylgalactopyranoside* (VII).

Condensation of acetone with 6-tosyl α-methylgalactopyranoside (I) furnished 6-tosyl 3 : 4-monoacetone α-methylgalactoside (VIII), and this with methyl iodide and silver oxide gave 6-*tosyl* 3 : 4-*monoacetone* 2-*methyl α-methylgalactoside* (IX). Treatment of the latter with acid methyl alcohol afforded 6-*tosyl* 2-*methyl α-methylgalactopyranoside* (X), which by the agency of dilute alkali was converted into 2-*methyl* 3 : 6-*anhydro-α-methylgalactopyranoside* (XI).

In view of the unique properties displayed by the 2 : 4-dimethyl derivatives of 3 : 6-anhydromethylgalactoside (Haworth, Jackson, and Smith, *Nature*, 1938, **142**, 1075; J., 1940, 620) it was decided to prepare for study the 2-methyl and the 4-methyl derivative of 3 : 6-anhydro-α-methylgalactopyranoside. The source of the 4-methyl derivative was the hitherto unknown ditosyl methylgalactoside, obtained by direct treatment of α-methylgalactopyranoside with *p*-toluenesulphonyl chloride in pyridine solution (Haworth, Jackson, and Smith, *loc. cit.*). The structure (II) assigned to the *ditosyl* derivative of α-methylgalactoside is based upon the following experimental facts. The ditosyl derivative can be obtained from 6-tosyl α-methylgalactopyranoside (I) by further treatment of the latter with *p*-toluenesulphonyl chloride. This demonstrates that one of the tosyl residues of (II) is attached to position 6, and it follows that the second tosyl group can occupy any one of the positions 2, 3, and 4. When the ditosyl α-methylgalactoside (II) was treated with acetone in the presence of sulphuric acid, condensation occurred with the formation of a *monoacetone ditosyl α-methylgalactoside* (III). By analogy with the behaviour of 6-tosyl α-methylgalactopyranoside (Ohle and Thiel, *Ber.*, 1933, **66**, 528) and β-methylgalactopyranoside (Bell and Williamson, J., 1938, 1198), which are known to give 3 : 4-monoacetone derivatives when condensed with acetone, it seemed probable that the acetone residue in (II)

was also attached to positions 3 and 4, in which case the second tosyl group in (III) and therefore in (II) would be located in position 2. This view was confirmed by the observation that treatment of 6-tosyl 3 : 4-monoacetone α-methylgalactopyranoside (VIII) with *p*-toluenesulphonyl chloride furnished 2 : 6-ditosyl 3 : 4-monoacetone α-methylgalactopyranoside, identical with the ditosyl monoacetone α-methylgalactoside (III) obtained from (II). It is clear, therefore, that the two tosyl groups of (II) must occupy positions 2 and 6.



When 2 : 6-ditosyl α-methylgalactoside (II) was warmed with N-aqueous-alcoholic sodium hydroxide, one tosyl group was eliminated, with the formation of 2-*tosyl* 3 : 6-*anhydro*-α-*methylgalactopyranoside* (V) in a manner analogous to the conversion of 6-tosyl α-methylgalactopyranoside into 3 : 6-anhydro-α-methylgalactoside (Ohle and Thiel, *loc. cit.*; Percival and Forbes, *Nature*, **1938**, **142**, 1076; Haworth, Jackson, and Smith, *loc. cit.*). Prolonged treatment of 2 : 6-ditosyl α-methylgalactoside with 3N-sodium hydroxide results in the removal of the tosyl group from C_2 with the formation of 3 : 6-anhydro-α-methylgalactopyranoside. This observation proved, not only that the C_2 tosyl group could be removed, but also that its removal was not accompanied by a Walden inversion. Methylation of (V) with silver oxide and methyl iodide proceeded smoothly and there was produced 2-*tosyl* 4-*methyl* 3 : 6-*anhydro*-α-*methylgalactoside* (VI), from which the tosyl group in position 2 was removed without Walden inversion by more drastic treatment with aqueous alcoholic 3N-sodium hydroxide at 60°. In this way there was obtained crystalline 4-*methyl* 3 : 6-*anhydro*-α-*methylgalactopyranoside* (VII). Proof that no Walden inversion occurred at C_2 during the conversion of (VI) into (VII) was forthcoming from the fact that methylation of (VII) with silver oxide and methyl iodide yielded 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactopyranoside, which was characterised by its almost immediate transformation with hydrogen chloride into the crystalline β-form of 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactopyranoside (XII).

The 2-*methyl* 3 : 6-*anhydro*-α-*methylgalactopyranoside* (XI) was prepared by the following series of reactions which leave no doubt as to its constitution. 6-Tosyl α-methylgalactoside (I) was condensed with acetone in the presence of sulphuric acid and there was obtained 6-tosyl 3 : 4-monoacetone α-methylgalactoside (VIII). By means of silver oxide and methyl iodide this was transformed into the corresponding crystalline 6-*tosyl* 2-*methyl* 3 : 4-*monoacetone* α-*methylgalactoside* (IX). Removal of the acetone residue was easily effected with methyl-alcoholic hydrogen chloride, and there resulted 6-*tosyl* 2-*methyl* α-*methylgalactopyranoside* (X), and this upon treatment with N-aqueous-alcoholic sodium hydroxide gave the required crystalline 2-methyl α-methylgalactopyranoside (XI). That the galactose configuration still existed in the latter was proved by its conversion with silver oxide and methyl iodide into 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactoside, which under the influence of a trace of hydrogen chloride yielded crystalline 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactopyranoside (XII).

Experimental.

2 : 6-*Ditosyl* α-*Methylgalactopyranoside* (II).—(a) *From* α-*methylgalactopyranoside.* Anhydrous α-methylgalactoside, prepared from the monohydrate (5 g.) by heating in a vacuum at 110° until all water had been eliminated, was dissolved in anhydrous pyridine (15 c.c.) and treated with *p*-toluenesulphonyl chloride (2 g.) for 12 hours at room temperature and

for 2 days at 30°. The reaction mixture was warmed to 50°, then poured with stirring into water and subsequently triturated with fresh portions of water in order to remove as much pyridine as possible. Trituration with acetone at room temperature dissolved the ditosyl α-methylgalactoside and the crystalline 6-tosyl α-methylgalactoside was filtered off and washed with acetone (yield 1·5 g.), m. p. and mixed m. p. 175° (decomp.) (after recrystallisation from ethyl alcohol).

Removal of the acetone from the mother-liquors gave a syrup, which was dissolved in chloroform and the solution was extracted several times with dilute sulphuric acid to remove pyridine, with sodium bicarbonate solution (twice), water (once), and then dried over anhydrous sodium sulphate. Distillation of the solvent gave a syrup, which was dissolved in a small volume of hot ethyl alcohol. The solution was seeded with a crystal of 2 : 6-ditosyl methylgalactoside prepared in a previous experiment (Haworth, Jackson, and Smith, J., 1940, 620), and allowed to crystallise. The crystals were filtered off, washed with a little ethyl alcohol, and after recrystallisation from the same solvent the 2 : 6-ditosyl α-methylgalactopyranoside (1·0 g.) had m. p. 148°; $[\alpha]_D^{18°}$ + 68° in pyridine (*c*, 1·0).

(b) *From 6-tosyl α-methylgalactopyranoside* (I). A solution of (I) (0·5 g.) in dry pyridine (2 c.c.) was allowed to react with *p*-toluenesulphonyl chloride (0·65 g.) for 6 hours at room temperature and for 2 days at 30°. A few drops of water were stirred into the reaction mixture, and after 30 minutes the product was dissolved in chloroform (20 c.c.). The chloroform solution was extracted with dilute sulphuric acid (twice), sodium bicarbonate solution (once), water (once), and then dried over anhydrous magnesium sulphate. Removal of the solvent gave a syrup, which was dissolved in the minimum amount of ethyl alcohol. On keeping, crystallisation of the 2 : 6-ditosyl α-methylgalactoside took place. The crystals were filtered off, washed with light petroleum, and recrystallised from ethyl alcohol (yield, 0·57 g.); m. p. 148°; $[\alpha]_D^{20°}$ + 66·5° in pyridine (*c*, 0·6). 2 : 6-*Ditosyl α-methylgalactoside* is readily soluble in pyridine, acetone, and chloroform; it is sparingly soluble in ethyl and methyl alcohol and insoluble in light petroleum (Found : C, 49·9; H, 5·2; OMe, 6·3; S, 12·5. $C_{21}H_{26}O_{10}S_2$ requires C, 50·2; H, 5·2; OMe, 6·2; S, 12·7%).

2 : 6-*Ditosyl* 3 : 4-*Monoacetone α-Methylgalactopyranoside* (III).—(a) *From* 2 : 6-*ditosyl α-methylgalactoside* (II). When a solution of (II) (1·0 g.) in dry acetone (170 c.c.) containing concentrated sulphuric acid (0·2 c.c.) was kept at room temperature, the specific rotation changed from $[\alpha]_D^{21°}$ + 86° (initial value) to + 110° (after keeping overnight). The solution was neutralised with solid sodium bicarbonate, filtered, and evaporated to dryness. The dry residue crystallised spontaneously, and after purification by recrystallisation from ethyl alcohol the 2 : 6-*ditosyl* 3 : 4-*monoacetone α-methylgalactoside* had m. p. 148°; $[\alpha]_D$ + 115° in pyridine (*c*, 0·6) (Found : C, 53·2; H, 5·5; OMe, 5·8; S, 11·8. $C_{24}H_{30}O_{10}S_2$ requires C, 53·1; H, 5·5; OMe, 5·7; S, 11·8%).

(b) *From* 6-*tosyl* 3 : 4-*monoacetone α-methylgalactoside* (VIII). Well-powdered 6-tosyl α-methylgalactopyranoside (1 g.) was shaken with acetone (170 c.c.) containing concentrated sulphuric acid (0·2 c.c.) for 2 hours until complete solution had been attained. After remaining for a further 12 hours at room temperature, the solution was neutralised with sodium bicarbonate, filtered, and evaporated to dryness under diminished pressure. The product was purified by extraction with benzene, and after removal of the solvent, followed by crystallisation from ethyl alcohol, the 6-tosyl 3 : 4-monoacetone α-methylgalactoside (0·75 g.) had m. p. 129° (Ohle and Thiel, *Ber.*, 1933, **66**, 528, give m. p. 129—130°).

This monotosyl compound (0·74 g.) was dissolved in dry pyridine (2·5 c.c.) and allowed to react with *p*-toluenesulphonyl chloride (0·56 g.) for 6 hours at room temperature and for 2 days at 30°. The reaction mixture was treated with a few drops of water, and after 15 minutes was diluted with chloroform (20 c.c.). The chloroform solution was washed with dilute sulphuric acid, sodium bicarbonate solution, water, and then dried over anhydrous magnesium sulphate. After filtration, followed by removal of chloroform and crystallisation from ethyl alcohol, the 2 : 6-ditosyl 3 : 4-monoacetone α-methylgalactoside had m. p. 148°; $[\alpha]_D^{18°}$ + 117° in pyridine (*c*, 0·3) (yield almost quantitative). This material gave no depression of the m. p. when mixed with that prepared as in (a).

A. *Preparation of* 2-*Methyl* 3 : 6-*Anhydro-α-methylgalactopyranoside* (XI).—6-*Tosyl* 3 : 4-*monoacetone* 2-*methyl α-methylgalactopyranoside* (IX).—A solution of 6-tosyl 3 : 4-monoacetone α-methylgalactoside (0·5 g.) in methyl iodide (5 c.c.) was refluxed for 6 hours in the presence of silver oxide (3 g.), the latter being added in small quantities during the first 3 hours. The excess of the methyl iodide was distilled, and the residue extracted with hot acetone. Removal of the solvent gave an almost quantitative yield of crystalline 6-*tosyl* 3 : 4-*monoacetone* 2-*methyl α-methylgalactoside*, m. p. 88°; $[\alpha]_D^{23°}$ + 99° in pyridine (*c*, 0·5) (after recrystallisation from ethyl alcohol–light petroleum). The compound is readily soluble in methyl and ethyl alcohol, ether, and pyridine, but insoluble in water and light petroleum (Found : C, 53·65; H, 6·45; OMe, 15·85; S, 7·7. $C_{18}H_{26}O_8S$ requires C, 53·7; H, 6·5; OMe, 15·4; S, 7·95%).

6-*Tosyl* 2-*methyl α-methylgalactopyranoside* (X). When a solution of 6-tosyl 3 : 4-monoacetone 2-methyl α-methylgalactoside (0·59 g.) in 1% methyl-alcoholic hydrogen chloride (100 c.c.) was refluxed for 4 hours, it showed $[\alpha]_D$ + 98° (initial value); + 64° (after 1 hour); + 41° (2 hours); + 27° (3 hours); + 27° (4 hours). Neutralisation of the solution with silver oxide, followed by filtration and removal of the solvent under reduced pressure, gave a colourless syrup (0·48 g.) which had $[\alpha]_D^{23°}$ + 27° in ethyl alcohol (*c*, 0·8). The syrupy 6-*tosyl* 2-*methyl methylgalactoside* did not reduce boiling Fehling's solution (Found : OMe, 16·6. $C_{15}H_{22}O_8S$ requires OMe, 17·1%).

2-*Methyl* 3 : 6-*anhydro-α-methylgalactoside* (XI). A solution of the syrupy 6-tosyl 2-methyl α-methylgalactoside (0·47 g.) in ethyl alcohol (10 c.c.) was heated with N-sodium hydroxide (2 c.c.) for 1 hour at 60°. The mixture was neutralised to phenolphthalein by a current of carbon dioxide and evaporated to dryness under reduced pressure. Extraction of the residue with ethyl alcohol gave syrupy 2-methyl 3 : 6-anhydromethylgalactoside, which distilled as a colourless liquid, b. p. (bath temp.) 165°/0·03 mm., $n_D^{16°}$ 1·4710, $[\alpha]_D^{21°}$ + 63° in ethyl alcohol (*c*, 0·3) (Found : OMe, 32·0%). After 3 days the distillate crystallised spontaneously, and when purified by recrystallisation from ethyl alcohol–light petroleum the 2-*methyl* 3 : 6-*anhydro-α-methylgalactopyranoside* had m. p. 102°; $[\alpha]_D^{16°}$ + 88° in water (*c*, 0·4) (Found : C, 50·0; H, 7·2; OMe, 32·0. $C_8H_{14}O_5$ requires C, 50·6; H, 7·4; OMe, 32·6%).

One treatment of this galactoside (0·03 g.) with silver oxide (0·5 g.) and methyl iodide (2 c.c.) under reflux for 6 hours yielded 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactoside (isolated by means of acetone). Exposure of the syrupy product to the action of dry hydrogen chloride for 30 seconds effected rapid isomerisation, and the 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactopyranoside readily crystallised (Haworth, Jackson, and Smith, J., 1940, 620). The product was dissolved in ether (2 c.c.), neutralised with silver oxide, filtered, and concentrated to dryness. One crystallisation from 1—2 parts of water gave the β-galactoside, m. p. and mixed m. p. 82°.

B. *Synthesis of* 4-*Methyl* 3 : 6-*Anhydro-α-methylgalactopyranoside* (VII).—Before attempting to synthesise this compound, the conditions were ascertained which would bring about the removal of the tosyl group from C_3 as well as the formation of the 3 : 6-anhydro-ring. It was found that when a solution of 2 : 6-ditosyl α-methylgalactopyranoside (0·1 g.) in ethyl alcohol (10 c.c.) and aqueous sodium hydroxide (5 c.c., 12%) was heated at 60° until a drop of the solution gave no turbidity on dilution with water, there was produced 3 : 6-anhydro-α-methylgalactoside. The solution was neutralised with carbon dioxide, and evaporated to dryness under diminished pressure. Extraction of the residue with ethyl alcohol gave 3 : 6-anhydro-α-methylgalactopyranoside, m. p. and mixed m. p. 139° (after recrystallisation from ethyl acetate).

2-*Tosyl* 3 : 6-*anhydro-α-methylgalactoside* (V). A solution of 2 : 6-ditosyl α-methylgalactoside (1 g.) in a mixture of ethyl alcohol (10 c.c.) and N-sodium hydroxide (3 c.c.) was heated for 1 hour at 60°. Carbon dioxide was passed through

the solution until this became neutral to phenolphthalein and it was then evaporated to dryness under diminished pressure. Extraction of the crystalline residue with acetone gave crystalline 2-*tosyl* 3 : 6-*anhydro*-α-*methylgalactopyranoside* (0·8 g.), m. p. 138°; $[\alpha]_D^{18°}$ + 56° in chloroform (*c*, 0·8) (after recrystallisation from ethyl alcohol) (Found : C, 50·7; H, 5·45; OMe, 9·5; S, 9·5. $C_{14}H_{18}O_7S$ requires C, 50·9; H, 5·5; OMe, 9·4; S, 9·7%). The substance is slightly soluble in ethyl and methyl alcohol, readily soluble in pyridine and chloroform. In another experiment 3 g. of the initial substance afforded 2·45 g. of the product.

2-*Tosyl* 4-*methyl* 3 : 6-*anhydro*-α-*methylgalactopyranoside* (VI). A solution of (V) (1 g.) in methyl iodide (5 c.c.) was refluxed for 6 hours with silver oxide (3 g.), the latter being added in small portions during the first 3 hours. After isolation by means of acetone, the product crystallised spontaneously, and when recrystallised from ethyl alcohol, in which it is sparingly soluble in the cold, the 2-*tosyl* 4-*methyl* 3 : 6-*anhydro*-α-*methylgalactopyranoside* had m. p. 126°; $[\alpha]_D^{23°}$ + 88° in chloroform (*c*, 0·4). The compound is readily soluble in pyridine and chloroform (Found : C, 53·1; H, 5·9; OMe, 18·7; S, 9·3. $C_{15}H_{20}O_7S$ requires C, 52·3; H, 5·8; OMe, 18·0; S, 9·3%).

4-*Methyl* 3 : 6-*anhydro*-α-*methylgalactopyranoside* (VII). A solution of the preceding compound (1·0 g.) in ethyl alcohol (10 c.c.) and aqueous sodium hydroxide (5 c.c., 12%) was heated for 30 hours at 60°, a drop of the reaction mixture then no longer giving a turbidity when added to water. The mixture was neutralised with carbon dioxide, and evaporated to dryness under reduced pressure. Extraction of the residue with acetone gave 4-*methyl* 3 : 6-*anhydro*-α-*methylgalactoside* as a syrup, which distilled as a colourless oil (0·4 g.), b. p. (bath temp.) 110°/0·03 mm.; $n_D^{20°}$ 1·4795; $[\alpha]_D^{19°}$ + 64° in water (*c*, 0·4). After two days the distillate crystallised, and recrystallisation from ethyl alcohol gave (VII); m. p. 55°; $[\alpha]_D^{19°}$ + 81° in methyl alcohol (*c*, 1·1); $[\alpha]_D^{16°}$ + 75° in water (*c*, 0·6) (Found : C, 50·6; H, 7·0; OMe, 32·4. $C_8H_{14}O_5$ requires C, 50·6; H, 7·4; OMe, 32·6%).

Methylation of 4-*Methyl* 3 : 6-*Anhydro*-α-*methylgalactopyranoside*.—Two treatments of the crystalline galactoside (0·1 g.) with silver oxide (1 g.) and methyl iodide (3 c.c.) gave 2 : 4-dimethyl 3 : 6-anhydro-α-methylgalactoside. After each methylation the product was isolated by means of acetone. Removal of the solvent gave a colourless, mobile liquid (0·11 g.); b. p. (bath temp.) 100°/0·02 mm.; $n_D^{18°}$ 1·4660; $[\alpha]_D^{18°}$ + 75° in water (*c*, 0·5) (Found : OMe, 45·7. Calc. for $C_9H_{16}O_5$: OMe, 45·6%). Treatment of this syrupy compound (20 mg.) with dry hydrogen chloride for about 30 seconds effected rapid isomerisation (Haworth, Jackson, and Smith, *loc. cit.*) and the β-form readily crystallised. The crystalline mass was dissolved in dry ether (5 c.c.), and any mineral acid neutralised with a little silver oxide. The solution was filtered and evaporated to dryness. One crystallisation of the product from 1—2 parts of water gave pure 2 : 4-dimethyl 3 : 6-anhydro-β-methylgalactopyranoside, m. p. and mixed m. p. 83°; $[\alpha]_D^{15°}$ − 78° in water (*c*, 0·5).

When conditions permit a more detailed examination of the 2-monomethyl and the 4-monomethyl 3 : 6-anhydro-α-methylgalactoside will be made.

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