299. *The Hydrolysis of* 3-p-*Toluenesulphonyl Derivatives of Galactose.*

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The preparation and alkaline hydrolysis of 3-*p*-toluenesulphonyl 2 : 4 : 6-trimethyl galactose is described. A trimethyl methylhexoside was obtained on hydrolysis from which on methylation and suitable treatment a good yield of tetramethyl galactopyranose anilide was obtained and no gulose derivatives were detected. It is concluded therefore that Walden inversion does not take place in this case on removal of the *p*-toluenesulphonyl residue. The resistance to hydrolysis of 3-*p*-toluenesulphonyl 2 : 4 : 6-trimethyl α-methylgalactoside with acid and alkali is discussed.

OLDHAM and ROBERTSON (J., 1935, 685) and Peat and Wiggins (this vol., p. 1088) point out that in the sugar series the removal of a *p*-toluenesulphonyl residue is not necessarily accompanied by a Walden inversion, but that when inversion is observed it is invariably accompanied by anhydro-ring formation. Similar conclusions are drawn by Irvine and Robertson (*Rec. Trav. chim.*, 1938, **57**, 575), who also point out that no Walden inversion has ever been authenticated involving ring formation other than of the ethylene oxide type, although Hess and Neumann (*Ber.*, 1935, **68**, 1360) claimed to have isolated a derivative of idose by the alkaline hydrolysis of 4-*p*-toluenesulphonyl 2 : 3 : 6-trimethyl glucose, but this claim is disputed by Freudenberg and Braun (*Ber.*, 1935, **68**, 1988).

An opportunity to test the possibilities of propylene oxide ring formation arose by the isolation of 3-p-*tolueneSulphonyl* 2 : 4 : 6-*trimethyl galactose* from the corresponding *methylgalactoside* by the method of Hess and Neumann (*loc. cit.*) *via* the 1-*chloro*-3-p-*toluenesulphonyl* 2 : 4 : 6-*trimethyl galactose*. As isolated, this substance was chiefly but not exclusively the β-form, but it has not yet been possible, as with the original galactoside (Percival and Somerville, J., 1937, 1615), to separate a pure stereochemical form by fractional crystallisation. The subsequent arguments, however, are not affected by the presence of some of the α-variety.

A crystalline anhydro-compound could not be obtained by treatment of 3-*p*-toluenesulphonyl 2 : 4 : 6-trimethyl galactose with sodium methoxide under various conditions, but with 5% sodium methoxide in methyl alcohol at 70° for 20 hours, and after suitable treatment, a syrup corresponding in properties to a trimethyl methylhexoside (A) was obtained in 50% yield. Complete methylation, hydrolysis, and anilide formation resulted in the isolation of tetramethyl galactopyranose anilide in good yield, and no other sugar could be detected. It must be admitted that, as no crystalline reference compounds of the other possibility, tetramethyl gulose, are yet available, a small quantity of this substance may have escaped notice, but (A) was undoubtedly mainly a mixture of trimethyl α- and β-methylgalactosides. The formation of this substance could be explained by the splitting off without inversion of the *p*-toluenesulphonyl residue, together with the "active" hydrogen atom on C_1 and the simultaneous entry of a methyl group in this position. Probably a more satisfactory explanation is that the *p*-toluenesulphonyl residue is eliminated from the 3-*p*-toluenesulphonyl 2 : 4 : 6-trimethyl β-galactose with its two potential *cis*-hydroxyl groups, without Walden inversion, to yield the 1 : 3-anhydride, and this subsequently breaks down in one direction only, *viz.*, at the link to C_1. Otherwise, tetramethyl gulose or tetramethyl galactose (if two inversions had taken place on C_3) and not trimethyl methylgalactoside would have resulted.

It might have been expected that the breaking of the hypothetical β-1 : 3-anhydro-ring would yield an α-galactoside, since rupture of an ethylene oxide ring with sodium methoxide involves a Walden inversion at the point of entry of the new methyl group (Robertson and Griffith, J., 1935, 1193; Peat and Wiggins, *loc. cit.*). In this case the inversion is only partial, presumably owing to the extra mobility of the groups on C_1 as distinct from those on other carbon atoms. A partial inversion on C_3 when 2-acetyl 6-trityl 3 : 4-anhydro-α-methylgalactoside is treated with sodium methoxide is recorded by Oldham and Robertson (*loc. cit.*) although Peat and Wiggins (*loc. cit.*) obtained

complete inversion with 2 : 6-dimethyl 3 : 4-anhydro-β-methylalloside, and it may also be recalled that Levene and Raymond (*J. Biol. Chem.*, 1933, **102**, 317) converted 1 : 2-monoacetone 3 : 5-anhydro-xylofuranose into 1 : 2-monoacetone 5-methyl xylofuranose by treatment with sodium methoxide. The present results show therefore that Walden inversion does not occur on the removal of a *p*-toluenesulphonyl residue from C_3 although a *cis*-hydroxyl group is available on C_1, and have a parallel in the observation of Peat and Wiggins (*loc. cit.*) that 3-*p*-toluenesulphonyl glucofuranose monoacetone may also be hydrolysed without Walden inversion.

Finally, we record that 3-*p*-toluenesulphonyl 2 : 4 : 6-trimethyl methylgalactoside was remarkably resistant to hydrolysis, although after 100 hours' treatment with sodium methoxide at 70°, crystalline 2 : 4 : 6-trimethyl methylgalactoside was isolated, showing, as expected, the absence of Walden inversion. Attempts to hydrolyse the glycosidic methoxyl residue with 7% aqueous-alcoholic sulphuric acid at 100° for as long as 50 hours were futile, much of the starting material being recovered unchanged. Although the galactoside in question contained some of the β-form, it was largely the α-variety, and the results are in contrast to the behaviour of the corresponding β-galactoside, which is readily hydrolysed by sodium methoxide (Bell and Williamson, this vol., p. 1196). From an inspection of models it would seem likely that the *p*-toluenesulphonyl residue in the α-form can approach so closely to the glycosidic hydrogen atom (*cis*) as to affect its properties. This could occur either by virtue of the purely mechanical shielding effect of the large aromatic residue or, more probably, by the formation of a bond, due to the existence of two forms in resonance, between the glycosidic hydrogen atom and the strongly electronegative oxygen atoms of the *p*-toluenesulphonyl residue. In the β-form the methoxyl residue is *cis*- and the hydrogen atom is *trans*- to the *p*-toluenesulphonyl residue on C_3, so the effect is not observed in this case.

Experimental.

3-p-*Toluenesulphonyl* 2 : 4 : 6-*Trimethyl Methylgalactoside*.—2 : 4 : 6-Trimethyl methylgalactoside (2 g.), m. p. 40—50°, $[\alpha]_D^{20°}$ + 108° in water (*c*, 0·6), was dissolved in pyridine (2·5 c.c.) and treated with *p*-toluenesulphonyl chloride (2·4 g.) at 0°. After 24 hours, water was added, and the mixture extracted with benzene, the extract being washed with dilute hydrochloric acid, sodium bicarbonate solution, and water, and dried over sodium sulphate. After removal of solvent under diminished pressure, a syrup was obtained which crystallised spontaneously (2·75 g.) and on recrystallisation from light petroleum (b. p. 60—80°) gave shining needles, m. p. 119—120°, $[\alpha]_D$ + 84° in chloroform (*c*, 0·5) (Found: C, 52·1; H, 7·0; OMe, 31·0. $C_{17}H_{26}O_8S$ requires C, 52·3; H, 6·7; OMe, 31·8%).

1-*Chloro*-3-p-*toluenesulphonyl* 2 : 4 : 6-*Trimethyl Galactose*.—The foregoing crystalline 3-p-*toluenesulphonyl* 2 : 4 : 6-*trimethyl methylgalactoside* (1 g.) was dissolved in acetic anhydride (6 c.c.), and the solution saturated with dry hydrogen chloride at − 18°. The containing tube was then sealed, and kept at room temperature for 3 days. On pouring the mixture on ice, a solid was obtained which was dissolved in benzene, washed with sodium bicarbonate solution, dried with sodium sulphate, and the benzene removed (diminished pressure) to yield a colourless syrup which crystallised spontaneously. The product (1·2 g.), after one recrystallisation from light petroleum (b. p. 60—80°), had m. p. 108°, $[\alpha]_D^{20°}$ + 136° in acetone (*c*, 0·5) (Found: C, 49·0; H, 6·1; OMe, 23·9; Cl, 9·7. $C_{16}H_{23}O_7ClS$ requires C, 48·7; H, 5·9; OMe, 23·6; Cl, 9·0%).

3-p-*Toluenesulphonyl* 2 : 4 : 6-*Trimethyl Galactose*.—The above *chloro*-compound (1 g.), dissolved in 90% aqueous acetone (10 c.c.), was shaken for 50 hours with silver carbonate (5 g.). After filtration and evaporation at 40°/20 mm., a crystalline mass was obtained which was recrystallised from methyl alcohol, yielding 3-p-*toluenesulphonyl* 2 : 4 : 6-*trimethyl galactose* (0·7 g.), m. p. 138°, $[\alpha]_D^{20°}$ in chloroform (*c*, 0·53) + 30° ⟶ + 96° in 96 hours (Found: C, 51·3; H, 6·6; OMe, 24·5. $C_{16}H_{24}O_8S$ requires C, 51·1; H, 6·4; OMe, 24·7%).

Alkaline hydrolysis. In a typical experiment, 3-*p*-toluenesulphonyl 2 : 4 : 6-trimethyl galactose (2·5 g.) in methyl alcohol (60 c.c.) containing sodium (1·5 g.) was heated at 70° for 20 hours. After the addition of water (5 c.c.), carbon dioxide was passed through the mixture for 1 hour, the precipitate filtered off, solvent removed under diminished pressure, and the product thoroughly extracted with boiling chloroform (1 l.). After removal of solvent, the

syrup (1·6 g.) was transferred to a small flask by means of ether, and finally distilled: (1) 0·8 g., b. p. 95—105° (bath temp.)/0·05 mm.; (2) 0·2 g., b. p. 105—150°; (3) residue, 0·5 g. Fraction (1) was non-reducing until warmed with dilute acid, and had $n_D^{20°}$ 1·4553, $[\alpha]_D^{20°}$ + 50° in water (*c*, 0·5) (Found: C, 50·4; H, 8·7; OMe, 52·3. Calc. for $C_{10}H_{20}O_6$: C, 50·8; H, 8·5; OMe, 52·5%). Fraction (2) had $n_D^{20°}$ 1·4650 and was faintly reducing; the quantity was insufficient for detailed examination. Hydrolyses carried out as above for periods of 2, 5, and 8 hours afforded (*a*) 8, (*b*) 38, and (*c*) 42% of the theoretical yields of the tetramethyl compound respectively; (*a*) was slightly reducing and may have contained the free anhydro-compound, but the poor yield precluded further investigation; the specific rotations of (*b*) and (*c*) were lower ($[\alpha]_D$ + 30°) than for the case given above, a fact which was thought to point to the presence of gulose derivatives, but tetramethyl galactose anilide was isolated from (*c*) as well as from the product of 20 hours' treatment as described below.

Methylation, and the Isolation of Tetramethyl Galactopyranose Anilide.—The substance from the 20 hours' treatment, having failed to crystallise, was subjected to two methylations by the Purdie method; the product (yield, quantitative) distilled completely at 95° (bath temp.)/0·05 mm. and showed $n_D^{19°}$ 1·4473, $[\alpha]_D^{20°}$ + 75° in water (*c*, 0·9) (Found: OMe, 60·6. Calc. for $C_{11}H_{22}O_6$: OMe, 62·0%).

After hydrolysis for 2 hours with 6% hydrochloric acid and neutralisation with silver carbonate, a portion of the reducing syrup so obtained (0·5 g.) was heated with aniline (0·4 g.) in alcohol (4 c.c.) for 4 hours at 100°. The crystalline anilide which separated on cooling was filtered off (0·4 g., m. p. 194°) and recrystallised once; m. p. 197°, unchanged on admixture with authentic tetramethyl galactopyranose anilide (Found: OMe, 40·0; N, 4·5. Calc. for $C_{16}H_{25}O_5N$: OMe, 39·8; N, 4·5%). The free sugar {0·1 g., $[\alpha]_D^{20°}$ + 80° in water (*c*, 0·3)}, isolated from the mother-liquors by addition of hydrochloric acid and suitable treatment, was examined for the presence of gulose derivatives but none was found.

Treatment of 3-p-*Toluenesulphonyl* 2 : 4 : 6-*Trimethyl Methylgalactoside with Sodium Methoxide.*—Hydrolysis was carried out at 70° in a 5% solution of sodium methoxide, the product being isolated by dilution of the reaction mixture with 3 vols. of water, followed by extraction with chloroform. Hydrolysis for 12 or for 24 hours was unsuccessful, the original material being recovered unchanged. Treatment for 100 hours, however, gave rise to the original trimethyl methylgalactoside, m. p. 45—50°, $[\alpha]_D^{20°}$ + 106° in water. Yield 40% of the theoretical.

Attempted Acid Hydrolysis.—A typical experiment is described. 3-*p*-Toluenesulphonyl 2 : 4 : 6-trimethyl methylgalactoside (0·4 g.) was dissolved in alcohol (5 c.c.), water (10 c.c.) and concentrated sulphuric acid (0·6 c.c.) were added, and the mixture was heated under reflux for 24 hours at 100°. On cooling, crystallisation ensued, and unchanged material (0·25 g.), m. p. 119°, was filtered off. After neutralisation of the mother-liquors with barium carbonate and evaporation to dryness, a further small quantity (0·05 g.) of unchanged material separated, but no reducing product was obtained. Similar results were obtained when the duration of the hydrolysis was 2, 3, 9, and 50 hours. Even on continuing the treatment for 95 hours at 90° it was still possible to isolate some crystalline starting material, although decomposition had undoubtedly occurred, since the final syrup was brown and reducing. A control experiment on 2 : 4 : 6-trimethyl methylgalactoside with 7% aqueous-alcoholic sulphuric acid under the same conditions showed that in this case hydrolysis was complete in less than 3 hours.

Attempts to prepare 1 : 3-di-*p*-toluenesulphonyl 2 : 4 : 6-trimethyl galactose directly from 2 : 4 : 6-trimethyl α-*d*-galactose were unsuccessful, only the 3-*p*-toluenesulphonyl derivative being isolated in poor yield.

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