152. *The Transformation of Glucose into Galactose and Gulose by Simple Optical Inversion.*

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INVESTIGATIONS in this laboratory have for some time been directed towards the elucidation of the mechanism involved in the interconversion of simple isomeric sugars. Light was thrown upon the subject with the discovery that the alkaline hydrolysis of 2 : 3-di-*p*-toluenesulphonyl 4 : 6-dimethyl α-methylglucoside led to the production of a 4 : 6-dimethyl 2 : 3-anhydro-α-methylhexoside along with a 4 : 6-dimethyl α-methylhexoside, which was not a glucose derivative and was tentatively described as a derivative of altrose (Mathers and Robertson, J., 1933, 1076). The natural conclusion to be drawn from this result was that the derivative of altrose owed its formation to Walden inversions within the glucose molecule, which were conditioned by the hydrolysis of the *p*-toluenesulphonyl groups (cf. Phillips, J., 1923, **123**, 44; 1925, **127**, 399).

Cognate researches have shown, however, that such an interpretation is inadequate, since it soon became evident that the alkaline hydrolysis of fully substituted derivatives of glucose containing only one *p*-toluenesulphonyl group was not accompanied by Walden inversion within the molecule. For example, 3-*p*-toluenesulphonyl diacetone glucose gave a quantitative yield of diacetone glucose, and 4-p-*toluenesulphonyl* 6-*trityl* 2 : 3-*dimethyl* α-*methylglucoside* an almost quantitative yield of 6-trityl 2 : 3-dimethyl α-methylglucoside. It was equally significant that the alkaline hydrolysis of 2-p-*toluenesulphonyl* 3-*benzoyl* 4 : 6-*benzylidene* α-*methylglucoside* led to the production of a 4 : 6-*benzylidene* 2 : 3-*anhydro*-α-*methylhexoside*, and this in turn, on treatment with sodium methoxide, was converted into a *monomethyl* 4 : 6-*benzylidene* α-*methylhexoside* which was not a derivative of glucose (Griffith and Robertson, unpublished result).

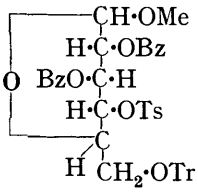
It was therefore suggested (Robertson and Oldham, *Nature*, 1934, **133**, 871) that anhydro-formation may be a necessary precursor to this type of inversion, which follows as a consequence of the opening of the anhydro-ring. It is obvious, however, that inversion is also possible during the formation of the anhydro-linkage. In the examples described above, anhydro-formation was of necessity ethylene-oxidic in character, and the possibility that the opening of other anhydro-linkages may be accompanied by inversion has not yet been examined exhaustively. In this connection it is interesting to note that the hydrolysis of 4-p-*toluenesulphonyl* 2 : 3-*dimethyl* α-*methylglucoside* with aqueous methyl-alcoholic sodium hydroxide solution leads essentially to the production of 2 : 3-dimethyl α-methylglucoside. The presence of a small amount of a substance containing a double bond, probably a glucoseen derivative, has also been demonstrated. This result shows either that the 4 : 6-anhydro-linkage is not produced to any appreciable extent, or that, when produced, it is immediately reopened under the given conditions without inversion. Investigations on the well-known 3 : 6-anhydro-derivative of glucose have not yet been completed.

The above views receive substantial support from the fact that we have succeeded in converting *d*-glucose into *d*-galactose and *d*-gulose * by forming an anhydro-ring between positions 3 and 4 in the glucose chain and subsequently opening the ring under the influence of acid. 2 : 3-Dibenzoyl α-methylglucoside (Mathers and Robertson, *loc. cit.*), on successive treatments with triphenylmethyl chloride and *p*-toluenesulphonyl chloride, yielded

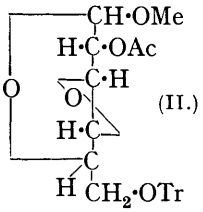
* This sugar, in accordance with the older nomenclature, was described as *l*-gulose in a previous communication (*Nature*, 1935, **135**, 103).

crystalline 4-p-*toluenesulphonyl* 2 : 3-*dibenzoyl* 6-*trityl* α-*methylglucoside* (I). The substance was identical with that prepared by condensing 4-*p*-toluenesulphonyl 2 : 3-dibenzoyl α-methylglucoside (Bell, J., 1934, 1177) with triphenylmethyl chloride. On alkaline hydrolysis and subsequent acetylation, (I) was converted into an amorphous *monoacetyl* 6-*trityl anhydro*-α-*methylhexoside*. This material was, however, considered to be homogeneous, since an analogous series of experiments proceeding from 4-*p*-toluenesulphonyl 2 : 3-diacetyl β-methylglucoside (Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366) led ultimately to the production of a crystalline *monoacetyl* 6-*trityl anhydro*-β-*methylhexoside*, which, incidentally, appeared to be identical with that described by Muller (*Ber.*, 1934, **67**, 422). The position of the anhydro-linkage must be either 2 : 4 or 3 : 4, and the ultimate production of a derivative of gulose, which involves inversions on carbon atoms 3 and 4, is almost conclusive proof that the anhydro-linkage is between positions 3 and 4. The amorphous material may therefore be described as a 2-acetyl 6-trityl 3 : 4-anhydro-α-methylhexoside and must correspond with one or other of the three configurations (II), (III), and (IV) shown below.

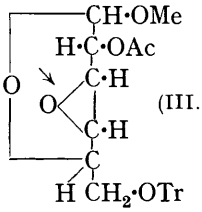
(I.)



(II.)



(III.)



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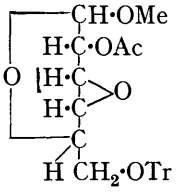

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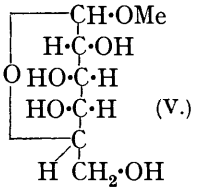
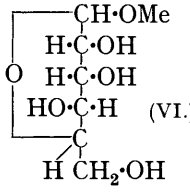


(VI.)



Evidence, which will be published shortly, has been adduced to show that ethylene oxide linkages are not readily formed in the *trans*-position, and structure (II) may therefore be discarded. Ferns and Lapworth (J., **1912, 101**, 273) have shown that the esters of the sulphonic acids are sharply distinguished from those of the carboxylic acids in their mode of reaction with alkali and alkyl oxides. The vulnerable point in each series may be represented simply as follows :

$$R{-}SO_2{-}O{-}R_1 \qquad R{-}CO{-}O{-}R_1$$

When this conception is considered in conjunction with the work of Phillips (*loc. cit.*), who has shown that the hydrolysis of *p*-toluenesulphonyl esters may be accompanied by change in configuration, it becomes clear that in the alkaline hydrolysis of (I) the configuration on carbon atom number 3 remains intact, while inversion is possible on carbon atom number 4. It follows that structure (III) is preferable to structure (IV) and the compound under consideration is therefore described as 2-*acetyl* 6-*trityl* 3 : 4-*anhydro*-α-*methylgalactoside*.

The opening of a 3 : 4 anhydro-linkage in the case under consideration should lead to derivatives of four hexoses, *viz.*, *d*-glucose, *d*-galactose, *d*-gulose, and *d*-allose. Derivatives of *d*-galactose (V) and *d*-gulose (VI) have actually been isolated, and this indicates that the opening of the anhydro-linkage in (III) takes place as indicated by the arrow. The configuration on carbon atom number 4 thus remains intact and a partial inversion on carbon atom number 3 explains the formation of derivatives of (V) and (VI). When (III) was treated with dry hydrogen chloride in acetone solution, the trityl residue was removed, the ethylene oxide ring was opened, and the resulting mixture of monoacetyl methylhexosides condensed with acetone to give a mixture of great complexity. The

exploration of this mixture is by no means complete and we wish to emphasise the fact that our knowledge of the reaction is still essentially qualitative. With a view to extending this knowledge we have commenced an investigation with compounds possessing the β-configuration, since β-derivatives are notable for their power of crystallisation. Two important facts, however, emerge. We have isolated from the above complex mixture a crystalline *monoacetyl monoacetone α-methylguloside* and a crystalline *monoacetyl monoacetone α-methylgalactoside*. It has not yet been found possible to ascribe definite structures to the above compounds, but the proof of their identity as derivatives of gulose and galactose respectively is fully described in the experimental part of this paper. Further investigation of the complex mixture has led to some indication of the presence of derivatives of allose.

Experimental.

The Alkaline Hydrolysis of 3-p-*Toluenesulphonyl Diacetone Glucose.*—3-*p*-Toluenesulphonyl diacetone glucose (Freudenberg, *Ber.*, 1922, **55**, 935), m. p. 120—121°, (4·35 g.) was dissolved in a hot mixture of alcohol (40 c.c.) and 4·9*N*-potassium hydroxide (40 c.c.) and boiled for 7 hours. The alcohol was distilled from the clear colourless solution under diminished pressure, the aqueous residue extracted five times with chloroform, and the extracts dried over anhydrous sodium sulphate and evaporated to dryness. The residue (2·67 g.) set spontaneously to a hard mass of crystals (yield, almost quantitative), m. p. 107—108° alone and on admixture with genuine diacetone glucose. The product was recondensed with *p*-toluenesulphonyl chloride, and a good yield of 3-*p*-toluenesulphonyl diacetone glucose obtained.

4-p-*Toluenesulphonyl* 6-*Trityl* 2 : 3-*Dimethyl* α-*Methylglucoside.*—6-Trityl 2 : 3-dimethyl α-methylglucoside (Robertson, J., 1933, 738), m. p. 169—170°, (10 g.) was dissolved in the minimum amount of pyridine, and *p*-toluenesulphonyl chloride (50% excess) added, followed after 4 days by water and benzene. The benzene layer was washed in succession with dilute hydrochloric acid, water, sodium carbonate solution, and water, dried, and evaporated to dryness. The residue (12·45 g.) crystallised completely and after one crystallisation from absolute alcohol pure 4-p-*toluenesulphonyl* 6-*trityl* 2 : 3-*dimethyl* α-*methylglucoside* was obtained in coarse needles, m. p. 146—147°, $[\alpha]_D$ + 66·3° in chloroform (c = 1·056) (Found : OMe, 15·1. $C_{35}H_{38}O_8S$ requires OMe, 15·05%).

The Alkaline Hydrolysis of 4-p-*Toluenesulphonyl* 6-*Trityl* 2 : 3-*Dimethyl* α-*Methylglucoside.*—The material (5·6 g.) was dissolved in benzene (50 c.c.), and a solution of sodium (7·5 g.) in methyl alcohol (100 c.c.) added. The resulting emulsion gave, on heating, a clear solution, which was boiled for 12 hours and cooled. Water and benzene were then added and the benzene layer was washed with dilute hydrochloric acid and with water, dried over anhydrous sodium sulphate, and evaporated. The residue (4·0 g.) crystallised spontaneously. On recrystallisation from absolute alcohol the material had m. p. 169—170°, alone and when mixed with authentic 6-trityl 2 : 3-dimethyl α-methylglucoside. Yield, almost quantitative.

4-p-*Toluenesulphonyl* 2 : 3-*Dimethyl* α-*Methylglucoside.*—The trityl residue was removed from 4-*p*-toluenesulphonyl 6-trityl 2 : 3-dimethyl α-methylglucoside (28·8 g.) by the method of Helferich and Klein (*Annalen*, 1926, **450**, 222). The product (18·7 g.) was a glass and analysis showed that it still contained triphenylcarbinol or unchanged material. This was in keeping with the fact that the yield was slightly in excess of the theoretical. No practical method of separation was available, so the crude material (18·5 g.) was treated with the mixture obtained by dissolving sodium (18·4 g.) in methyl alcohol (320 c.c.) and adding water (80 c.c.). On heating, the glass dissolved with the exception of a small and apparently crystalline residue, and the mixture was boiled for 9 hours. The methyl alcohol was evaporated, water added after cooling, and the residue of unchanged 4-*p*-toluenesulphonyl 6-trityl 2 : 3-dimethyl α-methylglucoside (4·7 g.) removed. The aqueous filtrate was extracted five times with chloroform; the extracts, after drying over anhydrous sodium sulphate, yielded a mobile syrup (2·0 g., A). The aqueous filtrate, after the addition of solid potassium carbonate, was again extracted five times with chloroform; these extracts yielded a syrup (4·4 g.), which set to a mass of crystals (B).

The syrup A (2·0 g.), $n_D^{15°}$ 1·4744, was dissolved in benzene and extracted repeatedly with water. The residue obtained from the benzene (0·4 g.) contained sulphur and was apparently unchanged material. The aqueous extract was extracted five times with chloroform; the extracts yielded a syrup (0·9 g.), $n_D^{15°}$ 1·4685, which vigorously absorbed bromine and therefore contained an unsaturated substance, probably a derivative of glucoseen. It is possible that the 4 : 6-anhydro-compound was also present in small amount. The aqueous extract was now

treated with solid potassium carbonate and again extracted five times with chloroform; the extracts yielded a syrup (0·4 g.), $n_D^{15°}$ 1·4702; this crystallised and proved to be identical with the crystalline material (B), which, alone or mixed with authentic 2 : 3-dimethyl α-methylglucoside (m. p. 80—83°), melted at 81—83°.

4-p-*Toluenesulphonyl* 2 : 3-*Dibenzoyl* 6-*Trityl* α-*Methylglucoside*.—2 : 3-Dibenzoyl α-methylglucoside (28 g.), prepared from 2 : 3-dibenzoyl 4 : 6-benzylidene α-methylglucoside by a slight variation of the method described by Mathers and Robertson (J., 1933, 1079), was dissolved in hot pyridine (20 c.c.), triphenylchloromethane (21 g.) added, and the mixture heated on a boiling water-bath for 2 hours. *p*-Toluenesulphonyl chloride (50% excess) was now added to the hot reaction mixture, which, after complete solution had been effected, was set aside in a warm place for at least 72 hours. The product was isolated in the usual manner and crystallised from absolute alcohol. The yield was variable, usually about 76%, but declined to about 50% on working with larger quantities. 4-p-*Toluenesulphonyl* 2 : 3-*dibenzoyl* 6-*trityl* α-*methylglucoside* crystallised in prisms, m. p. 163—164°; $[\alpha]_D$ + 66·3° in chloroform (c = 2·044). It was soluble in acetone, benzene, chloroform, and ether, but sparingly soluble or insoluble in other solvents (Found: OMe, 4·0. $C_{47}H_{42}O_{10}S$ requires OMe, 3·9%. 0·1412 G. used 5·3 c.c. of N/10-sodium hydroxide. Calc., 5·3 c.c.).

2-*Acetyl* 6-*Trityl* 3 : 4-*Anhydro* α-*methylgalactoside*.—When the above compound was boiled with 2N-sodium hydroxide (1 part, 10% excess), water (2 parts), and acetone (4 parts) for 1 hour, a homogeneous solution was obtained. This, made definitely alkaline by the addition, if necessary, of more sodium hydroxide solution, was boiled for another 30 minutes, the acetone distilled under diminished pressure, the residue extracted with benzene, and the extract washed with water. The product obtained on evaporation of the benzene was a glass which, treated with acetic anhydride in pyridine solution, gave in almost theoretical yield a product which could not be crystallised and had the empirical composition of a monoacetyl trityl anhydro-α-methylhexoside. The above structure has been ascribed to it (Found: OMe, 6·2; CH_3·CO, 8·5. $C_{28}H_{28}O_6$ requires OMe, 6·7; CH_3·CO, 9·3%).

The Partial Hydrolysis of 2-*Acetyl* 6-*Trityl* 3 : 4-*Anhydro*-α-*methylgalactoside in Acetone containing Dry Hydrogen Chloride*.—Dry hydrogen chloride (17 g.) was passed into a cooled solution of the material (71 g.) in acetone (200 c.c.), the mixture was kept for 1 hour at room temperature, and after neutralisation with silver carbonate, filtration, and evaporation to small bulk, the residue was poured into water containing a little pyridine. After a few minutes the precipitated triphenylcarbinol was filtered off, and the filtrate extracted six times with chloroform, which removed a syrup (A) (27·7 g.). The aqueous solution was shaken with silver carbonate to remove traces of chlorine, treated with hydrogen sulphide, filtered, and evaporated to dryness; the residue, treated with acetone, gave immediately a crystalline monoacetyl methylhexoside (2·9 g.) (Found: OMe, 12·9; CH_3·CO, 18·0. $C_9H_{16}O_7$ requires OMe, 13·1; CH_3·CO, 18·3%). The material was, however, obviously a mixture, since it had m. p. 145—160°. It showed $[\alpha]_D$ + 123·5° in water (c = 1·525) and on alkaline, followed by acid, hydrolysis the rotation became + 158° and + 48·3° respectively (after allowing for changes in concentration). In spite of the close approximation of these figures to those of glucose, no tetra-acetyl α-methylglucoside was obtained on submitting the material to acetylation, and no α-methylglucoside on deacetylation. In view of what follows it seems probable that this material represents a mixture of gulose and galactose derivatives.

The remainder of the material from the original aqueous solution (5·5 g.) consisted of a syrup which reduced Fehling's solution distinctly and has not been further investigated (Found: OMe, 9·6; CH_3·CO, 21·0%).

Examination of the chloroform extract (*A*). The syrup (27·7 g.), on treatment with ether, immediately deposited a crystalline substance, which was washed with ether (B, 3·3 g.); the mother-liquors on longer standing deposited a different crystalline substance (C, 4·9 g.). The residue (D, 19 g.) was a syrup which showed no further signs of crystallisation.

Examination of the crystalline material (*B*). The material was homogeneous, m. p. 176—178°, showed $[\alpha]_D$ + 76·8° in chloroform (c = 3·796), and was insoluble in light petroleum, practically insoluble in ether, sparingly soluble in water, and soluble in other solvents. It was shown to be a *monoacetyl monoacetone* α-*methylguloside* (Found: OMe, 11·3; CH_3·CO, 15·4. $C_{12}H_{20}O_7$ requires OMe, 11·2; CH_3·CO, 15·5%). The substance was deacetylated with boiling aqueous sodium hydroxide, and extraction with chloroform after addition of potassium carbonate gave *monoacetone* α-*methylguloside* in 98% yield; prisms, m. p. 132—133°, $[\alpha]_D$ + 88·5° in chloroform (c = 3·349) (Found: OMe, 13·2. $C_{10}H_{18}O_6$ requires OMe, 13·2%).

The above monoacetone α-methylguloside was hydrolysed with N/50-sulphuric acid to

remove the acetone group, but it was unexpectedly found that the methylgulosidic group was being removed at the same time. The reaction was therefore continued until equilibrium was attained (8 hours), the rotation changing from + 94·7° to − 17·9° (allowing for change of concentration), and the free sugar was isolated by neutralising the reaction mixture with barium carbonate, evaporating it to dryness, and extracting the residue with methyl alcohol. In this way a syrup was obtained, which was converted into gulosazone, m. p. 156°. The specific rotation of gulose is given as − 20·4° (Blanksma and van Ekenstein, *Centr.*, 1908, II, 1583).

Examination of the crystalline material (*C*). This material, isomeric with the material (B), consisted of prisms, m. p. 101—102°, was considerably more soluble, and showed $[\alpha]_D$ +127·3° in chloroform (c = 3·034). It was shown to be a *monoacetyl monoacetone α-methylgalactoside* (Found: OMe, 11·1; CH_3·CO, 17·1. $C_{12}H_{20}O_7$ requires OMe, 11·2; CH_3·CO, 15·5%). On deacetylation in the same manner as before, it yielded monoacetone α-methylgalactoside in theoretical yield, prisms, m. p. 102—104° (this m. p. was mistakenly given as 109—110° in *Nature*, 1935, **135**, 103), $[\alpha]_D$ + 147·9° in chloroform (c = 1·18), + 168·6° in water (c = 1·091) (Found: OMe, 12·8. Calc. for $C_{10}H_{18}O_6$: OMe, 13·2%).

Monoacetone α-methylgalactoside was submitted to partial hydrolysis with 10% aqueous acetic acid; the rotation changed from + 175·1° to + 179·5° in 45 minutes (allowing for change of concentration). Acetone was detected in the distillate by means of the iodoform reaction. The product (98% yield) crystallised completely and after recrystallisation from absolute alcohol did not depress the m. p. of authentic α-methylgalactoside. It showed $[\alpha]_D$ + 175·5° in water (c = 1·068). Fischer (*Ber.*, 1895, **28**, 1157) gives $[\alpha]_D$ + 179° for α-methylgalactoside. Confirmatory proof of its identity was obtained by acid hydrolysis, the rotation falling to + 76·6° (allowing for change of concentration). The rotation of galactose in water is + 81°. This was followed by the conversion of the free sugar into galactosazone (m. p. and mixed m. p.) and by the formation of the anilide of galactose, m. p. 151°, mixed m. p. 151°.

Examination of the residue (*D*). This is involved and by no means complete. After deacetylation by means of sodium hydroxide solution at the ordinary temperature, monoacetone α-methylgalactoside (2·0 g.) and monoacetone α-methylguloside (0·6 g.) were isolated. When monoacetone α-methylgalactoside is hydrolysed with N/50-hydrochloric acid, the rotation indicates that 58% of the material is hydrolysed to the free sugar in 8 hours, whereas the corresponding derivative of gulose is completely hydrolysed in a similar period. A further attempt to isolate α-methylguloside from monoacetone α-methylguloside by hydrolysis with 5% aqueous acetic acid resulted in a partial removal of the gulosidic methyl group. The problem was finally solved by using N/500-sulphuric acid in the hydrolysis. The rotation changed to a final value of + 111·9° in 2¼ hours (allowing for change of concentration). *α-Methylguloside*, isolated in the usual way, was a syrup, $[\alpha]_D$ + 109·7° in water (c = 1·184) (Found: OMe, 15·8. $C_7H_{14}O_6$ requires OMe, 15·9%), which after solidifying crystallised from ethyl acetate in prisms, m.p. 77—79°.

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