65. *Walden Inversion in the Altrose Series.*

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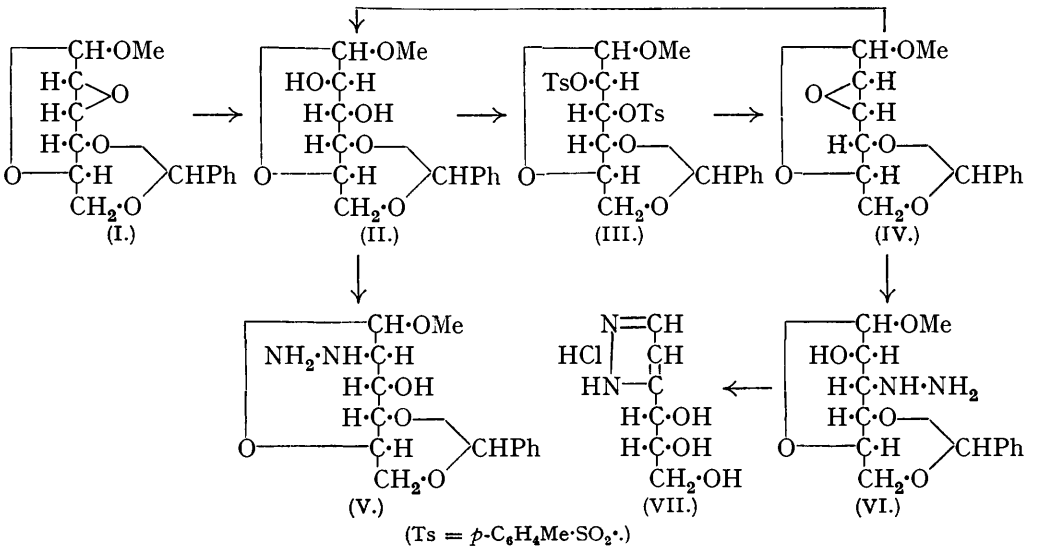
The formation of 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside from 4 : 6-benzylidene α-methylaltroside is described. Hydrazine hydrate opens the ethylene oxide rings of 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside and 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside with the production of 4 : 6-*benzylidene* 2-*hydrazino*-α-*methylaltroside* and 4 : 6-*benzylidene* 3-*hydrazino*-α-*methylaltroside*. The position of the hydrazino-group in the latter was proved by the preparation therefrom of pyrazolyl-5-α-glycerol hydrochloride. The anhydro-ring in 2-methyl 3 : 6-anhydro-α-methyl-altroside, as in glucose, is stable to alkali. No method could be found for preparing a 3 : 4-anhydro-derivative from altrose, and it was concluded that the *cis*-position of the hydroxyl groups concerned precluded such formation. Walden inversion would therefore appear to be a necessary adjunct to ethylene oxide ring production in this hexose.

IT has been shown (Robertson and Griffith, J., 1935, 1193) that the alkaline hydrolysis of 2 : 3-di-*p*-toluenesulphonyl 4 : 6-benzylidene α-methylglucoside leads to the formation of 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (I), from which it was possible to derive small quantities of 4 : 6-benzylidene α-methylaltroside (II) by further alkaline treatment. We now describe, in a continuation of this work, the formation of anhydro-derivatives from altrose. A modification of the method described by Robertson and Griffith for the alkaline hydrolysis of (I) gave a means of ready access to (II). This compound, when condensed with *p*-toluenesulphonyl chloride in pyridine solution, gave a crystalline product, 2 : 3-*di*-p-*toluenesulphonyl* 4 : 6-*benzylidene* α-*methylaltroside* (III), isomeric with the glucose derivative which formed their starting material. Treatment of this substance with sodium methoxide solution resulted in a stoicheiometric yield of 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside (IV), which gave no depression of melting point when mixed with the specimen prepared by Robertson and Griffith from 2-*p*-toluenesulphonyl 4 : 6-benzylidene α-methylglucoside. When these analogous *p*-toluenesulphonyl derivatives of glucose and altrose are submitted to alkaline hydrolysis, Walden inversion occurs at the third carbon atom in each case, with the formation of anhydro-derivatives of different hexoses (*i.e.*, of allose and mannose). Hydrolysis of (IV) with aqueous potash, by a modification of the method of Robertson and Griffith, gave a quantitative yield of (II).



(Ts = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}$.)

The ethylene oxide rings of (I) and (IV) have been opened by the action of various reagents such as potassium hydroxide, sodium methoxide, ammonia, and some dilute acids.

We have used hydrazine hydrate as a hydrolysing agent for this purpose. The reactions were carried out with a 50% solution of hydrazine in water in sealed tubes at 120°, the time required for heating being greater in the case of (I), possibly because of its lesser solubility in water. The compounds obtained, which we shall name A (from I) and B (from IV), were crystalline isomeric hydrazino-sugars, m. p. 196° and 144°, respectively, and by analogy with previous hydrolyses were assumed to be derivatives of altrose. Treatment of B with concentrated hydrochloric acid at room temperature stripped the molecule of benzylidene and altrosidic methyl groups, and led to the subsequent formation of the hydrochloride of pyrazolyl-5-α-glycerol (VII), identical with that isolated by Freudenberg and Rosen (*Ber.*, 1923, **56**, 1243). In B, therefore, the hydrazino-group is in position 3 in the altrose molecule, and B must be 4 : 6-*benzylidene* 3-*hydrazino*-α-*methylaltroside* (VI). It follows that the isomer, A, is 4 : 6-*benzylidene* 2-*hydrazino*-α-*methylaltroside* (V).

The formation of the 3 : 6-anhydro-ring in altrose was brought about by a synthesis from 3-*p*-toluenesulphonyl 4 : 6-benzylidene 2-methyl α-methylaltroside (Robertson and Griffith, *loc. cit.*). By preferential hydrolysis of this compound with hydrochloric acid the benzylidene residue was removed, and the resulting crystalline product, 3-p-*toluenesulphonyl* 2-*methyl* α-*methylaltroside*, was benzoylated to give 3-p-*toluenesulphonyl* 4 : 6-*dibenzoyl* 2-*methyl* α-*methylaltroside*, m. p. 113°. By alkaline hydrolysis of this substance it should theoretically be possible to obtain two anhydro-derivatives, one with an ethylene oxide ring in positions 3 and 4, the other with a butylene oxide ring in positions 3 and 6. The hydrolysis was attempted by heating under reflux with sodium methoxide solution, but was accompanied by the development of a deep red colour and decomposition of the sugar. When carried out under milder conditions, *e.g.*, at room temperature, the reaction resulted in the preferential hydrolysis of benzoyl residues, leaving 3-*p*-toluenesulphonyl 2-methyl α-methylaltroside. The product, obtained in low yield, was crystalline, m. p. 108°, and for reasons given below, was concluded to be 2-*methyl* 3 : 6-*anhydro*-α-*methylaltroside*. The 3 : 4-anhydro-derivative was not formed. The anhydro-compound isolated was stable to the action of 2N-potassium hydroxide in a sealed tube at 110° for a prolonged time, and to similar treatment with a 10% solution of sodium in methyl alcohol. When heated under reflux with 5% hydrochloric acid, the altrosidic methyl group was removed, and a syrup was obtained which reduced Fehling's solution and had the composition of a monomethyl anhydro-hexose. The anhydro-ring remained unopened. The ethylene oxide ring in the hexoses is readily opened when submitted to conditions such as those outlined above, but the butylene oxide ring in 3 : 6-anhydroglucose is stable. This similarity led to the conclusion that the anhydro-derivative of altrose contained the butylene oxide ring, and that the reducing sugar obtained by the hydrolysis of the altrosidic methyl group was 2-*methyl* 3 : 6-*anhydroaltrose*. The formation of this reducing sugar is of interest in connection with the work of Robertson and Griffith (*loc. cit.*) on the removal of the altrosidic methyl group from α-methylaltroside, and its 2- and 3-methyl and 2 : 3-dimethyl derivatives. In each of these cases the removal of the altrosidic methyl group led to the production of a non-reducing anhydro-derivative, and a small amount of reducing sugar, instead of the free sugar and its methylated analogues. This anhydro-ring could only have been in positions 1 : 4 or 1 : 6, and its failure to form after the removal of the altrosidic methyl group of 2-methyl 3 : 6-anhydro-α-methylaltroside shows that in the examples quoted by Robertson and Griffith it has been in the 1 : 6-position. Methylation of 2-methyl 3 : 6-anhydro-α-methylaltroside by means of the Purdie reagents gave a fully methylated derivative, which was a syrup, 2 : 4-*dimethyl* 3 : 6-*anhydro*-α-*methylaltroside*.

The difficulty of forming a 3 : 4-anhydro-derivative from altrose had been exemplified by our failure to obtain such a compound in our synthesis of 2-methyl 3 : 6-anhydro-α-methylaltroside. We therefore attempted a second approach to this compound. The condensation of triphenylmethyl chloride with 3-*p*-toluenesulphonyl 2-methyl α-methylaltroside gave a faintly coloured glass, which, when freed from triphenylmethanol, had the approximate composition of 3-p-*toluenesulphonyl* 6-*triphenylmethyl* 2-*methyl* α-*methylaltroside*, and appeared to be a mixture of this substance and the starting material. Acetylation of this glass yielded crystalline 3-p-*toluenesulphonyl* 4-*acetyl* 6-*triphenylmethyl* 2-*methyl* α-*methylaltroside*, m. p. 165°. This compound, on alkaline hydrolysis, might be expected

to give 6-triphenylmethyl 2-methyl 3 : 4-anhydro-α-methylhexoside, but attempts to perform this reaction with various alkaline reagents failed : the use of a low alkaline concentration resulted in the preferential hydrolysis of the acetyl group, leaving a glass similar to 3-*p*-toluenesulphonyl 6-triphenylmethyl 2-methyl α-methylaltroside; with stronger concentrations a deep coloration developed and the sugar was completely resinified, leaving triphenylmethanol. In altrose the hydroxyl groups attached to carbon atoms 3 and 4 are in *cis*-positions in the molecule, and failure to form an ethylene oxide ring between these two carbon atoms indicates that the occurrence of Walden inversion from a *trans*- to a *cis*-formation is a necessary part of ethylene oxide ring production of this type. Mueller, Moricz, and Verner (*Ber.*, 1939, **72**, 745) encountered similar difficulties in an attempt to form a 3 : 4-anhydro-derivative from galactose, the hydroxyl groups attached to carbon atoms 3 and 4 in this sugar also being in the *cis*-position.

Experimental.

Action of Aqueous Potassium Hydroxide on 4 : 6-*Benzylidene* 2 : 3-*Anhydro-α-methylalloside.*—The substance (10 g.), together with a solution of potassium hydroxide (13 g.) in water (350 ml.), was heated under reflux until it had been totally transformed into water-soluble product (25 hrs.). The cold solution was extracted with chloroform, and the extract dried (sodium sulphate) and evaporated to dryness. By repeated treatment of the residual syrup with methyl alcohol an almost theoretical yield of 4 : 6-benzylidene α-methylaltroside (II) (10·67 g.), m. p. 170°, was obtained. The uncrystallised residue (0·005 g.) was deduced to be a mixture of product and starting material.

2 : 3-*Di*-p-*toluenesulphonyl* 4 : 6-*Benzylidene* α-*Methylaltroside* (III).—4 : 6-Benzylidene α-methylaltroside (5 g.) and a 20% excess of *p*-toluenesulphonyl chloride (10 g.) were dissolved in the minimum volume of pyridine and after 72 hours the solution was diluted with water and extracted with benzene. The extract was washed, dried (sodium sulphate), and evaporated to dryness. The white crystalline residue (7 g.) had m. p. 170—175°, and was recrystallised from methyl alcohol until the m. p. was constant at 179°; $[\alpha]_D^{15°}$ + 46·9° in chloroform (c = 1·002) (Found : C, 57·0; H, 5·0; S, 10·8; OMe, 5·3. $C_{28}H_{30}O_{10}S_2$ requires C, 56·95; H, 5·1; S, 10·85; OMe, 5·25%). Yield, 6 g.

Alkaline Hydrolysis of 2 : 3-*Di*-p-*toluenesulphonyl* 4 : 6-*Benzylidene* α-*Methylaltroside.*—The material (10 g.) was heated on a water-bath with a solution of sodium (1·5 g.) in methyl alcohol (100 ml.) for 12 hours; on cooling, long white needles separated. These were washed with methyl alcohol (yield, 5·5 g.) and recrystallised from acetone–methyl alcohol (yield, 5·3 g.). This substance had the same physical constants as 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside (IV), m. p. 147°, $[\alpha]_D^{15°}$ + 108·1° in chloroform (c = 1·63), and did not depress its m. p.

Action of Hydrazine Hydrate on 4 : 6-*Benzylidene* 2 : 3-*Anhydro-α-methylalloside.*—The material (5 g.), together with an aqueous solution of hydrazine hydrate (20 ml. of 50/50), was heated in a sealed tube at 120° for 30 hours; a compound of different crystalline form separated on cooling. This dissolved on warming, leaving a trace of starting material, which was filtered off. The aqueous solution of hydrazino-hexoside and hydrazine was evaporated to dryness under diminished pressure, and the residue maintained at 90° for 15 minutes to remove traces of hydrazine. Recrystallisation of the product proved to be difficult, as it readily decomposed in the presence of air or when warmed with organic solvent. The latter decomposition took place with explosive violence when such a solution was evaporated under diminished pressure. By solution in chloroform and rapid reprecipitation with light petroleum 4 : 6-*benzylidene* 2-*hydrazino-α-methylaltroside* (V) was obtained in colourless microprismatic needles, m. p. 144°, $[\alpha]_D^{15°}$ + 67·96° in chloroform (c = 1·09) (Found : N, 9·1. $C_{14}H_{20}O_5N_2$ requires N, 9·4%). It depressed the m. p. (196°) of 4 : 6-benzylidene 3-hydrazino-α-methylaltroside (below) to 129°.

Action of Hydrazine Hydrate on 4 : 6-*Benzylidene* 2 : 3-*Anhydro-α-methylmannoside.*—The material (5 g.) was heated with hydrazine hydrate (15 ml. of 50/50) in a sealed tube for 12 hours at 110°. The white solid that separated from the cold solution in needles (5 g.) was more stable than the above hydrazino-derivative and could be left in air for a considerable time. It decomposed when warmed with organic solvents, in which it was less soluble. A suitable crystallising medium could not be found, but the substance, having been freed from superficial impurities by washing, had a sharp m. p. 196°; $[\alpha]_D^{17°}$ + 53·7° in pyridine (c = 0·55) (Found : N, 9·2. $C_{14}H_{20}O_5N_2$ requires N, 9·4%). The hydrazino-group was shown, by the preparation of pyrazylglycerol hydrochloride, to be on the third carbon atom of the hexose molecule. The substance was therefore 4 : 6-*benzylidene* 3-*hydrazino-α-methylaltroside* (VI).

Action of Concentrated Hydrochloric Acid on 4 : 6-*Benzylidene* 3-*Hydrazino-α-methylaltroside.*—A solution of the material (4 g.) in the minimum volume of concentrated hydrochloric acid was kept for 12 hours at room temperature, then washed with ether to remove benzaldehyde, and evaporated to dryness in a vacuum desiccator. The friable solid (3 g.) obtained was recrystallised from propyl alcohol, forming pale yellow needles, m. p. 138°, $[\alpha]_D^{15°}$ + 4·8° in water (c = 10·9) (Found : Cl, 18·2; N, 14·1. Calc. for $C_6H_{10}O_3N_2$,HCl : Cl, 18·2; N, 14·4%), of pyrazolyl-5-α-glycerol hydrochloride [Freudenberg and Rosen, *loc. cit.*, give m. p. 139°; $[\alpha]_{5461}$ + 5·6° in water (c = 10·3)].

Partial Hydrolysis of 3-p-*Toluenesulphonyl* 4 : 6-*Benzylidene* 2-*Methyl* α-*Methylaltroside.*—The substance (5·0 g.) was dissolved in a solution of hydrochloric acid (6 ml., 0·6 N) in acetone (144 ml.) and heated on a water-bath until the optical rotation was constant (2½ hrs.), $[\alpha]_D$ + 82·0°, allowance being made for change in concentration. Water (20 ml.) was added, the solution neutralised with barium carbonate and filtered, and the acetone evaporated. The solid separated from the aqueous residue was extracted with chloroform to remove benzaldehyde, the extract evaporated to small bulk, and warmed almost to the b. p., and light petroleum added until crystallisation began. 3-p-*Toluenesulphonyl* 2-*methyl* α-*methylaltroside* (3·5 g.) separated in needles, m. p. 118°, $[\alpha]_D^{15°}$ + 88·1° in chloroform (c = 1·044) (Found : C, 49·8; H, 6·0; OMe, 17·0. $C_{15}H_{22}O_8S$ requires C, 49·8; H, 6·1; OMe, 17·1%).

Acetylation of this substance by the usual method yielded a syrup.

3-p-*Toluenesulphonyl* 4 : 6-*Dibenzoyl* 2-*Methyl* α-*Methylaltroside.*—3-*p*-Toluenesulphonyl 2-methyl α-methylaltroside (5 g.) was dissolved in the minimum volume of pyridine and kept with a 20% excess of benzoyl chloride (5·5 ml.) for 24 hours; the mixture was then diluted with water and extracted with chloroform. The syrup (8·5 g.) isolated from the dried extract (sodium sulphate) crystallised on treatment with methyl alcohol; yield, 8·0 g., m. p. 113°, $[\alpha]_D^{16°}$ + 94·69° in chloroform (c = 1·109) (Found : C, 61·1; H, 5·3; S, 5·5; OMe, 10·8. $C_{29}H_{30}O_{10}S$ requires C, 61·1; H, 5·3; S, 5·6; OMe, 10·9%).

Alkaline Hydrolysis of 3-p-*Toluenesulphonyl* 4 : 6-*Dibenzoyl* 2-*Methyl* α-*Methylaltroside.*—The material (20 g.) was heated under reflux with methyl alcohol (250 ml.) in which sodium (1·5 g.) had been dissolved; the solution became dark red. After 5 hours, water was added and the alkaline solution was made slightly acid, neutralised with barium carbonate, filtered, and evaporated to dryness. The residue was extracted with chloroform and the highly coloured extracts were treated with charcoal, until the colour was considerably diminished, and then evaporated to dryness. The coloured syrup obtained crystallised after repeated treatments with ethyl alcohol and light petroleum; m. p. 100° (2·5 g.). After several recrystallisations 2-*methyl* 3 : 6-*anhydro-α-methylaltroside* was obtained in fairly large, prismatic crystals (2 g.) of constant m. p. 107—108°, $[\alpha]_D^{14°}$ + 105·1° in chloroform (c = 1·087) (Found : C, 50·8; H, 7·5; OMe, 32·3. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4; OMe, 32·6%).

No other anhydro-derivative could be isolated in the above reaction. With the aim of getting the 3 : 4-anhydro-derivative various modifications were attempted and, as it was considered that the above treatment might have been too drastic, these were mainly carried out at lower temperature and in lesser concentration. The following is a typical example : The material (15 g.) was dissolved in methyl alcohol (150 ml.), and sodium (1·0 g.) in methyl alcohol (20 ml.) added. After 18 hours, the product was extracted as a syrup (8 g.), which on recrystallisation from methyl alcohol was found to be 3-*p*-toluenesulphonyl 2-methyl α-methylaltroside (6 g.), m. p. 118°.

Action of 2N-*Hydrochloric Acid on* 2-*Methyl* 3 : 6-*Anhydro-α-methylaltroside.*—A solution of the material (8·0 g.) in 2N-hydrochloric acid was heated under reflux for 10 hours in presence of animal charcoal. Coloration due to decomposition took place and further treatment with charcoal was needed before a colourless solution was obtained. After neutralisation and extraction an amber-coloured syrup (2·8 g.) was isolated, which reduced Fehling's solution. This was 2-*methyl* 3 : 6-*anhydroaltrose*, $n_D^{16°}$ 1·4878, $[\alpha]_D^{16°}$ + 81·27° in chloroform (c = 2·1045), + 106·3° in water (c = 1·105); no mutarotation was observed even in the presence of a trace of aqueous ammonia (Found : C, 47·5; H, 6·7; OMe, 17·4. $C_7H_{12}O_5$ requires C, 47·7; H, 6·8; OMe, 17·6%).

2 : 4-*Dimethyl* 3 : 6-*Anhydro-α-methylaltroside.*—After fifteen treatments of 2-methyl 3 : 6-anhydro-α-methylaltroside with the Purdie reagents the *dimethyl* compound was obtained as a colourless syrup, $n_D^{16°}$ 1·4720, $[\alpha]_D^{18°}$ + 69·04° in chloroform (c = 1·095) (Found : OMe, 45·1. $C_9H_{16}O_5$ requires OMe, 45·6%).

Action of Triphenylchloromethane on 3-p-*Toluenesulphonyl* 2-*Methyl* α-*Methylaltroside.*—The substance (5·4 g.) and an equivalent proportion of triphenylchloromethane (4·4 g.) were dis-

solved in the minimum volume of pyridine and heated at 100° for 2 hours with exclusion of moisture. After dilution with water, the product was extracted in the usual manner. The pale yellow glass isolated (Found : OMe, 8·9. $C_{34}H_{36}O_8S$ requires OMe, 10·2%) consisted of a mixture of triphenylmethanol, tritylated and untritylated material. It was dissolved in benzene, and light petroleum added until no further precipitate appeared. The mother-liquor was decanted, and a solution of the syrupy precipitate in benzene evaporated to dryness. The residual glass (8·8 g.) was a mixture of 3-p-*toluenesulphonyl* 6-*triphenylmethyl* 2-*methyl* α-*methylaltroside* and starting material (Found : OMe, 11·2%).

The impure product obtained above (5 g.) was acetylated with acetic anhydride in pyridine solution. The crystalline compound isolated (5·5 g.) was recrystallised to constant m. p. from acetone–ethyl alcohol. 3-p-*Toluenesulphonyl* 4-*acetyl* 6-*triphenylmethyl* 2-*methyl* α-*methylaltroside* had m. p. 165°, $[\alpha]_D^{15°}$ + 72·4° in chloroform (c = 1·008) (Found : C, 66·9; H, 5·8; S, 4·95; OMe, 9·7. $C_{36}H_{38}O_9S$ requires C, 66·9; H, 5·9; S, 4·95; OMe, 9·6%).

Action of Hydrolysing Agents on 3-p-*Toluenesulphonyl* 4-*Acetyl* 2-*Methyl* α-*Methylaltroside.*—*Alcoholic potassium hydroxide.* The material (6·5 g.) was dissolved in a 5% solution of potassium hydroxide in water (25 ml.) and ethyl alcohol (225 ml.) and heated under reflux for 3 hours. A deep red colour rapidly developed and the product isolated was mainly triphenylmethanol.

Sodium hydroxide in acetone solution. The material (11 g.) was dissolved in a solution of sodium hydroxide (25 ml. of 2N) in acetone (100 ml.) and water (50 ml.) and heated under reflux for 2 hours. The acetone was evaporated, and the aqueous residue extracted with benzene. From the extract a glass was obtained which appeared to be 3-*p*-toluenesulphonyl 6-triphenylmethyl 2-methyl α-methylaltroside. The acetyl group had been preferentially hydrolysed, and resinification had taken place.

Sodium methoxide solution. Treatment of the material with a 2·5% solution of sodium in methyl alcohol at 60° led to a great deal of charring and decomposition.

The above are examples of methods used in an attempt to form a 3 : 4-anhydro-derivative of altrose from this substance, and the failure to form such a compound led to the conclusion that Walden inversion was occurring on the third carbon atom on hydrolysis of the *p*-toluenesulphonyl residue. The subsequent formation of a *trans*-ethylene oxide ring did not take place and, instead, the sugar decomposed.

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