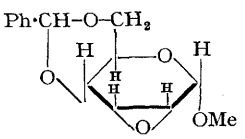
4. *Some Observations on the Ring Scission of* 4 : 6-*Benzylidene* 2 : 3-*Anhydro* α-*Methylmannoside with Ammonia.*

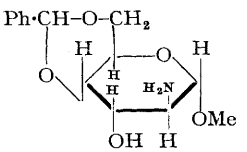
By L. F. Wiggins.

The secondary product of the anhydro ring scission of 4 : 6-benzylidene 2 : 3-anhydro α-methylmannoside with ammonia is shown not to be a derivative of glucosamine but a secondary amine. The product of Myers and Robertson (*J. Amer. Chem. Soc.*, 1943, **65**, 8), obtained by the hydrolysis of 3-amino 4 : 6-benzylidene α-methylaltroside, is not Fischer's methyl "epiglucosamine" but 3-amino 1 : 6-anhydro altrose.

It has been generally held hitherto that the ring scission, with ammonia, of an ethylene oxide anhydro ring compound of the sugar series, in which the ring does not involve a primary carbon atom, takes place with Walden inversion and gives rise to two isomeric amino sugar derivatives, which it may or may not be possible to isolate depending on their ease of separation. Thus, 4 : 6-benzylidene 2 : 3-anhydro α-methylalloside (I) gave 2-amino 4 : 6-benzylidene α-methylaltroside (II) together with 3-amino 4 : 6-benzylidene α-methylglucoside (III) (Peat and Wiggins, *J.*, 1938, 1810). Similarly James, Smith, Stacey, and Wiggins (*Nature*, 1945, **156**, 308) have shown that the ethylene oxide ring in 1 : 6-2 : 3-dianhydro β-talose (IV) opens under the influence of ammonia giving 2-amino 1 : 6-anhydro β-galactose (V) and 3-amino 1 : 6-anhydro β-idose (VI).



(I.)



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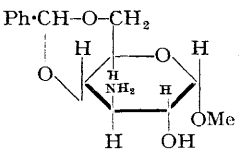

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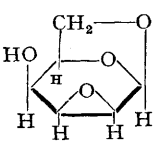

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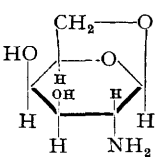

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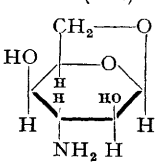
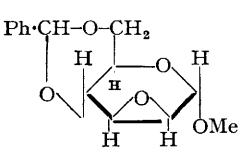


(VI.)

An instance in which this general scheme does not hold has now been found. Myers and Robertson (*loc. cit.*) treated 4 : 6-benzylidene 2 : 3-anhydro α-methylmannoside (VII) with ammonia. According to the general theory outlined above they should have obtained two compounds, 2-amino 4 : 6-benzylidene α-methylglucoside (VIII) (a glucosamine derivative) and 3-amino 4 : 6-benzylidene α-methylaltroside (IX), and indeed these authors did obtain two compounds which they believed were the derivatives of glucose and altrose [(VIII) and (IX)]. This assumption was natural, since ring scission of a very similar compound, 4 : 6-dimethyl 2 : 3-anhydro β-methylmannoside, had already been carried out with the formation of 2-acetamido 4 : 6-dimethyl β-methylglucoside (a glucosamine derivative) and 3-acetamido 4 : 6-dimethyl β-methylaltroside (Haworth, Lake, and Peat, *J.*, 1939, 274), Myers and Robertson had isolated 3-amino 4 : 6-benzylidene α-methylaltroside (IX) (A) as the main product, and the secondary product (B), supposedly a glucosamine derivative (2-acetamido 3-acetyl 4 : 6-benzylidene α-methylglucoside), characterised as its acetate (X) in small yield. The present author has now carried out similar experiments and has obtained from (VII) the altroside (IX) (giving a diacetate, m. p. 196°) in 92·3% yield and the secondary component (isolated as a diacetate, m. p. 237°, $[\alpha]_D$ + 45·31°), the so-called glucosamine derivative, in small yield. The analytical figures, however, were not in agreement with the formulation of this secondary product as (X). Moreover, 2-*acetamido* 3-*acetyl* 4 : 6-*benzylidene* α-*methylglucoside* (X) was synthesised from natural glucosamine and this compound had constants (m. p. 203—205°, $[\alpha]_D$ + 33°) different from those of the product (B). It was clear either that the product (B) had resulted from a side reaction or that the general theory of anhydro ring scission was not applicable in this case.



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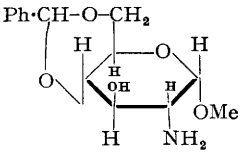
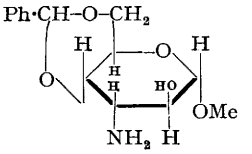
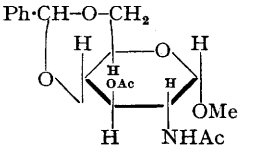


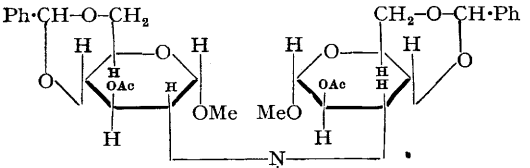
(VIII.)



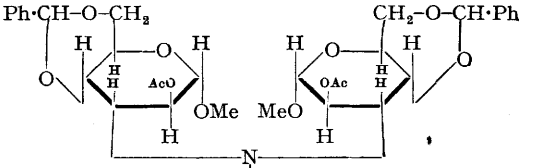
(IX.)



(X.)



(XI.)



(XII.)

The *compound* (B) had a high melting point, and the analytical figures suggested that it contained one atom of nitrogen combined with two aldose residues. This idea was supported by the fact that a molecular weight determination (Rast) gave a value of 630 whereas (X) requires 365. The analysis of (B) conforms to one or other of the structures represented by (XI) and (XII), either of which could arise by the scission of the ethylene oxide ring of 4 : 6-benzylidene 2 : 3-anhydro α-methylmannoside (VII) through the agency of the basic 3-amino 4 : 6-benzylidene α-methylaltroside (IX) and subsequent acetylation of the product.

This reaction, of course, would be subsidiary to the main ring opening of the anhydro mannoside with ammonia whereby the 3-amino altroside is produced. This view was confirmed by the following synthesis. 4 : 6-Benzylidene 2 : 3-anhydro α-methylmannoside was treated with pure 3-amino 4 : 6-benzylidene α-methylaltroside; after acetylation of the product, a substance, tentatively represented by (XII), identical with the product (B) was obtained in quite good yield, although no other crystalline product could be isolated. It must be emphasised, however, that the representation of (B) by (XII) and not by (XI) is based solely on analogy with the observed effects of anhydro ring fission with simple reagents. Further work on the substance (B), with a view to a more definite elucidation of its structure, is being carried out.

The glucosamine derivative, 2-acetamido 3-acetyl 4 : 6-benzylidene α-methylglucoside, was synthesised as follows. *N*-Carbobenzoxy-α-methylglucosaminide (Neuberger, *J.*, 1939, 122) was converted by hydrogenation into α-methylglucosaminide and thence into the *N*-acetyl derivative which on treatment with benzaldehyde gave 2-acetamido 4 : 6-benzylidene α-methylglucoside from which 2-acetamido 3-acetyl 4 : 6-benzylidene α-methylglucoside was obtained by further acetylation.

Myers and Robertson (*loc. cit.*) claimed to have partially hydrolysed 3-amino 4 : 6-benzylidene α-methylaltroside (IX) with dilute aqueous hydrochloric acid and obtained what they described as 3-amino β-methylaltroside hydrochloride having m. p. 209° and $[\alpha]_D$ — 149° (in water) and as being identical with Fischer's methyl epiglucosamine hydrochloride (*Ber.*, 1920, **53**, 836). If this compound is in truth formed its formation must involve inversion on C_1 without loss of methoxyl, since the starting material is a derivative of α-methylaltroside. This is a rather unusual phenomenon since the reaction was carried out in aqueous medium. Moreover, it was observed by Peat and Cutler (*J.*, 1938, 274) that many derivatives of β-methylglucosaminide were converted almost quantitatively and irreversibly into the corresponding α-form. The present author, however, found that partial hydrolysis of (IX) with oxalic acid in acetone was possible and 3-*amino* α-*methylaltroside*, m. p. 120°, $[\alpha]_D$ + 109·0°, and its *hydrochloride*, m. p. 208—209° (decomp.), $[\alpha]_D$ + 88·2°, were isolated. These compounds by virtue of their high positive rotations could certainly be fairly described as glucosides of the α-type. In order to try to clear up the anomaly presented by the work of Myers and Robertson, their experiments on the hydrolysis of 3-amino 4 : 6-benzylidene α-methylaltroside were repeated; the product isolated was 3-*amino anhydro altrose hydrochloride* having m. p. 215—216° (decomp.) and $[\alpha]_D$ — 171·9°, and not Fischer's methyl epiglucosamine hydrochloride. This amino anhydro altrose was clearly identical with Levene and Meyer's (*J. Biol. Chem.*, 1923, **55**, 221) anhydro epiglucosamine, m. p. 216° (decomp.) and $[\alpha]_D$ — 172° (2·5% HCl), and although Levene and Meyer ascribed to it a 1 : 2-anhydro structure, in the light of modern work which has shown that altrose itself readily forms a 1 : 6-anhydride (altrosan) (Richtmyer and Hudson, *J. Amer. Chem. Soc.*, 1935, **57**, 1716; 1940, **63**, 961) it is fairly certain that the anhydro epiglucosamine is 3-amino 1 : 6-anhydro altrose.

Experimental

4 : 6-Benzylidene 2 : 3-anhydro α-methylmannoside was obtained according to the procedure of Robertson and Griffith (*J.*, 1935, 1193).

The Action of Ammonia on 4 : 6-*Benzylidene* 2 : 3-*Anhydro* α-*Methylmannoside*.—The anhydro mannoside (4 g.) was heated in a sealed tube with 200 c.c. of methyl alcohol (saturated with ammonia at 0°) at 130° for 48 hours. Evaporation of the solvent gave a solid residue (4·25 g.) which after careful fractional crystallisation gave (A) m. p. 190—191° (yield, 3·97 g.), and a syrupy residue (0·22 g.). The compound (A) was 3-amino 4 : 6-benzylidene α-methylaltroside and was obtained in 92·3% yield, assuming complete conversion of the anhydro sugar into amino sugars. It showed $[\alpha]_D$ + 93·8° in chloroform (*c*, 1·44) (Found : C, 59·4; H, 6·7; N, 5·4. Calc. for $C_{14}H_{19}O_5N$: C, 59·8; H, 6·8; N, 5·0%).

The syrupy residue showed $[\alpha]_D$ +90·6° in chloroform (*c*, 3·2). It was acetylated by dissolving it in pyridine (5 c.c.) and adding acetic anhydride (0·5 c.c.) and leaving at room temperature for 7 days. After being poured into water, the product was extracted with chloroform and the extract washed with dilute sulphuric acid, sodium bicarbonate solution, and with water, dried ($MgSO_4$), and evaporated. Yield, 0·16 g. of a syrup which partly crystallised. The crystalline *substance* (B) was isolated in thick needles by recrystallisation from alcohol. Yield, 0·025 g., m. p. 235—238°. Repeated recrystallisation raised the m. p. to 237—238°; $[\alpha]_D$ +45·3° in chloroform (*c*, 1·305) [Found : C, 60·9; H, 5·8; N, 1·9; *M*, 630 (Rast). $C_{34}H_{41}O_{13}N$ requires C, 60·8; H, 6·1; N, 2·1%; *M*, 671 (cf. Calc. for $C_{18}H_{23}O_7N$: C, 59·1; H, 5·8; N, 3·8%; *M*, 365)].

3-*Acetamido* 2-*Acetyl* 4 : 6-*Benzylidene* α-*Methylaltroside*.—3-Amino 4 : 6-benzylidene α-methylaltroside (0·4 g.) was dissolved in dry pyridine (5 c.c.), acetic anhydride (0·6 c.c.) added and the mixture kept overnight at room temperature. The mixture was poured into water and the *product* extracted with chloroform. The extract was washed with 5% sulphuric acid, sodium bicarbonate solution, and water, dried ($MgSO_4$), and the chloroform removed. The residual syrup crystallised on trituration with alcohol and recrystallised from alcohol in small prisms. Yield, 0·3 g.; m. p. 194—196°; $[\alpha]_D$ +20·0° in chloroform (*c*, 1·6) (Found : C, 59·6; H, 6·2; N, 4·0. $C_{18}H_{23}O_7N$ requires C, 59·1; H, 6·3; N, 3·8%).

Treatment of 4 : 6-*Benzylidene* 2 : 3-*Anhydro* α-*Methylmannoside with* 3-*Amino* 4 : 6-*Benzylidene* α-*Methylaltroside*.—The anhydro mannoside (0·3 g.) together with 3-amino 4 : 6-benzylidene α-methylaltroside (0·3 g.) was heated in dry methyl alcohol (100 c.c.) solution in a sealed tube at 150° for 12 hours. The solution was evaporated to a syrup which would not crystallise. It was acetylated by leaving it at room temperature for 24 hours with dry pyridine (15 c.c.) and acetic anhydride (8 c.c.). The product was isolated by pouring the mixture into water, when a crystalline precipitate was obtained. This was collected and, recrystallised from alcohol, formed stout needles. Yield, 0·16 g.; m. p. 237—238° not depressed in admixture with product (B) above; $[\alpha]_D$ +46·0° in chloroform (*c*, 1·395).

The mother liquors, after removal of the crystalline precipitate, were extracted with chloroform, and the extract was washed with dilute sulphuric acid, dilute sodium bicarbonate solution, and water, dried ($MgSO_4$), filtered, and evaporated. The residual syrup would not crystallise.

Partial Hydrolysis of 3-*Amino* 4 : 6-*Benzylidene* α-*Methylaltroside*.—The compound (2·3 g.) was dissolved in acetone (100 c.c.), oxalic acid (3·5 g.) dissolved in 20 c.c. of water added, and the mixture boiled for 15 hours and then evaporated to small bulk. Water (30 c.c.) was added and benzaldehyde removed by extraction with ether. Crystalline barium hydroxide (11·5 g.) was dissolved in water and added to the aqueous solution, the precipitated barium oxalate removed by filtration, and excess of Ba^{++} removed by titration with N-sulphuric acid, so that neither Ba^{++} nor SO_4^{--} was present. The

filtered solution was evaporated to dryness, and the crystalline residue was recrystallised, with some difficulty, from dioxan. Yield, 0·6 g.; m. p. 120°. A syrupy residue (C) remained. The crystalline *substance* showed $[\alpha]_D$ +109·9° in water (*c*, 2·985) (Found: C, 43·8; H, 7·8; N, 7·9. $C_7H_{15}O_5N$ requires C, 43·5; H, 7·9; N, 7·3%). It gave a crystalline *hydrochloride* on titration with hydrochloric acid, followed by evaporation and recrystallisation from alcohol–water, m. p. 208° (decomp.); $[\alpha]_D^{17°}$ +88·2° in water (*c*, 1·15) (Found: Cl, 15·4. $C_7H_{15}O_5N$,HCl requires Cl, 15·5%).

The syrupy residue (C) showed $[\alpha]_D^{17°}$ +73° in water (*c*, 2·745) and this also yielded the same hydrochloride after titration with hydrochloric acid. Yield, 0·7 g.

This substance was heated under reflux with 1% methyl alcoholic hydrogen chloride for 18 hours but there was only a small decrease in the specific rotation and clearly no complete change over to the β-form had occurred; + 93·7° (initial); + 84·4° (¼ hr.); + 78·1° (2¾ hrs.); + 78·1° (5 hrs.); + 74·0° (9 hrs.); + 75° (18 hrs.). The initial hydrochloride was recovered in 50% yield after this treatment.

Treatment of 3-*Amino* 4 : 6-*Benzylidene* α-*Methylaltroside with* 1% *Hydrochloric Acid.*—The substance (1 g.) was dissolved in 160 c.c. of 1% aqueous hydrochloric acid and the solution heated at 100° for 28 hours (Myers and Robertson, *loc. cit.*). The $[\alpha]_D$ changed as follows: + 90·0° (initial value); + 72·0° (1½ hrs.); + 68·6° (4 hrs.); + 60·0° (10 hrs.); + 22° (15 hrs.); + 11° (20 hrs.); + 9° (24 hrs.); + 8° (28 hrs.). At this stage the solution was evaporated under diminished pressure. The *product*, twice recrystallised from alcohol–acetone–water in small prisms, was isolated in small yield, and had m. p. 215—216° (decomp.) (turned grey at 200°); $[\alpha]_D$ − 171·9° in water, − 172·2° in 2·5% hydrochloric acid (Found: C, 36·2; H, 6·1; N, 7·3. $C_6H_{11}O_4N$,HCl requires C, 36·1; H, 6·1; N, 7·1%). It was 3-amino-1 : 6-anhydro altrose hydrochloride. Myers and Robertson (*loc. cit.*) give m. p. 209° (decomp.), $[\alpha]_D$ − 149° in water for their product alleged to be 3-amino β-methylaltroside. Levene and Meyer (*loc. cit.*) give m. p. 216° (decomp., changing colour at 190°), $[\alpha]$ − 172° in 2·5% hydrochloric acid for their anhydro epiglucosamine hydrochloride.

Synthesis of 2-*Acetamido* 3-*Acetyl* 4 : 6-*Benzylidene* α-*Methylglucoside.*—*N*-Carbobenzoxyglucosamine prepared by the method of Chargraff and Bovarnick (*J. Biol. Chem.*, 1937, **118**, 421) was converted into the corresponding α-methylglucosaminide according to Neuberger (*loc. cit.*) and subsequently hydrogenated over Raney nickel at 150° for 7 hours at 80°. The filtered solution was evaporated to a syrup and acetylated with methyl alcoholic acetic anhydride. The resulting crystalline *N*-acetyl α-methylglucosaminide was benzylidenated without further purification and *N*-acetyl 4 : 6-benzylidene α-methylglucosaminide isolated, m. p. 255—256°; $[\alpha]_D$ + 40·0° in chloroform (*c*, 1·5). Neuberger (*J.*, 1941, 507) gave m. p. 255°; $[\alpha]_D$ + 19°. The 2-acetamido 4 : 6-benzylidene α-methylglucosaminide (0·5 g.) was dissolved in pyridine (10 c.c.), acetic anhydride (2 c.c.) added, and the mixture left at room temperature for 48 hours. Thereafter it was poured into water and the *product* extracted with chloroform. The extract was washed with dilute sulphuric acid, sodium bicarbonate solution, and water. After being dried ($MgSO_4$), the chloroform extract was evaporated and the crystalline residue recrystallised from methyl alcohol; m. p. 203—205°; $[\alpha]_D$ + 33·0°. Yield, 0·3 g. (Found: C, 59·2; H, 6·1. $C_{18}H_{23}O_7N$ requires C, 59·2; H, 6·3%). The corresponding compound of the β-series is described by Myers and Robertson (*J. Amer. Chem. Soc.*, 1943, **65**, 8) and has m. p. 158° and $[\alpha]_D$ − 12·9° in chloroform.

The author desires to express his thanks to Professor W. N. Haworth, F.R.S., for the interest he has shown in this work.

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