341. *Derivatives of* 1 : 6-*Anhydro*-β-D-*idose*.

By L. F. Wiggins.

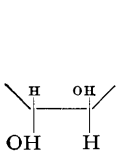
The formation of 1 : 6-anhydro-derivatives of hexoses is discussed. A new crystalline derivative of D-idose is described, namely 2 : 3 : 4 : 6-*tetra-acetyl β-methylidoside*.

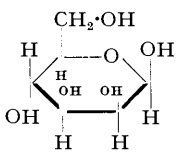
In an earlier communication (*J.*, 1944, 522) it was shown that galactose was converted, through its 2-tosyl derivative, into 2 : 3-anhydro-β-methyltaloside. The 4 : 6-benzylidene derivative of this compound underwent ring scission with sodium methoxide to give mainly 4 : 6-benzylidene 3-methyl β-methylidoside (A), together with a little 4 : 6-benzylidene 2-methyl β-methylgalactoside (B). The formation of these two products was in accord with the accepted theory of anhydro-ring scission. In experiments designed to determine its constitution, the compound (*A*) was hydrolysed first to 3-methyl β-methylidoside, then under more drastic conditions to a product which should have been 3-methyl idose. It was observed, however, that the product possessed only slight reducing power towards Fehling's solution; moreover oxidation of the sugar with bromine did not give pure 3-methyl idonic acid or its lactone, since the derived non-crystalline amide contained much less nitrogen than the theoretical, and gave only $\frac{1}{4}$ of the expected yield of hydrazodicarbonamide on being treated with Weerman's reagent. These facts which suggested that some modification of the reducing group of 3-methyl idose impeded its oxidation with bromine have now received a ready explanation in the light of the recent work of Sorkin and Reichstein (*Helv. Chim. Acta*, 1945, **28**, 1). These authors have shown that idose tends to undergo internal anhydride formation involving the reducing group and the hydroxyl at C_6. Thus, hydrolysis of β-methylidoside led to the formation of 1 : 6-anhydro-β-idose, and thence to that of the 2 : 3 : 4-triacetate. Sorkin and Reichstein also showed that

the crude hydrolysis product of β-methylidoside reduced Fehling's solution only about one-fifth as strongly as did glucose, and that bromine oxidation of this product gave only a 20% yield of idonic acid. Thus the 3-methyl idose described in 1944 was probably a mixture of 3-methyl idose and 3-methyl 1 : 6-anhydro-β-idose. The bromine oxidation product was therefore a mixture of 3-methyl 1 : 6-anhydro-β-idose and 3-methyl idonic acid lactone, and the amide prepared therefrom also contained the 1 : 6-anhydro-compound as an impurity, thus accounting for its low nitrogen value and for the low yield of hydrazodicarbonamide obtained on treatment with Weerman's reagent.

Another example of the spontaneous formation of 1 : 6-anhydroidose has been observed. When 3-acetamido 2-acetyl 4 : 6-benzylidene β-methylidoside (Wiggins, *loc. cit.*) was hydrolysed with concentrated hydrochloric acid, the product after re-acetylation was found to be 3-acetamido 2 : 4-diacetyl 1 : 6-anhydro-β-idose, a substance already prepared by James, Smith, Stacey, and Wiggins (*J.*, 1946, 625) by the ring scission with ammonia of both 2 : 3- and 3 : 4-1 : 6-dianhydro-β-talose. Since there are now three different derivatives of idose which have been shown to undergo 1 : 6-anhydro-ring formation in aqueous solution, it is reasonable to suppose that this phenomenon is common to all derivatives of idose in which the hydroxyl groups at C_1 and C_6 are unsubstituted.

Although several hexoses, for example, D-glucose and D-mannose, form 1 : 6-anhydrides under pyrogenetic conditions, only two, namely D-idose and D-altrose, are known to undergo 1 : 6-anhydro-ring formation under ordinary conditions in solution. It is interesting to note that β-D-idose and β-D-altrose have identical arrangements of the hydrogen and hydroxyl groups about C_2 and C_3 (I), and moreover these are the only aldohexoses of the D-series which possess this arrangement. The configuration of the hydrogen and hydroxyl groups about C_1 can vary in any sugar, but clearly the sugar must be of the β-form when 1 : 6-anhydro-ring formation takes place. It would appear that neither of the particular configurations about C_2 and C_3, taken separately, is responsible for the spontaneous ring-formation, because neither β-D-mannose (II) which has the same arrangement of hydrogen and hydroxyl about C_2 as altrose and idose, nor β-D-allose (III), which has the same configuration about C_3 as altrose and idose, undergoes spontaneous 1 : 6-anhydride formation.


(I.)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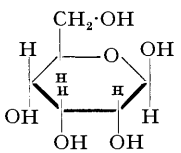
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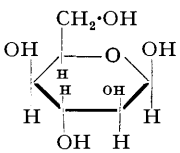
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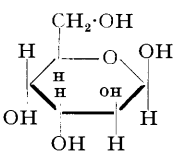
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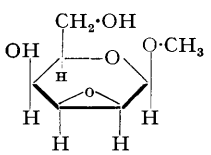
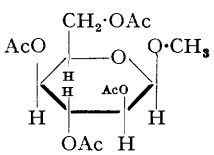

(VI.)

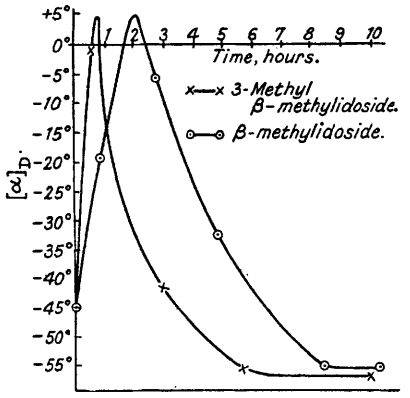

(VII.)

The position of the hydroxyl group at C_4 is evidently not critical in regard to 1 : 6-anhydro-ring formation, because the configuration at that point is different in idose (IV) and altrose (V).

It is not yet clear why this particular orientation of groups on C_2 and C_3 of an aldohexose should facilitate the formation in solution of the 1 : 6-anhydro-ring, and it can only be pointed out at this stage that this configuration does play a critical part in the phenomenon.

Sorkin and Reichstein (*loc. cit.*) obtained 1 : 6-anhydro-β-D-idose, and thence the characteristic triacetate, by hydrolysis of 4 : 6-benzylidene β-methyl-D-idoside. The same compound has now been obtained by a somewhat different route, and the observations of Sorkin and Reichstein confirmed. 2 : 3-Anhydro-β-methyltaloside (VI) (*J.*, 1944, 522) was treated with aqueous potassium hydroxide at room temperature. Ring scission took place very slowly and was complete in 792 hours. After acetylation 2 : 3 : 4 : 6-*tetra-acetyl* β-*methylidoside* (VII) was isolated in 65% yield. No derivative of β-methylgalactoside was isolated. The constitution of (VII) follows from the earlier work on the ring scission of 2 : 3-anhydro-β-methylidoside. De-acetylation of (VII) gave liquid β-methylidoside which defied all attempts at crystallisation. Sorkin and Reichstein (*loc. cit.*) also did not obtain it crystalline. The

hydrolysis of β-methylidoside by N-sulphuric acid was followed polarimetrically. It proceeded according to the graph shown in the figure, in which the hydrolysis curve of 3-methyl β-methylidoside is also shown. From the hydrolysis mixture triacetyl 1 : 6-anhydro-β-D-idose was isolated after acetylation. It had constants in close agreement with those recorded by Sorkin and Reichstein (*loc. cit.*). That the hydrolysis of both β-methylidoside and its 3-methyl derivative proceeded in a strikingly similar way is apparent from the figure. It is probable that in each case the first peak in the curves represents the removal of the glycosidic methyl group, and the subsequent fall in specific rotation indicates the formation of the 1 : 6-anhydro-ring.



Hydrolysis of β-methylidoside and its 3-methyl ether with N-sulphuric acid.

Experimental.

Hydrolysis of 2 : 3-Anhydro-β-methyltaloside with Potassium Hydroxide.—The taloside (1·005 g.), prepared according to the method described by Wiggins (*loc. cit.*), was left in the cold with 5% aqueous potassium hydroxide (25 c.c.) and the reaction followed polarimetrically: $[\alpha]_D$ −90·0° (initial value); −88·5° (3·5 hours); −85·0° (6 hours); −83·1° (23 hours); −80·0° (39 hours); −76·3° (63 hours); −67·4° (135 hours); −61·9° (189 hours); −52·7° (548 hours); −51·7° (620 hours); −50·2° (792 hours); −50·2° (840 hours). Thereafter the solution was heated at 100° for 2 hours without there being any further change in specific rotation. The solution was neutralised with N-sulphuric acid, and the mixture evaporated in the presence of a little barium carbonate, dried, and acetylated by treatment with acetic anhydride (10 c.c.) and pyridine (15 c.c.). After 48 hours at 30°, the mixture was poured into ice–water and then extracted with chloroform. The extract was washed successively with 5% sulphuric acid, dilute sodium hydrogen carbonate solution, and water. After being dried ($MgSO_4$), the solution was filtered, and the solvent removed under diminished pressure. The syrupy residue (1·7 g.) crystallised on cooling. Recrystallised from alcohol it formed feathery needles (1·3 g.; 65%) of 2 : 3 : 4 : 6-*tetra-acetyl β-methylidoside*, m. p. 112—113°, $[\alpha]_D^{20°}$ −64·1° (*c*, 1·56 in chloroform). A m. p. in admixture with tetra-acetyl β-methylgalactoside showed a marked depression (Found: C, 49·8; H, 6·2. $C_{15}H_{22}O_{10}$ requires C, 49·7; H, 6·1%).

β-Methylidoside.—The tetra-acetate (1·2 g.) was dissolved in dry methyl alcohol, a small piece of sodium was added, and the solution was left overnight and then evaporated to a syrup (0·5 g.) which could not be induced to crystallise. It showed $[\alpha]_D$ −40·8° (*c*, 10 in water) (Found: OMe, 15·5. Calc. for $C_7H_{14}O_6$: OMe, 16·0%). Sorkin and Reichstein give $[\alpha]_D$ −81·1° in water.

Acid Hydrolysis of β-Methylidoside.—β-Methylidoside (0·3534 g.) was dissolved in N-sulphuric acid (10 c.c.), and the mixture heated on a boiling water-bath, the reaction being followed polarimetrically (see figure). The solution was neutralised with barium carbonate and filtered, the residue washed with hot water, and the combined filtrates evaporated to dryness. The residue was dissolved in a little water, filtered, and evaporated to a syrup (0·25 g.) which defied all attempts at crystallisation. It showed $[\alpha]_D$ −66·3° (*c*, 4·468 in water). The solution was only very slightly reducing to Fehling's solution, and in all probability this contained a considerable amount of 1 : 6-anhydro-β-idose. The syrup (0·2 g.) was acetylated by boiling it for 0·5 hour with acetic anhydride (10 c.c.) and fused sodium acetate (1 g.). The mixture was poured on ice, and after an hour's stirring, complete solution took place. The solution was neutralised with sodium hydrogen carbonate, and the product extracted several times with chloroform. The chloroform extract was washed with water, dried ($MgSO_4$), filtered, and evaporated. A syrupy product was obtained which gradually crystallised. After being drained on porous tile, the solid was recrystallised several times from water. The product, which crystallised in small platelets, had m. p. 85·5—86·5° and showed $[\alpha]_D$ −73·1°. These figures are in close agreement with those (m. p. 86—87°, $[\alpha]_D$ −73·6° in chloroform) given by Sorkin and Reichstein (*loc. cit.*) for triacetyl 1 : 6-anhydro-β-idose.

Hydrolysis of 3-Acetamido 2-Acetyl 4 : 6-Benzylidene β-Methylidoside.—The compound (0·183 g.) was heated at 100° with 10% hydrochloric acid (10 c.c.) for 3½ hours. The solution showed $[\alpha]_D$ −35·0° at this stage. It was then evaporated to dryness without neutralisation, and the syrup obtained was immediately acetylated by treatment with acetic anhydride (4 c.c.) and pyridine (5 c.c.) for 3 days at room temperature. The product was poured into water, the solution extracted with chloroform, and the extract washed successively with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), filtered, and evaporated. A semicrystalline mass was obtained which, recrystallised from alcohol, formed stout needles (0·15 g.), m. p. 245°, $[\alpha]_D^{18°}$ −73·6° (*c*, 1·467 in chloroform). It was 3-acetamido 2 : 4-diacetyl 1 : 6-anhydro-β-idose, identical in m. p., mixed m. p., and specific rotation with that obtained by the ring scission of either 2 : 3- or 3 : 4-1 : 6-dianhydro-β-talose with ammonia (see James, Smith, Stacey, and Wiggins, *J.*, 1946, 625).

The A. E. Hills Laboratories,
The University, Edgbaston, Birmingham, 15.

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