Structure and Reactivity of Anhydro-sugars. Part III. An Interpretation of Some Reactions of* 3 : 6-*Anhydro*-D-*hexoses.*

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Syntheses of phenyl 3 : 6-anhydro-α-D-galactopyranoside, and of phenyl 3 : 6-anhydro-α-D-glucopyranoside and derivatives thereof, are described. The action of acids on these anhydro-compounds has been investigated. An explanation is put forward, on the basis of conformational analysis, of the anomerisations produced by methanolic hydrogen chloride on the derivatives of 3 : 6-anhydro-D-glucose, 3 : 6-anhydro-D-galactose, 3 : 6-anhydro-D-mannose, and their 2-deoxy-analogues, as described in the preceding paper.

THE dicyclic systems in the methyl 3 : 6-anhydro-D-glucosides and methyl 3 : 6-anhydro-D-galactosides and their derivatives are affected in unusual ways by acidic reagents (for a full account see Haworth, Jackson, and Smith, *J.*, 1940, 620; Haworth, Owen, and Smith, *J.*, 1941, 88; for a review see Peat, *Adv. Carbohydrate Chem.*, 1946, **2**, 37). In the preceding paper we described an extension of this work of Haworth *et al.* (*loc. cit.*) and outlined the preparation and some reactions with acidic reagents of derivatives of 3 : 6-anhydro-D-mannose, 3 : 6-anhydro-2-deoxy-D-glucose, and 3 : 6-anhydro-2-deoxy-D-galactose.

From an examination of models, Haworth, Owen, and Smith (*loc. cit.*) concluded that the disposition of the 4- and 5-hydroxyl groups in the methyl 3 : 6-anhydro-D-glucosides allows the formation of two distinct dicyclic systems: the hydrofuran 3 : 6-anhydro-ring can be formed with the sugar in either the pyranose or the furanose form. There is considerable strain when the sugar is in the pyranose form, but little when it is in the furanose form. Hence the pyranose ⟶ furanose (P ⟶ F) conversion observed on treating methyl 3 : 6-anhydro-α(or β)-D-glucopyranoside with methanolic hydrogen chloride is an intramolecular rearrangement with loss of strain. In the galactose series a P ⟶ F rearrangement is impossible for steric reasons (see Haworth, Owen, and Smith, *loc. cit.*) and so the pyranose derivatives are converted into the strainless open-chain form.

The above workers demonstrated that the transformations (P ⟶ F, and α ⟶ β) observed with the methyl 3 : 6-anhydro-D-glycosides did not pass through a stage involving the free reducing sugar. Peat (*loc. cit.*) suggested that the rearrangements proceed by proton attack on the oxygen atom in the pyran ring with the intermediate formation of an ion in which $C_{(1)}$ of the sugar is a carbonium cation. The nature of substituents on $C_{(1)}$ will affect the ease with which it can be converted into a carbonium cation. Consequently in a consideration of the rearrangements occurring with methyl 3 : 6-anhydro-D-hexosides it was thought worth while to examine the behaviour of phenyl 3 : 6-anhydro-D-hexosides.

Phenyl α-D-galactopyranoside was converted into phenyl 3 : 6-anhydro-α-D-galactoside by the procedure described in the preceding communication. Methylation readily afforded the 2 : 4-di-*O*-methyl derivative. Similarly, phenyl 3 : 6-anhydro-α-D-glucopyranoside was synthesised, and was found to be unchanged after treatment with acidic reagents (0·1N-sulphuric acid, or methanolic 1% hydrogen chloride) at room temperature. More vigorous conditions (*e.g.*, 0·1N-sulphuric acid at 100°) result in hydrolysis and 3 : 6-anhydro-D-glucose can be isolated. A P ⟶ F rearrangement was not observed in any experiment with

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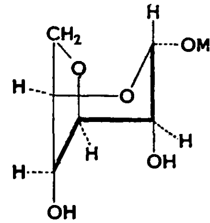
phenyl 3 : 6-anhydro-α-D-glucopyranoside. Furthermore, no α ⟶ β isomerisation was found when phenyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α-D-galactoside was treated with hydrogen chloride in non-hydroxylic solvents. These results can be explained satisfactorily on Peat's ionic mechanism. The substitution of the methyl group at $C_{(1)}$ by the more electrophilic phenyl residue would tend to stabilise the bond between $C_{(1)}$ and the oxygen atom in the pyran ring, thereby reducing protonation of the oxygen atom in the ring; the tendency to form the carbonium-cation intermediate would be reduced and so intramolecular rearrangement inhibited. It is very probable that the same ionic mechanism operates during the α ⟶ β anomerisations and so this conversion also would be expected to be sluggish or non-existent for phenyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α-D-galactoside.

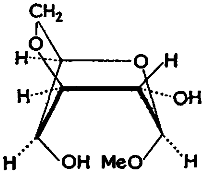
Although the mechanism suggested by Peat (*loc. cit.*) explains the manner of the P ⟶ F and α ⟶ β rearrangements studied by Haworth *et al.* (*loc. cit.*), and the loss of molecular strain by ring contraction clearly causes the former change, reasons for the greater stability of the β- over the α-form have not been outlined. It is our purpose in this communication to propose a possible explanation.

The stereochemistry of pyran derivatives is similar to that of *cyclo*hexane compounds (see Angyal and Mills, *Ann. Rev. Pure Appl. Chem.*, 1952, **2**, 185) and the explanation now put forward is based on the concept of non-bonded interactions which has been developed from considerations of the chemical reactivity of *cyclo*hexane compounds (cf. Barton, *Chem. and Ind.*, 1953, 664; *J.*, 1953, 1027).

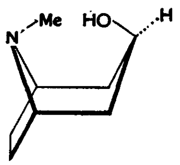
When a 3 : 6-anhydro-bridge is introduced into methyl α-D-glucopyranoside, vibration of the molecule at $C_{(3)}$–$C_{(4)}$–$C_{(5)}$ is prevented and so (I) and (II) are the two possible conformations of methyl 3 : 6-anhydro-α-D-glucopyranoside. Both (I) and (II) may be regarded as 6- and 7-membered ring systems in which the chair form of the pyran ring necessitates the 7-membered ring's being in a boat form, and *vice versa.* The possible conformations of methyl 3 : 6-anhydro-D-hexosides therefore bear a close resemblance to the structures which occur in tropine and ψ-tropine. Sparke (*Chem. and Ind.*, 1953, 749) indicates that (IV) probably represents the more stable conformation of ψ-tropine, although the energy barrier between the forms (III) and (IV) is low (see also Cookson, *Chem. and Ind.*, 1953, 337). Now, (I) and (II) may also be regarded as composed of 5- and 6-membered rings fused together. The 5-membered hydrofuran ring will tend to exist as nearly planar as possible in both structures (I and II), and the shape of the molecule will therefore depend upon the non-bonded interactions between substituents at $C_{(1)}$ and $C_{(2)}$ with the hydrofuran ring and substituents attached thereto.



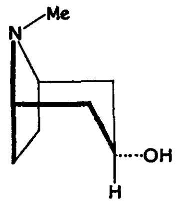
(I)



(II)



(III)



(IV)

The important non-bonded interactions which occur in the methyl 3 : 6-anhydro-D-hexosides, their 2-deoxy-analogues, and the methyl ethers of these compounds can readily be enumerated and assigned estimated values. The values ascribed to the non-bonded interactions (or i-units) are arbitrary figures arrived at from a consideration, with the aid of models, of the geometry of the molecules. The maximum of 10 was assigned to the interaction which introduces most strain into the molecule, *i.e.*, the interaction occurring when methoxyl residues are attached at $C_{(1)}$ and $C_{(4)}$ of the pyran ring when it is in the boat conformation. Values for other interactions can be scaled accordingly, and it follows that the greater the value of the i-unit of a particular arrangement of atoms, the greater is the strain within the molecule, *i.e.*, the higher the i-unit the lower is the molecular stability. The i-units for the α- and the β-forms of the methyl anhydrohexosides studied by Haworth *et al.* (*loc. cit.*) and by the authors (preceding paper) are shown in the Table for the boat and chair conformations of the pyran ring.

From a consideration of the strain introduced into the possible conformations by substituents at $C_{(1)}$, $C_{(2)}$, and $C_{(4)}$ in the anhydro-compounds it is now suggested that the stable conformations (*i.e.*, those with the smallest number of i-units) of methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-D-galactopyranoside and -D-glucopyranoside are those in which the β-isomer possesses the 6-membered pyran (sugar) ring in the boat form.

It is well known that methyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α-D-glucoside is converted by ethereal or chloroformic hydrogen chloride into the β-isomer. Likewise from the Table it would be expected that the most stable form of methyl 2 : 4-di-*O*-methyl-D-mannoside would be the α-form in the chair conformation. Therefore an acid-catalysed β ⟶ α anomerisation should occur under the conditions which effect the α ⟶ β change in the corresponding derivatives of 3 : 6-anhydro-D-glucose and 3 : 6-anhydro-D-galactose. In the previous paper this β ⟶ α transformation in the mannose series was described. Further, from the Table it would be expected that methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-α-D-glucoside and -galactoside under the same acidic conditions would be converted into αβ-mixtures, and this is in accordance with experiment (see previous paper). (It is considered that a difference of about 3 i-units is required for a complete transformation of one anomer into the other when both possible conformations exhibit instability denoted by 5 or more i-units.) The αβ-mixture of methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-D-glucoside would be expected to contain about 50% of each anomer since the chair form of the α-isomer and the boat form of the β-isomer appear to be under the same strain. Similar reasoning indicates that the α-anomer would be the major component of the αβ-product of acid treatment of methyl 3 : 6-anhydro-2-deoxy-4-*O*-methyl-α-D-galactoside. Experimental findings are in agreement with these conclusions (see previous paper). Likewise there is good agreement between experiments and deductions based on the values in the Table regarding the relative stabilities and rates of reaction of the methyl 3 : 6-anhydro-D-hexosides studied. It is realised that this treatment involves some over-simplification of the problem since dipole-moment and hydrogen-bonding effects are neglected, but it is our opinion that it provides at least a partial explanation of the α–β-isomerisations observed with this class of compounds.

3 : 6-Anhydro-derivative (pyranose form)	Isomer	A	B	C	D	E	F
Methyl D-glucoside	α	c	5	9	c	c or b	bβ
		b	8	10			
	β	c	8	12	b	b	
		b	4	5			
Methyl D-galactoside	α	c	3	5	c	c or b	bβ
		b	5	5			
	β	c	6	8	b	b	
		b	3	3			
Methyl D-mannoside	α	c	3	5	c	c	cα
		b	10	13			
	β	c	6	8	c or b	c or b	
		b	6	8			
Methyl 2-deoxy-D-glucoside	α	c	3	5	c	c	cα or bβ
		b	8	10			
	β	c	6	8	b	b	
		b	4	5			
Methyl 2-deoxy-D-galactoside	α	c	1	1	c	c	cα or (bβ)
		b	5	5			
	β	c	4	4	b	c or b	
		b	3	3			

A = Conformation (c = chair form, b = boat form).
B = Total i-units.
C = Total i-units in fully methylated derivative.
D = Predicted most stable conformation.
E = Predicted most stable conformation in fully methylated derivative.
F = Predicted most stable form in αβ-mixture of fully methylated derivative.

EXPERIMENTAL

Phenyl 6-O-*Toluene*-p-*sulphonyl*-α-D-*galactoside*.—Phenyl α-D-galactoside (9·95 g.) and toluene-*p*-sulphonyl chloride (7·35 g.) were allowed to react in pyridine (200 ml.) at 0° for 48 hr. and at room temperature for a further 3 hr. After isolation in the usual manner and recrystallisation from ethanol *phenyl* 6-O-*toluene* p-*sulphonyl*-α-D-*galactoside* (8·0 g., 52%) was obtained as colourless plates, m. p. 148°, $[\alpha]_D^{18}$ +90° (*c*, 1·0 in pyridine) (Found : C, 55·1; H, 5·6; S, 7·7. $C_{19}H_{22}O_8S$ requires C, 55·6; H, 5·4; S, 7·8%).

Phenyl 3 : 6-*Anhydro*-α-D-*galactoside*.—Phenyl 6-*O*-toluene-*p*-sulphonyl-α-D-galactoside (4·5 g.) was treated in ethanol (50 ml.) with N-sodium hydroxide (18 ml.) at 80—85° for 2 hr. The solution was neutralised (solid carbon dioxide) and concentrated under diminished pressure to a solid residue which was extracted with dry acetone. Evaporation of the extract gave a product which was recrystallised from chloroform–light petroleum (b. p. 60—80°). *Phenyl* 3 : 6-*anhydro*-α-D-*galactoside* was obtained in almost quantitative yield, having m. p. 152°, $[\alpha]_D^{21}$ +48·2° (*c*, 1·12 in $CHCl_3$) (Found : C, 60·8; H, 5·9. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%).

3 : 6-*Anhydro*-D-*galactose*.—Phenyl 3 : 6-anhydro-α-D-galactoside (0·223 g.) in water (20 ml.) and 2N-sulphuric acid (1 ml.) were heated at 100° and reaction followed polarimetrically. After 120 min. the solution was neutralised ($BaCO_3$) and after filtration was evaporated to dryness. The syrupy residue was extracted with ethanol. By removal of the solvent from the extract, 3 : 6-anhydro-D-galactose (0·1 g., 67%), $[\alpha]_D^{20}$ +20° (*c*, 1·0 in H_2O), was obtained as a colourless glass. The product, heated with phenylhydrazine (0·23 g.) in 36% aqueous acetic acid (5·0 ml.) at 70—75° for 2 hr., gave 3 : 6-anhydro-D-galactose phenylosazone, m. p. 216° (Found : N, 16·6. Calc. for $C_{18}H_{20}O_3N_4$: N, 16·5%). Haworth, Jackson, and Smith (*J.*, 1940, 620) report m. p. 216°.

Phenyl 3 : 6-*Anhydro*-2 : 4-*di*-O-*methyl*-α-D-*galactoside*.—Phenyl 3 : 6-anhydro-α-D-galactoside (1·5 g.) was methylated with methyl iodide and silver oxide in the presence of sufficient dry acetone to effect dissolution of the glycoside. Four treatments were carried out and *phenyl* 3 : 6-*anhydro*-2 : 4-*di*-O-*methyl*-α-D-*galactoside* (1·5 g., 90%) was obtained as a colourless mobile liquid, b. p. 165—170°/0·01 mm., $[\alpha]_D^{20}$ +45·5° (*c*, 1·8 in $CHCl_3$), n^{20} 1·5227 (Found : C, 63·9; H, 6·9. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%).

Acidic Hydrolysis of Phenyl 3 : 6-*Anhydro*-2 : 4-*di*-O-*methyl*-α-D-*galactoside*.—2N-Sulphuric acid (1 ml.) was added to a solution of phenyl 3 : 6-anhydro-2 : 4-di-*O*-methyl-α-D-galactoside (0·316 g.) in methanol (20 ml.), and the solution was heated under reflux, reaction being complete (polarimetry) in 170 min. The mixture was neutralised and worked up in the usual way. 3 : 6-Anhydro-2 : 4-di-*O*-methyl-D-galactose (0·15 g.) was obtained as a colourless glass, $[\alpha]_D^{20}$ +18° (*c*, 2·28 in H_2O), which was converted into crystalline 3 : 6-anhydro-2 : 4-di-*O*-methyl-*N*-phenyl-D-galactosylamine, m. p. 120°, $[\alpha]_D^{20}$ +52° (equil.; *c*, 0·2 in EtOH) {Haworth, Jackson, and Smith, *loc. cit.*, report m. p. 123°, $[\alpha]_D^{20}$ +56° (equil.)}.

Action of Chloroformic and Methanolic Hydrogen Chloride on Phenyl 3 : 6-*Anhydro*-2 : 4-*di*-O-*methyl*-α-D-*galactoside*.—A solution of the galactoside (0·443 g.) in chloroform (5 ml.) was saturated with dry hydrogen chloride and kept at room temperature for 3 days. No change in specific rotation occurred during this period. After neutralisation (Ag_2CO_3), filtration, and evaporation, unchanged galactoside (0·35 g.), b. p. 150—160°/0·01 mm., n^{20} 1·5222, $[\alpha]_D^{19}$ +49·2 (*c*, 1·3 in $CHCl_3$), was recovered. This glycoside was also unaffected by 1% methanolic hydrogen chloride for 24 hr. at room temperature.

Phenyl 3 : 6-*Anhydro*-α-D-*glucoside*.—A solution of phenyl α-D-glucopyranoside (10 g.) in dry pyridine (200 ml.) was cooled to 0°. During 1 hr. toluene-*p*-sulphonyl chloride (7·4 g.) was added and then the mixture was set aside at 0° for 48 hr. and thereafter at room temperature for 3 hr. Syrupy phenyl 6-*O*-toluene-*p*-sulphonyl-α-D-glucoside (5·1 g.) was isolated by the methods previously described. This syrup (5·0 g.) in ethanol (100 ml.) was converted by N-sodium hydroxide (20 ml.) at 80—85° during 2 hr. into *phenyl* 3 : 6-*anhydro*-α-D-*glucoside* which was extracted with ether–acetone (1 : 1, v/v). Distillation of the crude product yielded the anhydroglucoside as a colourless syrup (1·5 g., 16%), b. p. 170—175°/0·01 mm., $[\alpha]_D^{20}$ +21·1° (*c*, 1·3 in H_2O). Trituration with ether induced crystallisation and after recrystallisation from ether the colourless crystals had m. p. 85—86°, $[\alpha]_D^{20}$ +21·2° (*c*, 1·5 in H_2O) (Found : C, 60·2; H, 5·8. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%).

Action of Dilute Sulphuric Acid on Phenyl 3 : 6-*Anhydro*-α-D-*glucopyranoside*.—Phenyl 3 : 6-anhydro-α-D-glucopyranoside (0·19 g.) in 0·1N-sulphuric acid (20 ml.) underwent no reaction during several days ($[\alpha]_D$ +21·1° const.) and unchanged starting material was recovered.

If the compound (0·24 g.) in water (20 ml.) was treated with 2N-sulphuric acid (1·0 ml.) at

100°, reaction was complete (polarimetry) in 30 min. Neutralisation ($BaCO_3$) and evaporation gave a syrup from which 3 : 6-anhydro-D-glucose (0·15 g., 89%), m. p. and mixed m. p. 121°, $[\alpha]_D^{20}$ +54° (*c*, 2·1 in H_2O), was isolated by extraction with ethanol.

Action of Methanolic Hydrogen Chloride on Phenyl 3 : 6-*Anhydro*-α-D-*glucopyranoside*.—The substance was recovered unchanged after treatment with 1% methanolic hydrogen chloride at room temperature for 24 hr.

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