The Action of Alkali on Methyl 2:3-Anhydro-α-D-allopyranoside and 1:5-Anhydro-2-deoxy-3-O-toluene-p-sulphonyl-D-arabinohexitol

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Treatment of methyl 2:3-anhydro-α-D-allopyranoside with alkali yields methyl 3:6-anhydro-α-D-glucopyranoside as the only isolable product. Under similar reaction conditions 1:5-anhydro-2-deoxy-3-O-toluene-p-sulphonyl-D-arabinohexitol (the synthesis of which is described) rapidly loses the toluene-p-sulphonyloxy residue apparently without the formation of a 3:6-anhydro derivative. The relationship of these observations to those noted by Peat and Wiggins 3, following the treatment of methyl 2:4:6-tri-O-acetyl-3-O-toluene-p-sulphonyl-β-D-glucopyranoside with alkali, is discussed.

The action of alkali on methyl 2:4:6-tri-O-acetyl-3-O-toluene-p-sulphonyl-β-D-glucopyranoside has been found 3 to yield a mixture of methyl 2:3-anhydro- and 3:4-anhydro-β-D-allopyranosides and methyl 3:6-anhydro-β-D-glucopyranoside. These compounds were isolated as derivatives in which the anhydro-rings were preserved; the sensitivity of the latter compound towards acidic reagents resulted in its conversion to methyl 3:6-anhydro-β-D-glucofuranoside during the isolation procedure 2. Initially it was thought that the methyl 3:6-anhydro-β-D-glucopyranoside had arisen by direct intramolecular attack of the C₈-hydroxyl group on the C₃'-toluene-p-sulphonyloxy residue but it was later realised 3 that the first products of reaction were the two epoxide derivatives and that the 3:6-anhydro-compound resulted from intramolecular attack of the C₈-hydroxyl group on C₅in either or both of the 2:3- and 3:4-anhydro compounds. That the 2:3-anhydrocompound was involved in such a reaction was suggested by Ohle et al. 3, presumably on analogy with reactions in the furanose series 3; the formation of a 3:4-anhydro-compound is, however, precluded in this case. No experimental evidence has been obtained which would indicate the true course of reaction.

Methyl 2:3-anhydro- and 3:4-anhydro-α- and β-D-allopyranoside would be expected 4 to adopt half-chair in preference to half-boat conformations.

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(The presence of the epoxide ring requires that \(C_1:C_2:C_3:C_4\) and \(C_2:C_3:C_4:C_5\) be coplanar in the 2:3- and 3:4-epoxide compounds, respectively). An examination of accurate scale models reveals that in the half-chair conformation (I) of methyl 2:3-anhydro-\(\alpha\)-D-allopyranoside the \(C_4\)-hydroxyl group is well situated for nucleophilic attack on \(C_3\) to yield a 3:6-anhydro-\(\beta\)-glucopyranoside and that this is not the case in either of the half-chair conformations (e.g. II) of methyl 3:4-anhydro-\(\alpha\)-D-allopyranoside. Normal scission of the epoxide ring would be predicted in the latter case. Experimental evidence has been obtained which confirms these predictions.

Graded acidic hydrolysis of methyl 4:6-\(O\)-benzylidene-2:3-anhydro-\(\alpha\)-D-allopyranoside \(^5\) yielded methyl 2:3-anhydro-\(\alpha\)-D-allopyranoside (III) in good yield. The latter compound was only slowly attacked (\([\alpha]_D + 149^\circ \rightarrow + 142.5^\circ\) in 6 days) on treatment with \(N\) sodium hydroxide at room temperature. Elevation of the temperature to 50\(^\circ\) resulted in completion of reaction within 3 days. (\([\alpha]_D + 142.5^\circ \rightarrow + 37.8^\circ\)). Quantitative analysis of the reaction products was not possible because of the occurrence of some decomposition but methyl 3:6-anhydro-\(\alpha\)-D-glucopyranoside (IV) was the only isolable compound. Although some decomposition occurred the fall in \([\alpha]_D\) during the reaction indicated that methyl 3:6-anhydro-\(\alpha\)-D-glucopyranoside was the major, if not the sole product since the alternative products (methyl \(\alpha\)-D-glucopyranoside and methyl \(\alpha\)-D-allopyranoside) which would result from normal scission of the epoxide are strongly dextrorotatory (\([\alpha]_D + 158^\circ\) and \(+ 125^\circ\), respectively). These compounds could not be detected in the products of reaction. The known \(^2\) sensitivity of methyl 3:6-anhydro-\(\alpha\)-D-glucopyranoside towards acid is further illustrated by its conversion to methyl 3:6-anhydro-\(\alpha\)-D-glucofuranoside on short contact with the resin Amberlite IR-120 (H\(^+\) form).

The slow conversion of methyl 2:3-anhydro-\(\alpha\)-D-allopyranoside to methyl 3:6-anhydro-\(\alpha\)-D-glucopyranoside probably accounts for the low yield of 3:6-anhydro compound isolated in the reaction studied by Peat and Wiggins \(^1\). Further, a close analogy may be drawn with the conversion \(^6\) of 1:2-anhydro-\(\alpha\)-D-glucopyranose to 1:6-anhydro-\(\beta\)-D-glucopyranose under similar reaction conditions.

Since methyl 3:4-anhydro-\(\alpha\) or \(\beta\)-D-allopyranoside is apparently unknown and inaccessible a synthesis of a suitable 3:4-epoxide derived from 1:5-anhydro-2-deoxy-\(D\)-arabinohexitol (V) (1:2-dideoxy-\(D\)-"glucose") was examined. 1:5-Anhydro-2-deoxy-\(D\)-arabinohexitol (V) was obtained by sequential application of platinum catalysed hydrogenation and saponification to 3:4:6-tri-\(O\)-acetyl-\(D\)-glucal. Reaction of 1:5-anhydro-2-deoxy-\(D\)-arabinohexitol (V) with benzaldehyde at 115\(^\circ\) yielded a 4:6-\(O\)-benzylidene derivative (VI) which was readily converted to 1:5-anhydro:4:6-\(O\)-benzylidene-2-deoxy-3-\(O\)-toluene-\(p\)-

sulphonyl-\(\text{D-arabinohexitol}\) (VII). Graded acidic hydrolysis of the latter compound yielded 1:5-anhydro-2-deoxy-3-\(\text{O-toluene-}\text{p-sulphonyl-D-arabinohexitol}\) (VIII) (3-\(\text{O-toluene-}\text{p-sulphonyl-}1:2\text{-dideoxy-}\text{D-}\text{"glucose"}\)). Allocation of structures to these compounds was based on the following arguments. The 3-\(\text{O-toluene-}\text{p-sulphonate}\) (VIII) was different to the mono-\(\text{O-toluene-}\text{p-sulphonate}\) obtained by selective toluene-\text{p-sulphonylation}\ of 1:5-anhydro-2-deoxy-\text{D-arabinohexitol} (III). The structure of the latter compound was shown to be 1:5-anhydro-2-deoxy-6-\(\text{O-toluene-}\text{p-sulphonyl-D-arabinohexitol}\) (IX) by its ready consumption of approximately 1 mol. of metaperiodate. The formation of a seven membered 3:6-\text{O-benzylidene} ring in the reaction of 1:5-anhydro-2-deoxy-\text{D-arabinohexitol} (III) with benzaldehyde would seem very improbable in view of the fact that an alternative product is the six-membered 4:6-\text{O-benzylidene} compound the structure of which is related to trans-decalin. Whilst 3:6-\text{O-benzylidene-D-glucopyranose} derivatives are unknown, a wealth of examples of 4:6-\text{O-benzylidene-\text{D-glucopyranose}} derivatives is provided in carbohydrate chemistry. Seven-membered alkylidene rings, however, have been observed\(^7\), thus \text{D-mannitol} reacts with acetaldehyde to yield 1:3:2:5:4:6-\text{tri-O-ethylidene-D-mannitol}. Although this example is not strictly analogous to the case being considered here, it may be mentioned that formation of the 1:3- and 4:6-rings precedes formation of the 2:5-ring and that the six-membered cyclic acetals are more stable towards acid than the seven-membered cyclic acetal\(^8\). Thus compound (VI) is allocated the structure 1:5-anhydro-4:6-\text{O-benzylidene-2-deoxy-D-arabinohexitol}.

Treatment of 1:5-anhydro-2-deoxy-3-\(\text{O-toluene-}\text{p-sulphonyl-D-arabinohexitol}\) (VIII) with sodium hydroxide at \(50^\circ\) resulted in ready elimination of the toluene-\text{p-sulphonyloxy} group. Direct hydrolysis of the 3-\(\text{O-toluene-}\text{p-sulphonate}\) is ruled out since Peat has pointed out\(^9\) that, unless anhydro ring formation can occur, direct hydrolysis of carbohydrate toluene-\text{p-sulphonates} occurs slowly. Examination of the products of reaction revealed that the major product(s) were susceptible to attack by periodate. Further, on zone electrophoresis (ionophoresis) on paper in a borate buffer (pH 10) using the enclosed strip technique\(^10\), two components, detectable by the periodate-permanganate reagent\(^11\) were observed. The major component had an \(M_\text{r}\) value\(^10\) and properties identical with those of 1:5-anhydro-2-deoxy-\text{D-arabinohexitol} (III); the minor component had a higher \(M_\text{r}\) value. These observations are entirely consistent with the formation and reaction of 1:5:2:3-dianhydro-2-deoxy-\text{D-ribohexitol} (X) to yield a mixture of 1:5-anhydro-2-deoxy-\text{D-arabo} (III) and \text{D-xylohexitols} (XI) following the action of alkali on 1:5-anhydro-2-deoxy-3-\(\text{O-toluene-}\text{p-sulphonyl-D-arabinohexitol}\). Since the above products (III) and (XI) are susceptible to attack by metaperiodate and because 3:6-anhydro-D-glucopyranosides are resistant, it may be inferred that 1:5:3:6-dianhydro-2-deoxy-\text{D-arabinohexitol} must be formed to an insignificant extent, if at all, as a consequence of the action of alkali on 1:5-anhydro-2-deoxy-3-\(\text{O-toluene-}\text{p-sulphonyl-D-arabinohexitol}\).

Thus in the original experiments of Peat and Wiggins\(^1\) it is most probable that of methyl 2:3-anhydro-\text{\(\beta-D-allopyranoside}\) and methyl 3:4-anhydro-\text{\(\beta-D-allopyranoside}\), the first products of the action of alkali on methyl 2:4:6-\text{tri-O-acetyl-3-\(\text{O-toluene-}\text{p-sulphonyl D-glucopyranoside}\)}, the former but not

the latter yields methyl 3:6-anhydro-β-D-glucopyranoside on further action of alkali.

\[ \text{V } R^1 = R^2 = H \]
\[ \text{VI } R = H \]
\[ \text{VII } R^1 = \text{CH}_3 \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_3, R^2 = H \]
\[ \text{VIII } R^1 = \text{CH}_3 \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_3 \]
\[ \text{IX } R^1 = H, R^2 = \text{CH}_3 \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_3 \]

**EXPERIMENTAL**

*Methyl 2:3-anhydro-α-D-allopyranoside.* The method adopted was a modification of that reported by Gut and Prins.\(^2\)

A solution of methyl 2:3-anhydro-4:6-O-benzylidene-α-D-allopyranoside\(^2\) (1.75 g, m. p. 108°, \([\alpha]_D +140.2^\circ\) in chloroform) in 0.05 N hydrochloric acid (20 ml) and methanol (70 ml) was boiled under reflux for 2 h. After cooling and dilution with water (50 ml) the solution was concentrated at 35°, (bath)/16 mm, and deacetylated with methyl di-n-octylamine.\(^1\) After extraction with ether the neutral hydrolysate was concentrated at 60° (bath)/14—16 mm and the residue decolorized by dissolution in ethanol and treatment with charcoal. Concentration of the solution gave methyl 2:3-anhydro-α-D-allopyranoside (0.9 g, 77.5%), m. p. 105°, \([\alpha]_D +152^\circ\) (c, 1.0 in methanol). Gut and Prins\(^1\) quote m. p. 104—107°, \([\alpha]_D +152^\circ\) in methanol.

*Action of alkali on methyl 2:3-anhydro-α-D-allopyranoside.* (a) A solution of methyl 2:3-anhydro-α-D-allopyranoside (0.5 g) in N sodium hydroxide (5 ml) was stored at room temperature; \([\alpha]_D\) changed from 149° → 142.5° during 6 days. Elevation of the temperature to 50° caused a change in \([\alpha]_D +142.5^\circ \rightarrow +37.8^\circ\) (final constant value) during 3 days. Some decomposition occurred during this process. Calculated final value for complete conversion to methyl 3:6-anhydro-α-D-glucopyranoside was ca. +55°. After neutralisation of the reaction mixture with carbon dioxide and evaporation at 60°, (bath)/14—16 mm, the residue was extracted with boiling acetone during 30 min (acidic hydrolysis of the residue produced no substances reducing toward Fehling’s solution). The extract was decolorized with charcoal and evaporated at 40° (bath)/14—16 mm. Crystallization of the residue from ethyl acetate gave methyl 3:6-anhydro-α-D-glucopyranoside (0.28 g, 56% ) m. p. 108°, \([\alpha]_D +36.5^\circ\) (c, 0.5 in water). Haworth et al.\(^2\) record m. p. 108°, \([\alpha]_D +56^\circ\) in water for this compound.

(b) In a second experiment methyl 2,3-anhydro-α-D-allopyranoside (0.3 g) was treated with alkali at 56°C as described in (a). The reaction mixture was freed from cations by passage down a column of Amberlite IR-120 (H⁺ form). Evaporation of the eluate at 60°C, (bath) 14–16 mm, gave a syrupy residue which crystallized slowly. Methyl 3,6-anhydro-α-D-glucofuranoside (0.16 g, 53.3%) was subsequently isolated with m. p. 67°C, [α]D +164.5° (c, 0.5 in water). Haworth et al.¹ recorded m. p. 68°C, [α]D +164° in water for this compound. The infra-red spectrum (KBr disc) of the furanoside showed absorptions at 795 and 882 cm⁻¹ indicative ¹⁴ of the furanoside structure.

Treatment of an aqueous solution of methyl 3,6-anhydro-α-D-glucofuranoside with sodium metaperiodate using the conditions described elsewhere ¹⁵ resulted in zero consumption of oxidant during 24 h.

1,5-Anhydro-2-deoxy-D-arabinohexitol (1:2-dideoxy-D-"glucose"). A solution of amorphous 3,4,6-tri-O-acetyl-1,5-anhydro-2-deoxy-D-arabinohexitol (15 g, prepared by hydrogenation of an ethanolic solution of 3,4,6-tri-O-acetyl-D-glucose ¹⁶ in the presence of platinum oxide ¹⁷) in dry methanol (50 ml) was treated with a small amount of metallic sodium. ¹⁸ After 12 h the solution was diluted with water (10 ml) concentrated to small volume (ca. 5–10 ml) and then deionized by passage down a column of Amberlite IR-120 (H⁺ form). Evaporation of the eluate and recrystallization of the residue from chloroform-light petroleum (60–80°C) gave 1,5-anhydro-2-deoxy-D-arabinohexitol (6.1 g, 75%) m. p. 58°C, [α]D +16° (c, 2.0 in water). Fischer ¹⁴ records m. p. 86–87°C, [α]D +16.3° in water for the same compound prepared by a different method.

1,5-Anhydro-4:6:6:0-benzylidene-2-deoxy-D-arabinohexitol (4:6:0-benzylidene-1:2-dideoxy-D-"glucose"). A solution of 1,5-anhydro-2-deoxy-D-arabinohexitol (1 g) in freshly distilled benzaldehyde (5 ml) was maintained at 115°C for 45 min ¹⁹, a stream of carbon dioxide being passed continuously through the mixture during this period. The cooled mixture was diluted with light petroleum (60–80°C) and the crude product collected and washed with light petroleum (60–80°C). Recrystallization from ether-light petroleum (60–80°C) afforded 1,5-anhydro-4:6:6:0-benzylidene-2-deoxy-D-arabinohexitol (1.1 g, 69%) m. p. 98°C, [α]D –54.6° (c, 0.4 in ethanol). (Found: C 66.0; H 6.8. C₁₃H₁₄O₄ requires C 66.1; H 6.8.)

1,5-Anhydro-4:6:0-benzylidene-2-deoxy-3-O-toluene-p-sulphonyl-D-arabinohexitol (4:6:0-benzylidene-3-O-toluene-p-sulphonyl-1:2-dideoxy-D-"glucose"). A solution of 1,5-anhydro-4:6:6:0-benzylidene-2-deoxy-D-arabinohexitol (2 g) in dry pyridine (10 ml) was treated with a solution of toluene-p-sulphonyl chloride (2 g) also in dry pyridine (5 ml) at 35°C for 48 h. The crude product which separated on dilution of the reaction mixture with water was collected, washed with water and recrystallized from ethanol to yield 1,5-anhydro-4:6:0-benzylidene-2-deoxy-3-O-toluene-p-sulphonyl-D-arabinohexitol (2.2 g, 66.5%), m. p. 167°C, [α]D –31.7° (c, 0.44 in chloroform). (Found: C 61.55; H 5.6; S 8.4. C₁₇H₁₅O₄S requires C 61.5; H 5.6; S 8.2.)

1,5-Anhydro-2-deoxy-3-O-toluene-p-sulphonyl-D-arabinohexitol (3-O-toluene-p-sulphonyl-1:2-dideoxy-D-"glucose"). A solution of 1,5-anhydro-4:6:0-benzylidene-2-deoxy-3-O-toluene-p-sulphonyl-D-arabinohexitol (1 g) in methanolic hydrogen chloride (5 ml, 0.5% w/v) was boiled under reflux for 2 h. After cooling and dilution with water (10 ml) the solution was neutralised with sodium hydrogen carbonate, concentrated to small volume at 40°C, (bath) 14–16 mm, and finally freeze-dried. Recrystallization of the residue from chloroform-light petroleum (60–80°C) afforded 1,5-anhydro-2-deoxy-3-O-toluene-p-sulphonyl-D-arabinohexitol (0.51 g, 65.8%), m. p. 111°C, [α]D +23.4° (c, 0.51 in chloroform). (Found: C 51.7; H 6.3; S 10.6. C₁₃H₁₄O₄S requires C 51.65; H 6.0; S 10.6).

Action of alkali on 1,5-anhydro-2-deoxy-3-O-toluene-p-sulphonyl-D-arabinohexitol. (a) A solution of 1,5-anhydro-2-deoxy-3-O-toluene-p-sulphonyl-D-arabinohexitol (60.4 mg, 0.2 mmole) in ethanol (2.5 ml) and N sodium hydroxide (5 ml) was stirred at 50°C for 3 days. After neutralisation with N hydrochloric acid, aqueous sodium metaperiodate solution (15 ml, 0.25 M) was added and the volume rapidly adjusted to 50 ml. The consumption of periodate was determined by the standard procedure ⁹ of addition of excess arsenite solution and back titration with standard iodine solution using the appropriate blank solutions. A final constant uptake of 0.955 mole of periodate was observed after 30 min.

(b) A solution of 1,5-anhydro-2-deoxy-3-O-toluene-p-sulphonyl-D-arabinohexitol (0.15 g) in ethanol (5 ml) and N sodium hydroxide (10 ml) was stored at 50°C for 3 days, and then deionized by passage successively through Amberlite resins IR-120 (H⁺ form) and CG-400 (H₂O form). After concentration of the eluate to small volume (ca. 1 ml)

zone electrophoresis (ionophoresis) was carried out on Whatman No. 3 paper, using a borate buffer \( \text{pH} 10 \) and the enclosed strip technique \(^{10} \) at a potential gradient of 20–25 V/cm for 1.5 h. Using the periodate-permanganate reagent \(^{11} \) for detection, two zones were located; the major zone had a mobility and detection properties identical with that of 1:5-anhydro 2-deoxy-\( \beta \)-arabinohexitol whilst the minor zone had a higher mobility.

1:5-Anhydro-2-deoxy-6-O-toluene-p-sulphonyl-\( \beta \)-arabinohexitol \((6-O\text{-toluene-p-sulphonyl-1:2-dideoxy-\( \beta \)-glucose})\). To a cooled (0°) solution of 1:5-anhydro-2-deoxy-\( \beta \)-arabinohexitol (1 g) in dry pyridine (20 ml) a solution of toluene-\( p \)-sulphonyl chloride (1.3 g) also in dry pyridine (3 ml) was added. After storage at 0° for 2 h and then at room temperature overnight the mixture was diluted with water (50 ml) and extracted with chloroform \((4 \times 25 \text{ ml})\). The combined and dried (\( \text{MgSO}_4 \)) extracts were concentrated at 35° (bath)/14–16 mm, and, after drying over \( \text{P}_2\text{O}_5 \) in \( \text{vacuo} \), the residue was dissolved in the minimum volume of chloroform and diluted with continual stirring with light petroleum \((60–80^\circ)\) to turbidity. 1:5-Anhydro-2-deoxy-6-O-toluene-p-sulphonyl-\( \beta \)-arabinohexitol \((1.1 \text{ g}, 54 \%)\), m.p. 104°, \([\alpha]_D^2 +8.5^\circ \text{c, 1.0 in chloroform}) was obtained. (Found: C 51.6; H 6.0; S 10.5. \( \text{C}_{13}\text{H}_{14}\text{O}_{6} \text{S} \) requires C 51.65; H 6.0; S 10.6.)

A solution of the above compound \((60.4 \text{ mg}, 0.2 \text{ mmole})\) in water \((15 \text{ ml})\) was treated with aqueous sodium periodate \((15 \text{ ml}, 0.25 \text{ M})\) and the solution rapidly adjusted to 50 ml. The consumption of periodate was determined as described above and was as follows:

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REFERENCES


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