# 282. *Structure and Reactivity of Anhydro-Sugars. Part IV.*[1] *The Action of Alkali on 2-Deoxy-*D*-glucose: Structure of Isoglucal.*

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The primary product of the action of dilute aqueous potassium hydroxide on 2-deoxy-D-glucose is shown to be 3,6-anhydro-2-deoxy-D-glucose. This anhydride is also the chief product of the deacetylation by barium methoxide of 4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-glucose (" diacetyl pseudo-glucal ").

THE formation of saccharinic acids from aldoses and their *O*-substituted derivatives *via* α-dicarbonyl intermediates is dependent on the presence of a hydroxyl group at $C_{(2)}$.[2] Although removal or blocking of this hydroxyl group would preclude the formation of such intermediates, the well-known β-elimination might be expected to occur. Kenner and Richards[3] found that 2,3-di-*O*-methyl-D-glucose in lime-water gave no saccharinic acid, although increase in the ultraviolet absorption of the solution indicated that an αβ-unsaturated carbonyl system had been formed (Blair *et al.*[4] showed that an analogous β-elimination occurred on treatment of 3,5-di-*O*-benzoyl-2-deoxy-D-ribose with *N*-benzyl-*N*-phenylhydrazine).

In preliminary experiments it was found that in aqueous potassium hydroxide solution at 65—70°, 2-deoxy-D-glucose was partially converted into a new reducing compound which had a higher chromatographic mobility than the initial material. Determination of the amount of alkali neutralised during the reaction indicated that only 3—4% of the sugar had been converted into acidic products (arbitrarily calculated on the assumption that a sugar molecule gives rise to one monocarboxylic acid). No lactonisable acids were detected on paper chromatograms,[5] and it is envisaged that the small amounts of acids of low molecular weight might have arisen *via* reverse aldölisation. In addition, traces of material which migrated only very slowly on paper chromatograms were observed: these might have come from aldol condensations between sugar molecules. With reaction at higher temperatures several products having high chromatographic mobilities were detected but were not studied further.

The major product was isolated chromatographically pure by resolution on a cellulose column. It was a neutral syrup which was strongly reducing but did not decolorise bromine water. An iodometric titration[6] led to an estimated molecular weight of 145 (Calc. for an anhydrodeoxyhexose, 146). The compound (1 mol.) reduced periodate (0·95 mol.) without production of formaldehyde. The syrup was indistinguishable chromatographically from 3,6-anhydro-2-deoxy-D-glucose, and it yielded a crystalline 2,4-dinitrophenylhydrazone identical with that obtained from authentic 3,6-anhydro-2-deoxy-D-glucose.

It is considered that the 3,6-anhydride arises from the 2-deoxyhexose *via* 2,3-didehydro-2,3-dideoxy-D-glucose which is attacked at $C_{(3)}$ by the hydroxymethyl anion at $C_{(5)}$. This suggested intermediate is unknown in the free state. Deacetylation of its known 4,6-di-*O*-acetate gives rearrangement *via* the so-called " isoglucal " (I) and " protoglucal."[7] The suggested course of the alkaline conversion of 2-deoxy-D-glucose into its 3,6-anhydride, and the report by the original worker that " isoglucal " is a reducing compound, led us to re-examine its structure.

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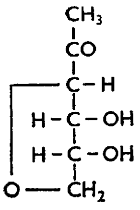
[1] Part III, Foster, Overend, and Vaughan, *J.*, 1954, 3625.
[2] Kenner, *Chem. and Ind.*, 1955, 727.
[3] Kenner and Richards, *J.*, 1956, 2921.
[4] Blair, Lipkin, Sowden, and Strobach, *J. Org. Chem.*, 1960, **25**, 1679.
[5] Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5859.
[6] Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289.
[7] Bergmann, *Annalen*, 1923, **434**, 79; Bergmann, Zervas, and Engler, *Annalen*, 1933, **508**, 25.

4,6-Di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-glucose on treatment with barium methoxide in methanol gave two products. These were readily resolvable by chromatography and the faster-moving component was present in only very small amounts. After neutralisation and removal of inorganic material and solvent the main residue was distilled to give a product indistinguishable chromatographically from 3,6-anhydro-2-deoxy-D-glucose. This material readily reduced Schiff's reagent in the cold, and when treated with *N*-benzyl-*N*-phenylhydrazine gave a crystalline derivative, m. p. 121°, which was shown to be identical with the *N*-benzyl-*N*-phenylhydrazone prepared from authentic 3,6-anhydro-2-deoxy-D-glucose. Bergmann[7] reported that this derivative of his " isoglucal " had m. p. 121—122°. It is concluded that " isoglucal " does not have structure (I), but is in fact the isomeric 3,6-anhydro-2-deoxy-D-glucose. It is noteworthy that when 3,6-anhydro-2-deoxy-D-glucose is heated with 0·05N-alkali at 65—70° it is partly converted into 2-deoxy-D-glucose and an equilibrium is established similar to that obtained when 2-deoxy-D-glucose is treated with alkali.



(I)

## EXPERIMENTAL

*Chromatographic Solvents.*—(A), Butan-1-ol–ethanol–water (4 : 1 : 5); (B), benzene–butan-1-ol–pyridine–water (1 : 5 : 3 : 3); (C), butan-1-ol–acetic acid–water (4 : 1 : 5). The organic layer of each mixture was used.

*Alkaline Treatment of* 2-*Deoxy*-D-*glucose.*—A solution of 2-deoxy-D-glucose (4 g.) in 0·1N-potassium hydroxide solution (60 ml.) was heated at 65—70° for 2 hr. [Diagnostic chromatography in solvent (A) indicated that the mixture contained starting material and another product.] After neutralisation with carbon dioxide, and filtration, the solution was evaporated to dryness. A concentrated ethanolic extract of the residue was fractionated on a cellulose column (30 × 3 cm.). Elution with solvent (A) gave (i) 3,6-anhydro-2-deoxy-D-glucose (0·1 g.), (ii) a mixture of 3,6-anhydro-2-deoxy-D-glucose and 2-deoxy-D-glucose (0·8 g.), and (iii) 2-deoxy-D-glucose (2·2 g.). Fraction (i) was a neutral syrup which readily reduced Fehling's solution and restored the colour to Schiff's reagent in the cold. It did not decolorise bromine water. Oxidation with alkaline iodine solution[6] indicated a molecular weight of 147 (144). Periodate oxidation (spectrophotometric determination[8]) of the syrup indicated that 1 mol. of the compound (assumed *M*, 146) reduced 0·95 mol. of the oxidant, without formation of formaldehyde (estimation by method of O'Dea and Gibbons[9]). The fraction had $[\alpha]_D^{20}$ +36·3° (*c* 1·1 in water) [Foster *et al.*[10] give $[\alpha]_D^{20}$ +37·1° (*c* 1·2 in water) for 3,6-anhydro-2-deoxy-D-glucose] and formed a 2,4-dinitrophenylhydrazone, m. p. 122—123° (decomp.). This derivative was identical (mixed m. p. and infrared spectra) with the 2,4-*dinitrophenylhydrazone*, m. p. 122—124° (decomp.) (Found: C, 45·2; H, 3·9; N, 17·3. $C_{12}H_{14}N_4O_7$ requires C, 44·4; H, 3·7; N, 17·3%), prepared from authentic 3,6-anhydro-2-deoxy-D-glucose (synthesised by the method of Foster *et al.*[10]).

*Treatment of* 4,6-*Di*-O-*acetyl*-2,3-*didehydro*-2,3-*dideoxy*-D-*glucose with Alkali.*—A solution of 4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-glucose (0·2 g.) (prepared according to Fischer's method[11]) in 0·1N-aqueous potassium hydroxide (10 ml.) was heated at 60—65° for 2 hr. The reaction was followed by removing samples at intervals, neutralising them with solid carbon dioxide, and examining them by chromatography. In solvents (A) and (B) a product with $R_F$ = 0·55 and in (C) with $R_F$ = 0·53 was detected [3,6-anhydro-2-deoxy-D-glucose showed $R_F$ values as follows: (A), 0·55; (B), 0·56; (C), 0·53] together with a much smaller amount of another substance, $R_F$ = 0·75 (A), 0·69 (B), 0·70 (C). A similar examination of the products obtained by treatment of the unsaturated sugar acetate with 0·02N-barium methoxide in methanol at room temperature, indicated the presence of a similar major product.

To a solution of 4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-glucose (1 g.) in dry methanol (10 ml.) and N-barium methoxide (0·2 ml.) was added at 0°. After 24 hr. at 0°, the solution was neutralised (carbon dioxide), and evaporated to dryness under diminished pressure, and

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[8] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 1216.
[9] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.
[10] Foster, Overend, Stacey, and Vaughan, *J.*, 1954, 3367.
[11] Fischer, *Ber.*, 1914, **47**, 196.

the syrupy residue was distilled. An oil (0·2 g., 32%), b. p. 106°/0·07 mm., $[\alpha]_D^{20}$ +33·2° (*c* 0·8 in water) was obtained. When warmed with an aqueous-alcoholic solution of *N*-benzyl-*N*-phenylhydrazine it yielded a crystalline derivative, m. p. 121° alone or in admixture with 3,6-anhydro-2-deoxy-D-glucose *N*-benzyl-*N*-phenylhydrazone (m. p. 120·5°).

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