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Note

The intramolecular cyclization of 3,6-anhydro-D-glucal

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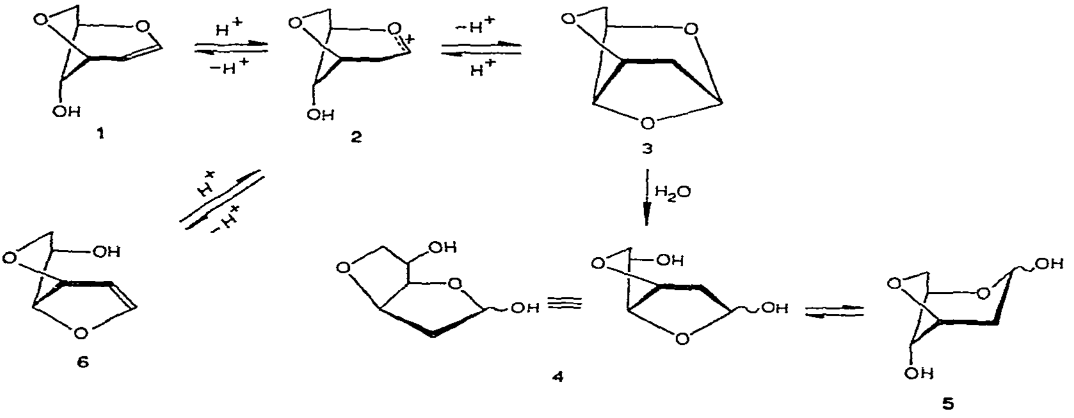
In a previous report[1], 3,6-anhydro-D-glucal (**1**) and its conversion into 3,6-anhydro-2-deoxy-D-*arabino*-hexose (**4**) and 2-(D-*glycero*-1,2-dihydroxymethyl)furan by treatment with dilute hydrochloric acid at room temperature have been described. We now report that the anhydride **1** undergoes complete intramolecular cyclization on storage in dry chloroform to give 1,4:3,6-dianhydro-2-deoxy-α-D-*arabino*-hexopyranose (**3**) (alternatively designated as 1,5:3,6-dianhydro-2-deoxy-α-D-*arabino*-hexofuranose).

Attention was drawn to this reaction in both laboratories when the n.m.r. spectrum of a solution of 3,6-anhydro-D-glucal (**1**) in deuteriochloroform was observed to change markedly over a period of several hours. This change was presumed to be catalysed by traces of acid in the deuteriochloroform used, and, not unexpectedly, it was effected more efficiently in dry chloroform containing hydrogen chloride. Chromatography on silica gel gave the major product of the reaction as a hygroscopic, low-melting solid, which was readily purified by sublimation. The product was



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assigned the structure 1,4:3,6-dianhydro-2-deoxy-α-D-*arabino*-hexopyranose (**3**) from the following evidence. Elemental analyses and accurate mass measurement revealed the molecular formula as $C_6H_8O_3$. The absence of an hydroxyl group was shown by infrared spectroscopy; n.m.r. spectroscopy also demonstrated that the product contained neither exchangeable protons nor olefinic linkages. Finally, hydrolysis with acid yielded exclusively 3,6-anhydro-2-deoxy-D-*arabino*-hexose[1] (**4**) in accord with the expected pattern of hydrolysis of the dianhydride **3**.

Bedford and Gardiner[2] have provided detailed analyses of the n.m.r. spectra of the closely related 1,4:3,6-dianhydro-α-D-glucopyranose and -D-mannopyranose, which were isolated after vacuum pyrolysis of 3,6-anhydro-D-glucose (or amylose) and 3,6-anhydro-D-mannose, respectively. The tentative assignments (Table I) of proton chemical shifts and coupling constants for the dianhydride **3** are in very good agreement with those of the foregoing compounds, when allowance is made for the presence of the deoxy group at C-2. It was also apparent from the complexity of the signals for H-3 and H-5 that there is a small coupling ($J \sim 1.5$ Hz) between these protons; such 4-bond couplings are well known to arise between equatorial protons on pyranoid rings[3].

TABLE I

PROTON CHEMICAL SHIFTS (τ VALUES) AND COUPLING CONSTANTS (Hz) AT 60 MHz FOR THE DIANHYDRIDE 3

H-1	H-2 (2 protons)	H-3	H-4	H-5	H-6 (2 protons)
4.38(d)	8.20(m)	5.53(m)	4.92(q)	5.76(m)	6.02(q)

$J_{1,2eq} = 1.5$, $J_{1,2ax} \sim J_{1,3} < 0.5$, $J_{2ax,2eq} = 12$, $J_{2ax,3} < 0.5$, $J_{2eq,3} = 6$, $J_{3,4} = 4.5$, $J_{3,5} \sim 1.5$, $J_{4,5} = 3$, $J_{5,6exo}$ 1.5, $J_{5,6endo} < 0.5$, $J_{6exo,6endo}$ 12.

Presumably, the dianhydride **3** is formed by intramolecular cyclization of the oxo-carbonium ion **2**, resulting from protonation of the glycal.

It is notable that 3,6-anhydro-D-glucal (**1**) exists preferentially (in chloroform) in the dianhydride form (**3**), whereas 3,6-anhydro-2-deoxy-D-*arabino*-hexose, which likewise could give the dianhydride under acidic conditions, does not cyclize (at least in aqueous solution). If the effect of the solvent change can be ignored, the relative stabilities of the ring systems here studied can be concluded to be **4** or **5**>**3**>**1** or **6**.

EXPERIMENTAL

Thin-layer chromatography (t.l.c.) was performed on Kieselgel G, and detection was effected with vanillin–sulphuric acid[4]. N.m.r. spectra were obtained at 60 MHz with either a Varian A60 or Perkin–Elmer R-10 spectrometer for deuteriochloroform solutions with tetramethylsilane as internal reference; infrared spectra were recorded on a Perkin–Elmer Infracord spectrometer.

*1,4:3,6-Dianhydro-2-deoxy-α-*D-arabino-*hexopyranose* (3). — To a solution of 3,6-anhydro-D-glucal[1] (1) {0.4 g, $[\alpha]_D -49°$ (*c* 1, methanol)*} in washed (H_2O) and dried ($CaCl_2$) chloroform (25 ml) was added chloroform (5 ml) saturated with hydrogen chloride; t.l.c. (dichloromethane–acetone, 5:1) showed that all the starting material had disappeared within 5 min. The solution was carefully neutralised with conc. ammonia (*ca.* 1 drop) and dried ($MgSO_4$). The solvent was then removed, and the residue was chromatographed on silica gel (dichloromethane–acetone, 5:1) to give the dianhydride **3** (0.26 g, 66%), m.p. ~25°, $[\alpha]_D +10 \pm 1°$ (*c* 1, chloroform), after sublimation at 60°(bath)/20 mmHg (Found: C, 55.7; H, 6.0. Mol. wt. 128.048. $C_6H_8O_3$ calc.: C, 56.25; H, 6.25%. Mol. wt. 128.047).

*Hydrolysis of 1,4:3,6-Dianhydro-2-deoxy-α-*D-arabino-*hexopyranose* (3) *with acid.* — A solution of **3** (60 mg) in water (5 ml) was stirred with Amberlite IR-120(H^+) resin (0.5 g) for 4 h at room temperature, after which time t.l.c. (dichloromethane–acetone, 5:1) showed that the reaction was completed to give a single product. The resin was filtered off, and the filtrate was concentrated to a syrup which was then redissolved in dichloromethane. The solution was filtered, dried ($MgSO_4$), and concentrated to afford a syrupy product **4** (61 mg), $[\alpha]_D +43 \pm 1°$ (*c* 1, water), which was indistinguishable (t.l.c., and infrared and n.m.r. spectroscopy) from authentic 3,6-anhydro-2-deoxy-D-*arabino*-hexose; lit.[1] +45° (*c* 1, water).

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*This rotation was inadvertently given as $[\alpha]_D +49°$ (*c* 1, methanol) in a previous paper (ref. 1).