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Note

Re-examination of the acid hydrolysis of 5,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose

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For the synthesis of 4-methylcoumarin-7-yl α-L-idopyranosiduronic acid, a convenient, sensitive substrate[1] for α-L-iduronidase (EC 3.2.1.76), we required quantities of suitable L-idopyranose derivatives. During the course of this work, a novel synthesis of L-idose (**1**) was reported[2], and has now been included, in modified form, in a treatise of reliable synthetic methods in carbohydrate chemistry[3]. This novel method was recommended because it involved fewer steps and gave better yields than previous syntheses, but we have found that the syrupy L-idose obtained thereby is impure and now describe a modified method for the synthesis of pure 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-L-idopyranose.

In the reported[2,3] synthesis, the D-*gluco*→L-*ido* transformation was achieved by an intramolecular displacement at C-5 during the synthesis of 5,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose (**2**). Hydrolysis was then claimed to give **1** in essentially quantitative yield. The stereoisomeric *gluco*-epoxide **3** gives[4] a mixture of products on hydrolysis, and the difference in behaviour of **2** and **3** was ascribed[2] to conformational features present in the acyclic transition-state involved in the reaction of **3**.

We experienced difficulties in two steps in this synthesis of L-idose. First, as previously reported[5], reaction of the 5-sulphonate **4** with sodium methoxide gave **2** contaminated with ~6% of an isomer; pure **2** could only be obtained by chromatography, which is undesirable for large-scale preparations. Further, when pure **2** was hydrolysed with dilute acid according to the published[2] method (25mM H_2SO_4, 45°, 2.5 h) and the resulting syrupy product was subjected to ion-exchange chromatography of the borate complexes[6], six components were detected (Table I, entry 1a). The expected product, L-idose (**1**) was a minor component, and the major product (62%) was 1,2-*O*-isopropylidene-β-L-idofuranose (**5**). The L-sorbose (**6**, 3%) probably arose from **1**[7]. Component **8** was tentatively identified as 2,5-anhydro-D-glucose, and component **9** was identified as 3,6-anhydro-L-idose (see below). This result was reproducible (Table I, entry 1b). During chromatog-

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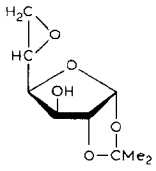

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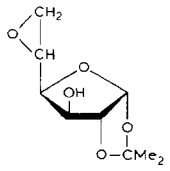

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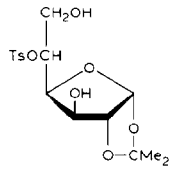

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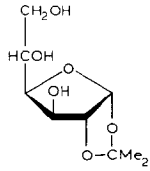

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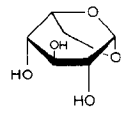

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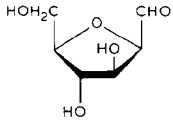

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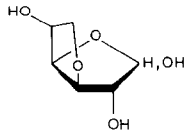

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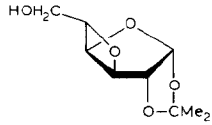

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TABLE I

COMPOSITION OF THE PRODUCT FROM HYDROLYSIS OF THE EPOXIDE **2**

Entry	*Conditions*			*Product[a] composition (%)*						
	Acid conc. (M)	*Temp. (deg.)*	*Time (h)*	**2**	**7**	**5**	**8**	**9**	**6**	**1**
1[b]	0.025	45	2.5	13	0	62	7	1	3	15
				18	0	56	7	1	1	18
2	0.025	50	4	7	0	41	12	1	1	40
3[b]	0.05	50	8	0	1	4	11	trace	3	81
				0	1	5	14	trace	3	76
4	0.1	50–60	3.5	0	2	trace	12	1	2	85
5	1	100	6	0	88	0	0	1	0	10

[a]Elution time (T_G) relative to that for glucose: **2**, 0; **7**, 0; **5**, 0.19; **8**, 0.33; **9**, 0.44; **6**, 0.94; **1**, 0.98.
[b]Duplicate experiments.

raphy, **2** gave a peak with considerable tailing (presumably due to decomposition) but no discrete peaks corresponding to the other components, which, therefore, were not artefacts produced during analysis.

The observation that L-idose was only a minor component of the syrup apparently conflicts with the claim[2] that pure L-idose was obtained. However, no evidence was presented[2] to indicate the purity of the syrupy product. Moreover, the conversion of this syrup into L-idose diethyl dithioacetal in good yield does not prove the presence of L-idose, since this derivative could be formed from products (for example, **2** or **5**) that are convertible into L-idose under vigorous acidic conditions. The presence of a significant amount of **5** is consistent with earlier work[8] which showed that conditions more vigorous than those noted above were required to hydrolyse **5** to L-idose.

When the temperature and reaction time were increased slightly, the extent of hydrolysis of **2** was much greater (Table I, entry 2). Under more vigorous conditions (entries 3 and 4) including those (entry 3) reported[8] for the hydrolysis of **5** to L-idose, the major product was L-idose with no residual **2**, but hydrolysis was not complete and some conversion into 1,6-anhydro-L-idose (**7**) had occurred.

In the more recent report[3] on this method for the synthesis of L-idose, an acid concentration (0.05M) higher than that in the earlier report[2] was used, without comment. It is clear from the data in Table I that the concentration of the acid used has a considerable influence on the product composition, and the use of 0.05M acid in our experiments did not give pure L-idose.

The purest sample of L-idose was obtained by hydrolysis of **5** in M H_2SO_4 at 50° for 3.5 h; the syrupy product comprised L-idose (92%), **5** (5%), **6** (2%), and **7** (1%). This result shows that, in the earlier experiments, **8** and **9** did not arise by hydrolysis of **5**, but must have originated from **2**. Component **9** was identified as 3,6-anhydro-L-idose by comparison with the product of hydrolysis of 3,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose[5].

After hydrolysis of the epoxide **2** under even more vigorous conditions[9] (M H_2SO_4, 100°, 6 h; Table I, entry 5), **8** disappeared and the product was preponderantly **7** (88%) together with L-idose (10%) and 3,6-anhydro-L-idose (**9**, 1%). The ratio of **7** to L-idose was similar to that previously reported[10]. Acetylation of the mixture followed by crystallisation gave pure 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-L-idopyranose, which is conveniently prepared by this route.

Buchanan and Oakes[5] found that 3,5-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (**10**), obtained by isomerisation of **2** in alkali, was hydrolysed in acid to **7** *via* an anhydro sugar and L-idose. When **10** was hydrolysed under the above mild conditions (0.05M, 45°, 2.5 h), the major product (T_G 0.28) was different from the compounds obtained by hydrolysis of **2**; hence, the unidentified component (**8**, T_G 0.33) was not 3,5-anhydro-D-glucose. Component **8** was stable in 0.1M acid at 50° for 3.5 h and thus is unlikely to be a terminal epoxide; **8** was hydrolysed under more vigorous conditions. 2,5-Anhydroaldoses are stable towards mild acid, but are destroyed under more vigorous conditions[4,11]. Thus, it is possible that **8** is the elusive 2,5-anhydro-D-glucose and that hydrolysis of the *ido*-epoxide parallels that of the *gluco*-epoxide **3** and gives L-idose by hydration of the epoxide, and 2,5-anhydro-D-glucose by an intramolecular reaction (presumably[2] *via* an acyclic transition-state). Support for this suggestion was obtained by using a specific assay (indole–hydrochloric acid[12,14]) for 2,5-anhydrohexoses. Both **2** and **3**, before and after hydrolysis, gave positive responses, with the *gluco*-epoxide **3** giving the greater response.

Thus, acid hydrolysis of **2** does not give a quantitative yield of L-idose, but, under suitable conditions, L-idose is the major product. The major pathway to L-idose first involves opening of the epoxide ring and then hydrolysis of the isopropylidene acetal, so that it is not necessary to invoke conformational differences between acyclic transition-states during hydrolysis to explain the behaviour of the *gluco*- (**3**) and *ido*-epoxide (**2**).

EXPERIMENTAL

Materials. — Chromatographically homogeneous samples of **2**, **10**, and 3,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose were prepared as described[5]. Deacetylation of 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-L-idopyranose[13] and 3,5,6-tri-*O*-acetyl-1,2-*O*-isopropylidene-β-L-idofuranose[1] gave **7** and **5**, respectively. Syrupy L-idose was prepared by deacetylation of 1,2,3,4,6-penta-*O*-acetyl-β-L-idopyranose[7]. 5,6-Anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose was prepared as described[14].

Chromatography. — Borate ion-exchange analysis[6] was carried out by the Macromolecular Analysis Service of the University of Birmingham. The T_G values are the retention times relative to that for D-glucose.

Acid hydrolysis of anhydro sugars. — (*a*) A solution of **2** (0.5 g) in 25mM H_2SO_4 (10 mL) was maintained at 45° for 2.5 h, cooled, neutralised with barium carbonate, filtered through Celite, and concentrated under reduced pressure. A solution of the syrupy residue in methanol was filtered and concentrated, to give a syrupy residue (0.42 g), $[\alpha]_D$ −21° (*c* 1, water); lit.[2] $[\alpha]_D$ −13° (water). The results of borate ion-exchange chromatography of this syrup are shown in Table I.

(*b*) The experiment was repeated as in (*a*), but with variations (enties 2–5) shown in Table I

(*c*) The anhydro sugar **10** was hydrolysed as in (*a*). Borate ion-exchange chromatography of the resulting, syrupy product showed a major peak with T_G 0.28.

(*d*) Hydrolysis of 3,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose, as in (*a*), gave a major product with T_G 0.44.

Indole assay[12]. — A solution of the sugar derivative (~1.4 mg) in 25mM H_2SO_4 (2 mL) was stored at 45° for 2.5 h, and then aqueous 5% HCl (2 mL) and 1% orcinol in spectroscopic ethanol (2 mL) were added. The mixture was kept at 95° for 5 min, cooled, and diluted with spectroscopic ethanol (2 mL), and the absorbance was measured at 490 and 520 nm against a reaction blank containing no sugar. The results were as follows:

	Weight (mg)	$A_{490} - A_{520}$
2	1.44	0.49
3	1.42	1.31
5	1.44	0.26
MAG[a]	2.98	0.01

[a] 1,2-*O*-Isopropylidene-α-D-glucofuranose.

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