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Note

Acetolysis–epimerisation studies

Part I. Acetolysis of L-rhamnose and some derivatives : formation of L-quinovose (6-deoxy-L-glucose)

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There are several examples[1,2] of sugar derivatives undergoing partial epimerisation at C-2 during acetolysis reactions. A *cis* configuration at C-2 and C-3 in furanoid derivatives appears to be a general requirement for the rearrangement, noted first[3] with D-mannofuranose derivatives. A revised mechanism has been proposed for the epimerisation in which a *cis* orientation becomes *trans* through the formation of a five-membered, acetoxonium ion intermediate. Previously, a seven-membered ion had been envisaged. There are several[4–10] related interconversions of carbohydrates and polyhydric alcohols involving neighbouring acyloxy-group participation.

Acetolysis has been widely used in both structural and preparative studies[11]. The conditions used are often very similar to those that cause anomerisation of sugar acetates[12–14]. It is important to define the conditions which promote epimerisation, and, as part[2] of a study of this process, we now report on the acetolysis of derivatives of L-rhamnose and D-mannose.

Earlier[3] results suggested that furanoid derivatives of L-rhamnose (**1**) should be partially converted into acetates of L-quinovose (**2**, 6-deoxy-L-glucose) during acetolysis. Treatment of 1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-rhamnofuranose (**3**) with an acetic acid–acetic anhydride–sulphuric acid mixture[3] (method *A*), followed by deacetylation of the product, gave **1** (45%) and **2** (55%) (g.l.c. of the *O*-trimethylsilyl derivatives). Fractional crystallization of the deacetylated product yielded crystalline **2** (38%), characterised as the diethyl dithioacetal. The crystallization mother liquors were concentrated and treated in a similar manner to give L-rhamnose diethyl dithioacetal. Recently[15], **2** has been synthesised in 60% yield by epimerisation of **1** in the presence of molybdic acid.

Likewise, acetolysis of 2,3-*O*-isopropylidene-L-rhamnose (**4**) yielded **1** (49%), **2** (43%), and an unidentified product (8%). The lower yield of **2** may be due to the fact that **4** is a mixture of furanoid and pyranoid forms. P.m.r. studies have shown[16] this to be so in aqueous medium.

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Acetylation of **1** with the acetolysis mixture[3] gave, after deacetylation, a mixture of **1** (79%) and **2** (21%). Acetylation of **1** with acetic anhydride–perchloric acid yielded only trace amounts of **2**.

Recent[17] equilibria studies show that, for aqueous solutions of **1** and D-mannose, the percentage of furanoid forms at equilibrium is small. Thus, if epimerisation during acetolysis involves furanoid forms, acetic acid–acetic anhydride must have a significant effect upon the proportion of furanoid forms. The equilibrium composition of unsubstituted sugars can be affected by the solvent[18]. Sowa[1] has proposed that epimerisation is related to the concentration of acetic acid in the acetolysis mixture. Rearrangement occurs in 10:1, but not in 1:1 acetic acid–acetic anhydride (*cf.* ref. 19). Under acetolysis conditions, D-ribose and 4-*S*-benzoyl-4-thioribopyranose derivatives[20] are converted into derivatives of ribose and to 4-thioribofuranose without epimerisation.

When **1** was acetolysed under the non-epimerising conditions, only a trace of **2** was detected in the deacetylated product. Similar treatment of **3** and **4** gave 21 and 13.5%, respectively, of **2**. Likewise 1,5,6-tri-*O*-acetyl-2,3-*O*-isopropylidene-D-mannofuranose (**5**) and 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**6**) yielded 44 and 30%, respectively, of D-glucose (Method *B*). Acetolysis of D-mannose in the 1:1 mixture gave no D-glucose. The proportion of D-glucose in the product mixtures, although not as high as that noted earlier[3], is not insignificant. The results show that the assumption that epimerisation is related to the acetic acid content of the acetolysis medium is not always justified.

1,2,3,4-Tetra-*O*-acetyl-L-rhamnopyranose (**7**), methyl α-L-rhamnopyranoside (**8**), and methyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranoside (**9**) did not epimerise during acetolysis. Previously[3] it had been shown that D-mannopyranose derivatives do not rearrange.

EXPERIMENTAL

Descending paper chromatography was carried out on Whatman No. 1 or 3MM paper with propyl alcohol–ethyl acetate–water[21] (7:1:2). Aniline hydrogen phthalate was used as a location reagent[22]. G.l.c. was performed on a Varian Aerograph (series 1400) gas chromatograph with a flame-ionisation detector. *O*-Trimethylsilyl derivatives were injected 1 h after preparation into a glass column (1.5 m × 3 mm i.d.) packed with 3% OV-1 on Chromosorb G. The column was programmed between 120–250° at 4°/min, and the injector port and detector temperatures were 280°. The carrier gas was nitrogen (15 kg/cm^2; 26 ml/min). Compounds **3**[16], **4**[23], **5**[24], **6**[25], **7**[26], **8**[27], and **9**[28] were prepared by the literature methods and, when subjected to appropriate acidic and alkaline hydrolyses, were found to be homogeneous with respect to the parent sugar.

Acetolysis procedures. — *Method* A[3]. A solution of the compound (1 g) in acetic acid (30 ml) and acetic anhydride (4 ml) was cooled to −5°, treated with conc. sulphuric acid (1.5 ml), and kept for 48–72 h at room temperature. The mixture was

then poured into ice–water (200 ml) and extracted with chloroform (3 × 75 ml), and the combined extracts were shaken successively with water, saturated aqueous sodium hydrogen carbonate, and water. The dried (Na_2SO_4) chloroform extract was evaporated *in vacuo* to a syrup, which was deactylated overnight at room temperature by treatment with a mixture of methanol (40 ml), water (5 ml), and triethylamine (5 ml). The mixture was evaporated *in vacuo* at 35° to a syrup which was then dried *in vacuo* over phosphorus pentoxide. A portion (10 mg) of the product dissolved in anhydrous pyridine (0.7 ml) was treated[27] with hexamethyldisilazane (0.3 ml) and chlorotrimethylsilane (0.1 ml), and aliquots of this mixture were used directly for g.l.c. analysis. Typical results were as follows:

Compound	*Anomer*	*Temperature (degrees)*	*Retention time*[a]
L-Rhamnose	α	163	0.46
	β	172	0.52
D-Quinovose	α	178	0.59
	β	184	0.64
D-Mannose	α	186	0.67
	β	193	0.74
D-Glucose	α	197	0.78
	β	203	0.86

[a]Retention time relative to *n*-docosane ($C_{22}H_{46}$).

Method B[1]. The compound (500 mg) was added portionwise to a mixture of acetic acid (20 ml), acetic anhydride (20 ml), and conc. sulphuric acid (1.2 ml) at −5°. The reaction solution was kept at 0° for 48 h, then treated with anhydrous sodium acetate (4.5 g), and evaporated to dryness *in vacuo* at 25–30°. Methanol (20 ml) was distilled from the residue which was then dissolved in saturated, aqueous sodium hydrogen carbonate (30 ml) and extracted with chloroform (3 × 30 ml). The combined extracts was washed with water, dried (Na_2SO_4), and evaporated, and the syrupy product was deacetylated, derivatised, and analysed as described in method *A*.

In the experiments using compounds **5** and **6**, the remaining deacetylated product (250–350 mg) was subjected to preparative paper chromatography. The appropriate areas corresponding to mannose and glucose were eluted with water, and the eluates were evaporated to dryness. D-Glucose was characterised as its diethyl dithioacetal, m.p. 125–127°, $[\alpha]_D^{20}$ −29.5° (*c* 2.4, pyridine) (lit.[30] m.p. 128°, $[\alpha]_D^{20}$ −29.8°); and D-mannose as the phenylhydrazone, m.p. 198–200°; lit.[31] m.p. 199–200°.

Large-scale acetolysis of **3**. — To a stirred, cooled solution of **3**[16] (5.5 g) in acetic acid (165 ml) and acetic anhydride (22 ml), conc. sulphuric acid (8.5 ml) was added. The reaction mixture was left for 48 h at room temperature and then treated with anhydrous sodium acetate (30 g). The resulting mixture was evaporated *in vacuo* at 25–30°, and several portions of methanol (50 ml) were distilled from the residue

which was then treated with water (150 ml) and extracted continuously with chloroform (450 ml) overnight. The extract was washed successively with saturated, aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated to yield a syrup (5.96 g), $[\alpha]_D^{22}$ −29° (*c* 14, methanol), which was dissolved in methanol (200 ml) and treated with triethylamine (30 ml) and water (30 ml) overnight at room temperature. Evaporation of the mixture gave a gum (2.93 g) which, on fractional crystallization from ethanol–ethyl acetate mixtures[15], yielded 6-deoxy-L-glucose (**2**; 1.19 g, 38%), m.p. 143–146°, $[\alpha]_D^{23}$ −29.8° (equil., *c* 5.5, water); lit.[32] m.p. 143–145°, $[\alpha]_D^{20}$ −30° (equil.). The product, on treatment with ethanethiol–zinc chloride[32], gave the diethyl dithioacetal, m.p. 96–98°, $[\alpha]_D^{22}$ +46.8° (*c* 1, water); lit.[32] m.p. 97–98°, $[\alpha]_D^{20}$ +47.1°.

The mother liquors remaining after the removal of **2** were concentrated *in vacuo*, and the syrupy residue was treated with ethanethiol–conc. hydrochloric acid[30] to yield L-rhamnose diethyl dithioacetal, m.p. 136–137°, $[\alpha]_D^{23}$ −12.5° (*c* 6.4, methanol); lit.[33] m.p. 136–137°, $[\alpha]_D^{25}$ −12.4°.

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