Preparative Flash Vacuum Thermolysis. Homolytic Cleavage of Isomannide and Isosorbide Dinitrate to 1,4,3,6-Dianhydrohexoses

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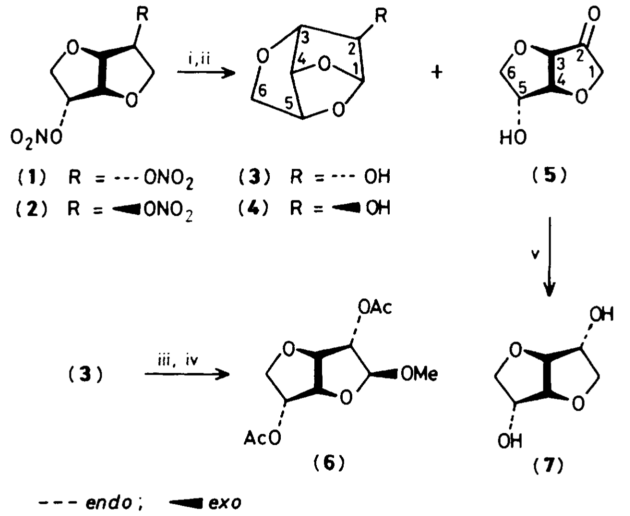
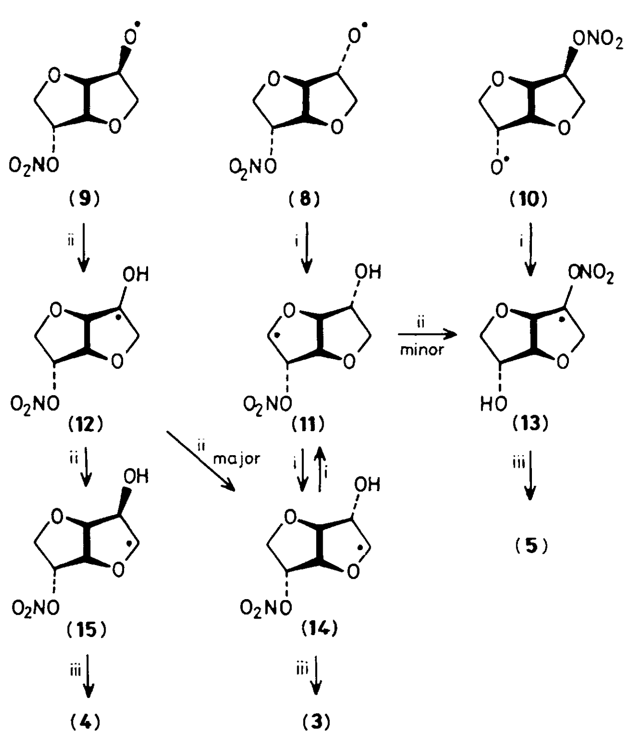
1,4,3,6-dianhydromannopyranose (**3**) can be conveniently prepared by flash vacuum thermolysis of isomannide dinitrate (**1**), while its epimer isosorbide dinitrate (**2**) yields a mixture of (**3**) and 1,4,3,6-dianhydrofructose (**5**), reflecting the restricted number of rearrangements, in one case with inversion of configuration, possible in the intermediate *cis*-fused furofuran radicals.

Pyrolysis[1] of hexoses, starch, or cellulose, besides extensive charring, leads to anhydrohexoses, mainly 1,6-anhydro-D-glucopyranose (laevoglucosan).[2] Other anhydrosugars are formed in acid catalysed pyrolysis[3] and eliminations, *e.g.* from acetates and toluene-*p*-sulphonates[4] and their chemistry has been explored.[5] Eliminations, thermal[6] or otherwise,[4] to dianhydroaldohexoses (trioxacyclononanes) are very rare[4] and proceed in extremely low yields. In contrast, dianhydromannitol (isomannide) and dianhydrosorbitol (isosorbide) are rapidly available by acid catalysed thermal dehydration.[7]



Scheme 1. *Reagents and conditions:* i, 400—450 °C, 0.05 mmHg, $-2NO_2$; ii, (**1**) → (**3**) + (**5**), (**2**) → (**3**) + (**4**) + (**5**); iii, MeOH, $HClO_4$; iv, Ac_2O, pyridine; v, $NaBH_4$.



Scheme 2. i, 1,5-H migration; ii, 1,2-H migration; iii, $-NO_2$.

We discovered recently[1] that flash vacuum thermolysis (f.v.t.) of benzene-1,2-dimethanol dinitrate occurs with loss of nitrogen dioxide to give *o*-hydroxymethylbenzaldehyde, equilibrating[8] with 1-hydroxyphthalan. The net result of this reaction is that one hydroxy group of benzene-1,2-dimethanol is oxidized to the aldehyde. This led us to investigate isomannide dinitrate (**1**) and isosorbide dinitrate (**2**)† as possible precursors for dianhydrohexoses.‡ Thus upon f.v.t. at 400—450 °C of (**1**) and (**2**), nitrogen dioxide was captured in the cold trap, while a viscous light yellow syrup, that partly crystallized, was deposited in the bend of the quartz tube.§ The pyrolysates, after extracting into water, were found to be exclusively dianhydrohexoses as analysed by ^{13}C n.m.r. spectroscopy. Compound (**1**) yielded 75—80% of 1,4,3,6-dianhydromannopyranose (**3**) and 5—10% of 1,4,3,6-dianhydrofructose (**5**). Dinitrate (**2**) gave 80% of a mixture of (**5**), (**3**), and 1,4,3,6-dianhydroglucopyranose (**4**) in a ratio 6 : 3 : 1 (Scheme 1).

Pure (**3**), which is virtually inaccessible by any other means,[6] was isolated as a stable crystalline solid, m.p. 94.5—97.0 °C,¶ after extracting the water solution of the pyrolysate from (**1**) with chloroform. On treatment in methanol with a trace of perchloric acid and subsequently with acetic anhydride and pyridine, (**3**) was converted into the known[10] 3,6-anhydro-α-methylmannofuranoside diacetate (**6**). The keto derivative (**5**),[11] a viscous liquid,¶ shows a ^{13}C carbonyl signal at δ 102.2 in the n.m.r. spectrum, that remains present in moderately dry dimethyl sulphoxide, together with a true carbonyl absorption at δ 212.6. This suggests that hydration of the carbonyl group[12] is occurring in (**5**), but not in its *exo*-epimer.[7] Dianhydromannitol (**7**), formed by reduction of the keto group with sodium borohydride, can only arise from (**5**). Besides, by yielding exclusively (**7**) and not its epimer dianhydrosorbitol, the reduction appears stereoselective. The third product (**4**), only formed from (**2**) as a minor component, was spectroscopically identical with an *X*-ray analysed sample.[13]

Homolytic cleavage of an N–O bond in symmetrical (**1**) generates only one oxy radical (**8**), while (**2**) yields two oxy radicals (**9**) and (**10**) (Scheme 2). Since 1,5-hydrogen migrations from carbon to oxygen and from carbon to carbon are much faster than the alternative 1,2-hydrogen migrations,[14] they will predominate, *e.g.*: (**8**) → (**11**) → (**14**) or (**10**) → (**13**).

When 1,5-hydrogen migrations are sterically impossible, as in the *exo*-oxy radical (**9**), 1,2-hydrogen migrations (**9**) → (**12**), (**12**) → (**14**) and (**12**) → (**15**) can proceed. Only the *endo*-nitrate group in (**14**) and (**15**) can undergo internal substitution with loss of nitrogen dioxide in the final step to the epimeric acetals (**3**) and (**4**). The *exo*-nitrate radical (**10**) will probably rearrange exclusively to radical (**13**), the direct

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† Although sugar nitrates are potentially explosive, their preparation is considered safe, (**2**) being a commercial coronary vasodilator.[9]

‡ Unsubstituted saccharides, *e.g.* sorbitol and methylglucoside, did not yield anhydro derivatives under f.v.t. conditions. Up to 650 °C these compounds passed through the quartz tube unchanged, but at around 700 °C they decomposed into a multitude of gaseous fragments.

§ *Warning:* An explosion screen was placed over all operations, which were carried out in a commercial apparatus as described in ref. 1, Fig. 1. On heating with i.r. lamps, 1.0—1.5 g quantities of molten (**1**) and (**2**) evaporated smoothly into the quartz tube, at a rate of 0.5 g h^{-1}, at a pressure of 0.05 mmHg. However in a run using 5.0 g of (**1**), it suddenly darkened and foamed up into the quartz tube, causing a vigorous explosion.

¶ *Selected spectroscopic data:* (**3**)$\delta_H(CDCl_3)$ 2.72 (br. d, 1H, *J* 7.0 Hz, OH), 3.74 (br. t, 1H, *J* 7.0 Hz, 2-H), 3.97 (dd, 1H, *J* −10.8, 2.1 Hz, 6-H), 4.08 (d, 1H, *J* −10.8 Hz, 6'-H), 4.16 (dd, 1H, *J* 5.0, 7.4 Hz, 3-H), 4.13 (dd, 1H, *J* 3.3, 2.1 Hz, 5-H), 5.23 (dd, 1H, *J* 5.0, 3.3 Hz, 4-H), 5.35 (d, 1H, *J* 1.5 Hz, 1-H); δ_c (D_2O) 71.5, 71.9, 72.4, 78.5, 83.9, 99.4; (**5**), isolated by h.p.l.c. (reversed phase); i.r. (NaCl), 1764 cm^{-1} (C=O); δ_H ($CDCl_3$) 3.61 (dd, 1H, *J* 9.2, 7.0 Hz, 6-H), 4.11 (dd, 1H, *J* 9.2, 6.5 Hz, 6'-H), 4.13 (d, 1H, *J* −17.5 Hz, 1-H), 4.23 (d, 1H, *J* −17.5 Hz, 1'-H), 4.31 (d, 1H, *J* 4.3 Hz, 3-H), 4.44 (pseudo q, 1H, *J ca.* 6 Hz, 5-H), 4.82 (pseudo t, 1H, *J ca.* 5 Hz, 4-H); δ_c (D_2O) 72.0, 73.0, 75.5, 82.9, 85.9, 102.2 [C=O as $C(OH)_2$].

precursor to ketone (**5**). Radical (**11**) also has an escape to (**5**) *via* (**13**). The *exo*-epimer[7] of (**5**) cannot arise from any of the radicals discussed. Formation of (**3**) from (**2**), *via* the major sequence (**9**) → (**12**) → (**14**), means inversion about C-2.[15] That (**3**) is formed in excess of (**4**) is surprising and indicates that the radical pathways possible in these rigid bicyclic structures are very specific.

It is concluded that sequential intermolecular radical pathways are surpressed in the dilute gas phase conditions of f.v.t., causing at the same time selective intramolecular formation of stable end products from the intermediate oxy radicals. Nevertheless oxygen centred radicals have not been widely explored in preparative strategies *via* f.v.t.[16]

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