46. *Steric Effects in the Oxidation of Hexitols with Periodate.*

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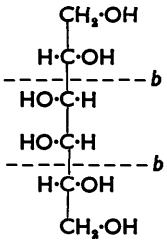
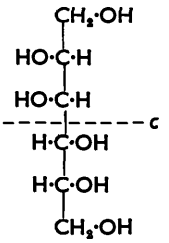
Oxidation of mannitol, dulcitol, and sorbitol with a limited quantity of sodium periodate is shown to involve preferential attack on *threo*-glycol groups.

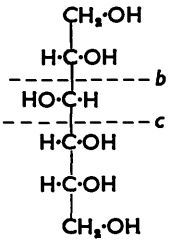
Although it is well known that hexitols react with excess of periodate to give 4 mols. of formic acid and 2 mols. of formaldehyde,[1] the intermediates involved have not been investigated. The first step in the reaction of a hexitol with periodate may yield a pentose and formaldehyde (route *a*), a tetrose and glycollaldehyde (route *b*), or two molecules of glyceraldehyde (route *c*). The relative importance of these three paths would be expected to depend on the stereochemistry of the hexitol. In the oxidation of cyclic glycols with periodate, *cis*-isomers generally react more rapidly than *trans*-isomers,[2] a result which has been interpreted in terms of cyclic intermediates involving the periodate. However, in the case of acyclic systems, *threo*-isomers (*i.e.*, "*trans*"-isomers on the Fischer convention) react more rapidly than *erythro*-isomers in a number of reactions which involve cyclic intermediates.[3] The difference in rate has been ascribed to the smaller non-bonded repulsions present in cyclic intermediates derived from the *threo*-isomers.[3] On this view, route *b* should be preferred to route *c* in the oxidation of dulcitol (I), while the reverse may be expected in the case of mannitol (II).



(I)



(II)



(III)

To check these predictions, 1 mol. of dulcitol and 1 mol. of mannitol were each oxidised with 0·1 mol. of sodium periodate; a large excess of hexitol was used to diminish further oxidation of the initial fission products. Under these conditions only *ca.* 1% of the initial products underwent further oxidation yielding formic acid. Production of formate esters [4] was negligible. Chromatographic examination of the products indicated that the oxidation of dulcitol gave a tetrose (DL-threose) while oxidation of mannitol gave mainly glyceraldehyde and only a trace of tetrose. In addition, both hexitols yielded a trace of pentose, the pentose spot from oxidised dulcitol being less intense than that from oxidised mannitol.

These results were confirmed by reaction of the oxidised hexitols with phenylhydrazine acetate. The resulting osazones were separated by chromatography on alumina.[5] Oxidised dulcitol gave glyoxal bisphenylhydrazone, DL-threosazone (DL-erythrosazone), and only a trace of glycerosazone. Oxidised mannitol yielded mainly glycerosazone, together with a smaller quantity of glyoxal bisphenylhydrazone and traces of erythrosazone and pentose osazone.

[1] Jackson, *Org. Reactions*, 1944, **2**, 341.
[2] Price and Knell, *J. Amer. Chem. Soc.*, 1942, **64**, 552; Klosterman and Smith, *ibid.*, 1952, **74**, 5336; Fleury, Courtois, and Bieder, *Bull. Soc. chim. France*, 1953, 543; see however Levesley, Waters, and Wright, *J.*, 1956, 840.
[3] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.
[4] Meyer and Rathgeb, *Helv. Chim. Acta*, 1949, **32**, 1102; Barker and Smith, *Chem. and Ind.*, 1952, 1035; Huffman, Lewis, Smith, and Spriestersbach, *J. Amer Chem. Soc.*, 1955, **77**, 4346; Gorin and Jones, *Nature*, 1953, **172**, 1051.
[5] Barry and Mitchell, *J.*, 1954, 4020.

Dulcitol is therefore oxidised mainly by route *b*, while mannitol reacts mainly by route *c*; both hexitols react to a small extent by route *a*. The preferential oxidation of *threo*-glycol groups, which occurs in both cases, is in agreement with the above predictions.

Chromatographic examination of the product from the reaction of 1 mol. of sorbitol with 0·1 mol. of sodium periodate, suggested that it contained comparable quantities of glyceraldehyde and erythrose, as well as traces of xylose and arabinose. Examination of the stereochemistry of sorbitol (III) shows that this result is also in agreement with the above views.

The comparatively high proportion of glyoxal bisphenylhydrazone, isolated from the reaction of phenylhydrazine acetate with oxidised mannitol, was unexpected, as glycollaldehyde produced by route *b* should be accompanied by an equimolecular quantity of tetrose. Although the ease with which glyoxal bisphenylhydrazone separates from solution [5] may explain the above results, it also seems possible that some of this compound was derived from glyoxal or glycollaldehyde produced by periodate oxidation of glyceraldehyde or erythrose.

Experimental

D-Erythrose and D-threose were prepared as described by Perlin and Brice.[6] DL-Glyceraldehyde was obtained commercially (L. Light and Co. Ltd.).

Periodate Oxidations.—0·5M-Aqueous solutions of the hexitols (100 c.c.) were mixed with equal volumes of 0·05M-sodium periodate at 20° (0·5M-dulcitol is supersaturated at 20°). After 30 min. the solutions gave negative tests for periodate. Formic acid was then estimated [7] by titration of 10 c.c. samples with 0·01N-sodium hydroxide (methyl-red). Titres: 0·45 c.c. (mannitol), 0·50 c.c. (dulcitol), 0·20 c.c. (sorbitol). 0·01N-Sodium hydroxide (0·7 c.c.) was then added to the neutralised samples to hydrolyse any formate esters present.[4] After 15 min. at room temperature, the solutions were back-titrated with 0·01N-sulphuric acid; not more than 0·1 c.c. of 0·01N-sodium hydroxide had been consumed by hydrolysis of formates.

Paper Chromatography of the Oxidised Hexitols.—Two solvents were used in descending chromatography on Whatman No. 1 paper: (*a*) butanol–benzene–pyridine–water (5 : 1 : 3 : 3) (upper layer); (*b*) ethyl methyl ketone saturated with water. The sugars were detected with aniline oxalate.

Oxidised mannitol and oxidised dulcitol each gave a faint pink spot; these moved at the same rate as arabinose and lyxose respectively (solvent *a*). In addition, oxidised dulcitol gave a yellowish-brown spot (R_F *ca.* 0·55 in solvent *a*) which fluoresced brightly in ultraviolet light; oxidised mannitol gave a brown, non-fluorescent spot in the same region. In solvent *b* the former travelled at the same rate as threose, while the latter corresponded to glyceraldehyde ($R_{threose}$ *ca.* 0·33). Erythrose had $R_{threose}$ 0·85 in solvent *b*. When the chromatogram of oxidised mannitol in solvent *b* was viewed under ultraviolet light a very faint fluorescent spot was observed in the tetrose region.

Oxidised sorbitol gave two faint pink spots which moved at the same rate in solvent *a* as xylose and arabinose. The spot corresponding to the latter was very faint. Chromatography in solvent *b* revealed spots travelling at the same rate as glyceraldehyde ($R_{threose}$ 0·30; brown spot) and erythrose ($R_{threose}$ 0·85; yellowish-brown, fluorescent spot).

None of these spots was due to impurities in the hexitols.

Preparation and Separation of the Osazones.—Oxidised mannitol and oxidised dulcitol (150 c.c.; prepared as above) were freed from iodate by addition of 0·5M-lead nitrate (4·2 c.c.). After 90 min. at 0°, the solutions were filtered and treated with glacial acetic acid (4·5 c.c.) and redistilled phenylhydrazine (3·6 c.c.). The osazones, collected after 3 days at 35°, were dissolved in benzene and chromatographed on alumina (Peter Spence and Sons Ltd., Type H). Minor fractions were identified by circular paper chromatography as described by Barry and Mitchell.[5]

(a) *Oxidised dulcitol.* The mixture of osazones (1·12 g.) was chromatographed on alumina (60 g.). Fractions 2 and 3 (0·63 g.; yellow solid), eluted with benzene (400 c.c.), were glyoxal bisphenylhydrazone which crystallised from benzene as pale yellow plates, m. p. and mixed m. p. 170—172°. Fractions 4—8 (0·03 g.; unidentified syrups) were eluted with benzene (250 c.c.), 4 : 1 benzene–ether (300 c.c.), and 1 : 1 benzene–ether (150 c.c.). Fraction 9

[6] Perlin and Brice, *Canad. J. Chem.*, 1956, **34**, 541.
[7] Halsall, Hirst, and Jones, *J.*, 1947, 1427.

(0·015 g.; semicrystalline syrup), eluted with ether (400 c.c.), was mainly glycerosazone. Fractions 10 and 11 (0·02 g.; unidentified syrups) were eluted with ether–ethanol and with ethanol. Fractions 12 and 13 (0·38 g.; yellow solid), eluted with 19 : 1 ethanol–water (450 c.c.), were DL-erythrosazone, which crystallised from benzene as fine yellow needles, m. p. 165—167° (Found: N, 18·4. Calc. for $C_{16}H_{18}O_2N_4$: N, 18·8%). Fischer and Tafel [8] report m. p. 166—167° for DL-erythrosazone. On a circular paper chromatogram the compound moved at the same rate as D-erythrosazone, m. p. 167°, prepared from D-erythrose. The mixed m. p. of the D- and DL-isomers was 165—167°. Fraction 14 (0·01 g.), eluted with 9 : 1 ethanol–water (500 c.c.), was erythrosazone contaminated with compounds which moved more slowly on a paper chromatogram.

(b) *Oxidised mannitol.* The mixture of osazones (0·83 g.) was chromatographed on alumina (35 g.). Fraction 1 (0·09 g.; unidentified syrup) was eluted with benzene (50 c.c.). Fraction 2 (0·11 g.; crystals), eluted with benzene (60 c.c.), was glyoxal bisphenylhydrazone which crystallised from benzene as pale yellow plates, m. p. and mixed m. p. 170—172°. Fraction 3 (0·02 g.; unidentified syrup) was eluted with benzene (100 c.c.) and 3 : 1 benzene–ether (30 c.c.). Fraction 4 (0·05 g.; syrup), eluted with 3 : 1 benzene–ether (40 c.c.), yielded glycerosazone (0·02 g.), identified as below, on crystallisation from benzene–light petroleum. Fractions 5 and 6 (0·37 g.; yellow crystals), eluted with 1 : 1 benzene–ether (250 c.c.) and ether (500 c.c.), were glycerosazone which crystallised from benzene as yellow plates, m. p. 130—132°. On a paper chromatogram the compound moved at the same rate as authentic glycerosazone; the mixed m. p. was 130—132°. Fractions 7 and 8 (0·07 g.; syrups), eluted by 9 : 1 ether–95% ethanol (150 c.c.), yielded glycerosazone (0·02 g.), identified as above. Fractions 9 and 10 (0·02 g.; syrups), eluted with 1 : 1 ether–95% ethanol (150 c.c.), contained glycerosazone and erythrosazone. Fraction 11 (0·02 g.; syrup), eluted by 95% ethanol (250 c.c.), was a mixture of glycerosazone, erythrosazone, and pentose osazone. Fraction 12 (0·015 g.; yellow solid), eluted by 9 : 1 ethanol–water (100 c.c.), was a pentose osazone.

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[8] Fischer and Tafel, *Ber.*, 1887, **20**, 1088.