1009. *Reaction of* L-*Threitol with Acetone.*

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On acid-catalysed reaction with acetone, L-threitol affords mainly the 1,2:3,4-di-*O*-isopropylidene derivative, together with a small amount of the 1,2-*O*-isopropylidene compound (isolated as the di-*O*-*p*-phenylazobenzoate).

In the acid-catalysed reaction of acetone with acyclic polyhydric alcohols, condensation usually involves terminal vicinal (α in Barker and Bourne's terminology [1]) and *threo*-diol groups (αT). Apparently no example has been recorded where *erythro*-diol groups (αC) are involved although simpler compounds such as *erythro*-1,2-diphenylethane-1,2-diol are known to condense with acetone.[2] Further, it is known [3] that α-rings may be formed more readily than αT-rings and that in compounds containing both types of ring the latter are more stable towards acid. It was therefore of interest to examine the acetone threitol reaction since, if formation of 1,3-dioxolan derivatives is assumed,[3,4] a competitive reaction is theoretically possible involving the formation of a di-*O*-isopropylidene derivative (two α-rings) and/or two mono-*O*-isopropylidene derivatives (α- and αT-ring).

When L-threitol, obtained by acidic hydrolysis of 1,3-*O*-benzylidene-L-threitol,[5] was treated with acetone and sulphuric acid under conditions where erythritol gave *ca.* 95% of the di-*O*-isopropylidene compound, the main product (*ca.* 80%) was also a di-*O*-isopropylidene derivative. The small amount of mono-*O*-isopropylidene derivative formed was isolated as the di-*O*-*p*-phenylazobenzoate, m. p. 198—199°, $[M]_{5461}$ −216° (in $CHCl_3$) which was clearly not enantiomorphous with 2,3-*O*-isopropylidene-1,4-di-*O*-*p*-phenylazobenzoyl-D-threitol {m. p. 192—194°, $[M]_{5461}$ +116° (in $CHCl_3$)}, obtained by sequential application of periodate oxidation, borohydride reduction, and *p*-phenylazobenzoylation to 3,4-*O*-isopropylidene-D-mannitol. The mono-*O*-isopropylidene derivative was identified as 1,2-isopropylidene-3,4-di-*O*-*p*-phenylazobenzoyl-L-threitol since its saponification gave a product which consumed 0·92 mol. of periodate and released 0·9 mol. of formaldehyde. Similar saponification of 2,3-*O*-isopropylidene-1,4-di-*O*-*p*-phenylazobenzoyl-D-threitol gave a product resistant to periodate oxidation.

Treatment of the di-*O*-isopropylidene-L-threitol with 70% acetic acid at 50° for 45 min. caused almost complete hydrolysis. However, the small amount of mono-*O*-isopropylidene derivative which survived was identified by conversion into 1,2-*O*-isopropylidene-3,4-di-*O*-*p*-phenylazobenzoyl-L-threitol, thereby indicating a 1,2:3,4-distribution of the cyclic ketal groups in the di-*O*-isopropylidene derivative. Thus, further support is provided for Barker and Bourne's contention [3] that α-ketal rings are formed in preference to αT-rings. Additionally, it seems likely that the products obtained [6] from erythritol are, respectively, 1,2:3,4-di-*O*-isopropylidene-erythritol and 1,2-*O*-isopropylidene-DL-erythritol.

Both L-threitol and erythritol gave crystalline tetra-*O*-*p*-phenylazobenzoates, further exemplifying [7] the value of this derivative for characterization.

Experimental

Infrared spectra for comparative purposes were obtained by using a Perkin–Elmer 21 spectrometer. Optical rotations of *p*-phenylazobenzoates were determined at 5461 Å on a type 143A Ericsson automatic polarimeter with a path length of 1 cm. Periodate oxidations

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[1] Barker and Bourne, *J.*, 1952, 905.

[2] Hermans, *Z. phys. Chem.*, 1924, **113**, 337.

[3] Barker and Bourne, *Adv. Carbohydrate Chem.*, 1952, **7**, 137.

[4] Mills, *Adv. Carbohydrate Chem.*, 1955, **10**, 1.

[5] Foster, Haines, Homer, Lehmann, and Thomas, *J.*, 1961, 5005.

[6] Speier, *Ber.*, 1895, **28**, 2531; Fischer and Rund, *Ber.*, 1916, **49**, 88.

[7] Baggett, Foster, Haines, and Stacey, *J.*, 1960, 3528.

were performed essentially by Jackson's method,[8] and formaldehyde was determined by the chromotropic acid method.[9]

Hydrolysis of 1,3-O-*Benzylidene*-L-*threitol*.—A solution of 1,3-*O*-benzylidene-L-threitol (1·18 g.; m. p. 134—135°, obtained from 1,3-*O*-benzylidene-L-arabinitol [5]) in 0·5N-sulphuric acid was kept at 95—100° for 1 hr. The cooled solution was extracted with benzene to remove benzaldehyde, then neutralised with methyl di-n-octylamine [10] and concentrated. Recrystallization of the residue (0·595 g.) from ethanol gave L-threitol (0·188 g., 26%), m. p. 88—89°, $[M]_{5461}$ −7° (*c* 0·4 in H_2O). In a subsequent experiment the yield of purified L-threitol was 75%.

Isopropylidene Derivatives of L-*Threitol*.—A mixture of acetone (100 ml.), concentrated sulphuric acid (0·4 ml.), and L-threitol (0·99 g.) was shaken overnight at room temperature. The mixture was then poured with vigorous stirring into 2% aqueous potassium carbonate (100 ml.) at such a rate that an acid pH did not develop. The acetone was removed by concentration under diminished pressure and the remaining aqueous solution was extracted with chloroform (40 ml.). Concentration of the dried ($MgSO_4$) extract gave a residue (1·35 g.), the infrared spectrum (liquid film) of which showed only weak absorption for hydroxyl at 3400 cm.$^{-1}$. Recrystallization of the residue from light petroleum (b. p. 60—80°) gave *di-O-isopropylidene*-L-*threitol*, m. p. 34—35°, b. p. 80°/0·2 mm., $[\alpha]_{5461}$ +3° (*c* 0·7 in $CHCl_3$), $[M]_{5461}$ +6° (Found: C, 59·4; H, 8·9. $C_{10}H_{18}O_4$ requires C, 59·4; H, 8·9%).

Subsequent continuous extraction of the aqueous solution with chloroform for 20 hr. followed by concentration of the dried ($MgSO_4$) extract gave a residue (0·266 g.) which was clearly a mixture of mono- and di-*O*-isopropylidene derivatives since it had $\nu_{max.}$ for hydroxyl at 3350 cm.$^{-1}$ but consumed only 0·6 mol. of periodate, releasing 0·6 mol. of formaldehyde. The latter value corresponds to an overall yield of *ca.* 11% of 1,2-*O*-isopropylidene-L-threitol. The mixture was *p*-phenylazobenzoylated in the usual way.[7] Recrystallization of the product from benzene–light petroleum (b. p. 60—80°) gave 1,2-O-*isopropylidene*-3,4-*di*-O-p-*phenylazobenzoyl*-L-*threitol*, m. p. 198—199°, $[\alpha]_{5461}$ −37° (*c* 0·4 in $CHCl_3$), $[M]_{5461}$ −216° (Found: C, 68·5; H, 5·3; N, 9·7. $C_{33}H_{30}N_4O_6$ requires C, 68·5; H, 5·2; N, 9·7%).

Under the same conditions erythritol (1·05 g.) gave crude crystalline di-*O*-isopropylidene derivative (1·6 g., 98%) which had m. p. 55—56° after recrystallization from ether–light petroleum (b. p. 60—80°).

Saponification and Periodate Oxidation of 1,2-O-*Isopropylidene*-3,4-O-p-*phenylazobenzoyl*-L-*threitol*.—A mixture of the di-*O*-*p*-phenylazobenzoate (35 mg.), ethanol (5 ml.), and potassium hydroxide (0·125 g.) was boiled for 5 hr. The solution was stored at 0° overnight, the potassium *p*-phenylazobenzoate was removed, and the filtrate was evaporated to dryness at *ca.* 50°/~12 mm. A solution of the residue in water (20 ml.) was extracted continuously with chloroform for 12 hr. and the dried ($MgSO_4$) extract was evaporated, yielding crude 1,2-*O*-isopropylidene-L-threitol (10 mg.). This compound consumed 0·92 mol. of periodate in $<$30 min. and none subsequently, and 0·9 mol. of formaldehyde was released.

After hydrolysis of the 1,2-*O*-isopropylidene-L-threitol with N-hydrochloric acid at 95—100° for 1 hr., the neutralized hydrolysate consumed 2·2 mol. of periodate, releasing 1·36 mol. of formaldehyde, corresponding to a ratio of oxidant consumed : formaldehyde released of 3 : 1·9. The expected ratio was 3 : 2.

Saponification of 2,3-*O*-isopropylidene-1,4-di-*O*-*p*-phenylazobenzoyl-D-threitol by the same procedure gave a product resistant to periodate oxidation. Further acidic hydrolysis gave a product for which the ratio oxidant consumed : formaldehyde released was 3 : 1·6.

Graded Acidic Hydrolysis of Di-O-*isopropylidene*-L-*threitol*.—A solution of the di-*O*-isopropylidene derivative (0·6 g.) in water (6 ml.) and acetic acid (14 ml.) was kept at 50° for 45 min. and then rapidly neutralized with 2N-sodium hydroxide. Extraction of the cooled solution with chloroform gave a small amount (18 mg.) of (presumably) starting material. Subsequent continuous extraction with chloroform for 40 hr. gave a product (26 mg.) which was esterified with *p*-phenylazobenzoyl chloride (0·2 g.) and pyridine (10 ml.) at 95—100° for 3 hr. The mixture was worked up in the standard manner [7] and afforded a product (0·1 g.) which on recrystallization from benzene–light petroleum (b. p. 60—80°) gave 1,2-*O*-isopropylidene-3,4-di-*O*-*p*-phenylazobenzoyl-L-threitol (60 mg.), m. p. 192—194°, $[\alpha]_{5461}$ −39°

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[8] Jackson, *Org. Reactions*, 1944, **2**, 341.

[9] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.

[10] Lester-Smith and Page, *J. Soc. Chem. Ind.*, 1948, **67**, 48.

(c 0·3 in $CHCl_3$), $[M]_{5461}$ −225°. The m. p. was undepressed on admixture with the authentic compound described above and the infrared spectra (KBr discs) of these compounds were indistinguishable.

Periodate Oxidation of 3,4-O-*Isopropylidene*-D-*mannitol*.—(*a*) A solution (50 ml.) of the isopropylidene compound (50 mg.) and sodium metaperiodate (0·27 g.) in water at room temperature consumed 1·95 mol. of oxidant after 4 min. and 2·03 mol. after 29 min. No further uptake was observed.

(*b*) A solution of the monoisopropylidene compound (1 g.) and sodium metaperiodate (5 g.) in water (*ca*. 150 ml.) was shaken for 1 hr. and then neutralised with barium hydroxide. Insoluble material was removed and sodium borohydride (2 g.) was added to the aqueous solution. After 12 hr. at room temperature, the pH of the solution was adjusted to 7·5 with acetic acid. The solution was concentrated and then continuously extracted with chloroform for 2 days. Concentration of the dried ($MgSO_4$) extract gave crude 2,3-*O*-isopropylidene-L-threitol (0·19 g.). The aqueous solution was freeze-dried and the residue was extracted with hot ethyl acetate. Concentration of the extract gave a further amount (0·38 g., total yield 79%) of the product which proved difficult to recrystallize. It was resistant to periodate oxidation. A portion was therefore *p*-phenylazobenzoylated yielding 2,3-O-*isopropylidene*-1,4-di-O-p-*phenylazobenzoyl*-D-*threitol*, m. p. 192—194° (from benzene–light petroleum), $[\alpha]_{5461}$ +20° (c 0·3 in $CHCl_3$), $[M]_{5461}$ +116° (Found: C, 68·3; H, 5·3; N, 9·6. $C_{33}H_{30}N_4O_6$ requires C, 68·5; H, 5·2; N, 9·7%).

p-*Phenylazobenzoylation of the Tetritols*.—A mixture of L-threitol (50 mg.), *p*-phenylazobenzoyl chloride (0·48 g.), and dry pyridine (20 ml.) was kept at 95—100° for 3 hr. and then worked up in the usual way,[7] to yield the *tetra*-O-p-*phenylazobenzoate* (0·32 g., 82%), m. p. 207—208° (from benzene–light petroleum), $[\alpha]_{5461}$ −36° (c 0·3 in $CHCl_3$), $[M]_{5461}$ −340° (Found: C, 70·3; H, 4·6; N, 11·5. $C_{56}H_{42}N_8O_8$ requires C, 70·5; H, 4·4; N, 11·7%). Likewise, erythritol gave a *tetra*-O-p-*phenylazobenzoate*, m. p. 186—187° (Found: C, 70·4; H, 4·9%).

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