98. *Dambonitol. Part II.* Oxidation by Periodic Acid and Sodium Metaperiodate.*

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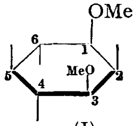
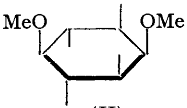
Periodic acid oxidation of dambonitol gives *meso-ribo*-β-hydroxy-αα′-dimethoxyglutaraldehyde of which some derivatives and a lactol have been obtained crystalline. Dambonitol is therefore 1 : 3-di-*O*-methyl*meso*inositol. On oxidation by sodium metaperiodate formic acid is slowly formed to a limiting value of nearly one mole per mole of dambonitol. A mechanism for the periodate oxidation is proposed.

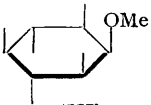
IN Part I * the isolation of dambonitol, a di-*O*-methylinositol, from the sera of the latices of *Dyera lowii* and *D. costulata* was described. As the cyclitol was optically inactive and did not form an *iso*propylidene derivative it was inferred that its structure was either (I) or (II). Further, dambonitol rapidly reacted with 2 mols. of sodium metaperiodate, producing only 0·2—0·3 equivalent of strong acid. On the assumption that dambonitol was cleaved to two mols. of *O*-methyltartronaldehyde and that this was not readily oxidised, dambonitol was considered to be 2 : 5-di-*O*-methyl*meso*inositol (II), and the small but finite amount of strong acid was attributed to the presence of the dialdehyde in the enol form :



(I)



(II)



(III)

$$\mathrm{OHC{\cdot}CH(OMe){\cdot}CHO \rightleftharpoons OHC{\cdot}C(OMe){:}CH{\cdot}OH} \quad \text{(IV)}$$

However, the assumption in this proof that *O*-methyltartronaldehyde would not be readily oxidised by excess of periodate was incorrect since malondialdehyde and related compounds containing active methylene groups are oxidised by periodic acid;[1] further, by analogy with *meso*inositol[2] and sequoyitol,[3] (III), 2 : 5-di-*O*-methyl*meso*inositol (II) should consume much more than 2 mols. of periodate and more than one equivalent of formic acid should be formed. The results recorded in Part I thus actually favour structure

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* Part I, Comollo and Kiang, *J.*, 1953, 3319.

[1] Huebner, Ames, and Bubl, *J. Amer. Chem. Soc.*, 1946, **68**, 1621.

[2] Fleury, Poirot, and Fieret, *Compt. rend.*, 1945, **220**, 664.

[3] Riggs, *J.*, 1949, 3199.

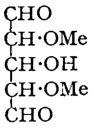
(I). We have investigated this further by working on a larger scale and isolating the oxidation product.

Dambonitol was purified until paper chromatography showed only one spot; Professor S. J. Angyal has told us that he has isolated *meso*inositol from crude dambonitol by use of a cellulose column and that careful demethylation of dambonitol gave a monomethyl-*meso*inositol, the infrared spectrum of which was identical with that of bornesitol.

The crude dialdehyde obtained by use of periodic acid [4] was a syrup. Extraction of this with absolute ethanol gave a further syrup which was strongly reducing towards Tollens's reagent and gave three crystalline dihydrazones and a crystalline dianil which behaved on analysis as derivatives of *meso-ribo*-β-hydroxy-αα′-dimethoxyglutaraldehyde (V), as expected from structure (I). When treated with dimedone in the presence of piperidine,[5] the syrup gave an anhydrobisdimedone derivative, which is stable to hot aqueous-alcoholic hydrochloric acid and is probably the pyran derivative (VI).

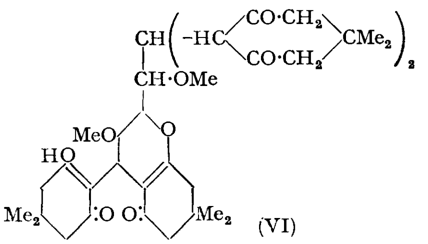
The syrupy dialdehyde gradually afforded crystals when kept *in vacuo* over phosphoric oxide; when recrystallised from ether, these showed on analysis the presence of three alkoxy-groups and a mol. of ethanol associated with one of the dialdehyde. The ethanol is not removed at 80° *in vacuo* over phosphoric oxide, and is thus not ethanol of crystallisation. The compound is not obtained unless ethanol is used during the working up and is probably an ethoxy-lactol (VII). Although it forms derivatives with carbonyl reagents it has no effect on Schiff's reagent.

It is thus proved that dambonitol is 1 : 3-di-*O*-methyl*meso*inositol (I). It remains to discuss why on oxidation with sodium metaperiodate (Part I) and direct titration with sodium hydroxide only 0·2—0·3 mol. of formic acid is detectable. The estimation of formic acid by direct titration after periodate oxidation has been shown to be reliable, *e.g.*, for glycerol and erythritol [6] and for αα′-trehalose.[7] However, the estimation of small amounts of formic acid is satisfactory only when the excess of periodate has been removed by ethylene glycol.[8] When this technique was used dambonitol gave larger but still inadequate amounts of formic acid (0·3—0·5 mol.) (controls gave theoretical results). It was then noted that after 2 mols. of periodate had been consumed and the solution neutralised, acidity gradually returned until after about 280 hours a total of 1 mol. of acid was estimated. It was established that formaldehyde was not oxidised by air to formic acid, and that the dialdehyde and the lactol (VII) were also stable under the conditions used.

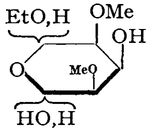


$$\begin{array}{l}\mathrm{CHO}\\ |\\ \mathrm{CH{\cdot}OMe}\\ |\\ \mathrm{CH{\cdot}OH}\\ |\\ \mathrm{CH{\cdot}OMe}\\ |\\ \mathrm{CHO}\end{array}$$

(V)



(VI)



(VII)

To account for the low yield of formic acid on oxidation of methyl cellobioside by potassium periodate Halsall, Hirst, and Jones [8] postulated that some lactol was formed and then oxidised to a formyl ester, which was only slowly hydrolysed. There is also evidence of formyl esters as intermediates in the periodate oxidation of lactose,[9] maltose,[10] and cellobiose.[11] By analogy we believe that dambonitol is first cleaved to the dialdehyde (VIII) which is partly oxidised to the 1 : 5-dialdehyde (V) and partly cyclised to the lactols (IX*a*) and/or (IX*b*). The lactol (IX*a*) is then further oxidised, yielding the formyl

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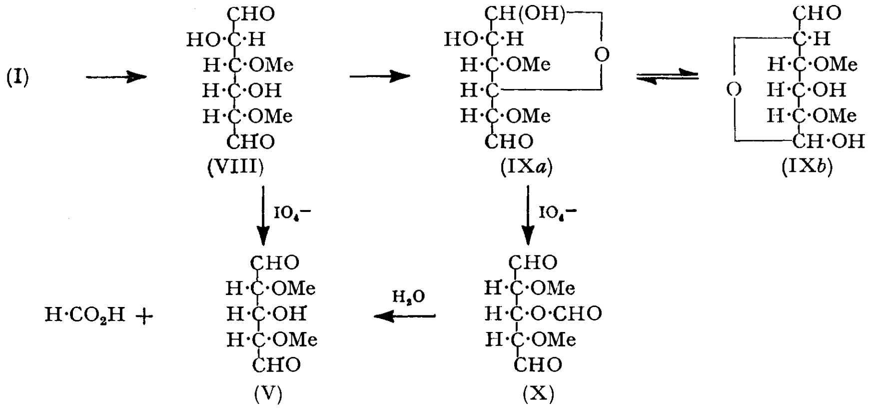
[4] Cf. Jackson and Hudson, *J. Amer. Chem. Soc.*, 1937, **59**, 994.
[5] Cf. Horning and Horning, *J. Org. Chem.*, 1946, **11**, 95.
[6] Malaprade, *Bull. Soc. chim.* (*France*), 1937, **4**, 906.
[7] Jackson and Hudson, *J. Amer. Chem. Soc.*, 1939, **61**, 1530.
[8] Halsall, Hirst, and Jones, *J.*, 1947, 1427.
[9] Meyer and Rathgeb, *Helv. Chim. Acta*, 1948, **31**, 1540.
[10] Morrison, Kuyper, and Orten, *J. Amer. Chem. Soc.*, 1953, **75**, 1502.
[11] Head and Hughes, *J.*, 1954, 603.

ester (X), which is slowly hydrolysed to the 1 : 5-dialdehyde (V) and formic acid. The isomeric lactol (IX*b*) is itself stable to periodate but, being in equilibrium with (IX*a*), is removed as oxidation proceeds. Thus finally one equivalent of formic acid is formed. In conformity, heating at 70° hastened the production of titratable acid. About 90% of the total titratable acid was recovered by steam-distillation.[12]



EXPERIMENTAL

Microanalyses are by Dr. W. Zimmermann, D.S.I.R.O., Melbourne.

Paper Chromatography of Dambonitol.—Twice recrystallised samples gave a strong spot for dambonitol and two other weak spots when the descending chromatogram was developed with 5% ammonical silver nitrate.[13] The average R_F values obtained with butan-1-ol–ethanol–water (4 : 1 : 5 v/v) on Whatman No. 1 paper at 29° were : dambonitol, 0·20; *meso*inositol, 0·09; a minor component, 0·14 (probably a monomethyl*meso*inositol; cf. Hirst, Hough, and Jones;[14] Ballou and Anderson [13]).

Periodic Acid Oxidation.—To a solution of periodic acid (*ca.* 0·03 mole) prepared from barium periodate[7] $Ba_2I_2O_9$ was added pure dambonitol (2 g., 0·01 mole). The mixture was left in the dark at room temperature for 4—5 hr. (by which time 2 mols. of periodic acid were consumed), then neutralised with excess of strontium carbonate at 70°. After filtration, the solution was evaporated to dryness in a vacuum at 70°. The residue was rubbed with absolute ethanol (20, 10, 10 ml.). The ethanol extract was centrifuged to remove (mainly) strontiun iodate and formate, concentrated on a steam-bath, and kept *in vacuo* over sodium hydroxide. The residue was again extracted with a small quantity of absolute ethanol, and the solution after filtration again concentrated to a syrup (*A*) *in vacuo* over sodium hydroxide.

The syrup (*A*) was kept *in vacuo* over phosphoric oxide until crystals began to appear, then extracted with hot absolute ether. Concentration of the solution gave crystals (0·3 g.) on cooling in ice-water. Repeated recrystallisation in the same way gave the *lactol*, m. p. 108—109°, readily soluble in water, ethanol, and benzene, but not in light petroleum, reducing Tollens's reagent but not Schiff's reagent (Found : C, 48·95, 48·45, 48·8, 48·1; H, 8·4, 8·1, 8·2, 7·8; OAlk, as OMe, 39·75, 39·85. $C_9H_{18}O_6$ requires C, 48·65; H, 8·15; 3OMe, 41·9%).

The syrup (*A*) dialdehyde (0·5 g.) was warmed with phenylhydrazine (1 ml.) and acetic acid (2 drops) in a little ethanol for about 10 min. Water was added to turbidity. On cooling, an oil separated out which solidified under ethanol. Repeated recrystallisation from aqueous ethanol gave the yellow *bisphenylhydrazone*, m. p. 139—140° (Found : C, 63·8; H, 6·75; N, 15·35, 15·0; OMe, 17·15. $C_{19}H_{24}O_3N_4$ requires C, 64·0; H, 6·8; N, 15·7; OMe, 17·35%). The same derivative was obtained from the crystalline lactol (VII).

The *bis*-p-*nitrophenylhydrazone*, similarly prepared from either material, had m. p. 212—214° (Found : C, 51·3; H, 5·3; N, 18·5. $C_{19}H_{22}O_7N_6$ requires C, 51·1; H, 5·0; N, 18·8%).

The orange-red *bis*-2 : 4-*dinitrophenylhydrazone*, prepared in absolute ethanol containing

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[12] Cf. Markham, *Biochem. J.*, 1942, **36**, 790.

[13] Ballou and Anderson, *J. Amer. Chem. Soc.*, 1953, **75**, 648.

[14] Hirst, Hough, and Jones, *J.*, 1949, 928.

a little concentrated hydrochloric acid and crystallised from ethanol–ethyl acetate, had m. p. 205—206° (Found : C, 42·55; H, 3·9. $C_{19}H_{20}O_{11}N_8$ requires C, 42·55; H, 3·75%).

The syrup (*A*) (0·6 g.) and *p*-nitroaniline (0·6 g.) were refluxed in hot ethanol (6 ml.) for 10 min. The solution became cloudy, and, on cooling in ice, deposited the *bis*-p-*nitroanil* which recrystallised from acetone as hydrated yellow needles, m. p. 181·5—182°. The water of recrystallisation was not removed at 100° *in vacuo* over phosphoric oxide during 36 hr. (Found: C, 52·2, 52·2; H, 5·6, 5·3; N, 12·6, 12·4. $C_{19}H_{20}O_7N_4,1H_2O$ requires C, 52·5; H, 5·1; N, 12·9%).

The syrup (*A*) (0·3 g. in 3 ml. ethanol) was heated with dimedone (0·4—0·5 g.) in the presence of 1 drop of piperidine at 100° for about 10 min. Water was then added to turbidity, and the mixture kept in a freezing mixture for about 4 hr. An oily *derivative* (VI) separated which solidified under ethanol. Recrystallisation from aqueous ethanol gave colourless needles, m. p. 221—222° (Found: C, 68·35, 68·45, 68·6; H, 7·8, 7·85, 8·1. $C_{39}H_{54}O_{10}$ requires C, 68·6; H, 8·0%).

Sodium Metaperiodate Oxidation.—(a) *Estimation of formic acid after reaction at room temperature.* Dambonitol (0·0651 g., 0·3125 millimole) was dissolved in a solution of sodium metaperiodate (1·223 millimole) in water (100 c.c.). The mixture was kept in the dark and aliquot portions (5 c.c.) were withdrawn at intervals. The amounts of periodate were determined as in Part I. The amounts of formic acid simultaneously liberated were determined by titration with 0·0098N-sodium hydroxide (methyl-red), 15—20 min. after pure ethylene glycol (*ca.* 1 c.c.) had been added. Each solution after neutralisation was kept in a stoppered flask and was periodically neutralised again until the solution remained yellow after 2 days. In a simultaneous blank determination with the same quantities of periodate, ethylene glycol, and methyl-red the total alkali uptake was negligible (0·04 c.c.). Typical results are tabulated.

Time (hr.)	4	19	24	44	68	92	116
Aliquot no.	(i)	(ii)	(iii)	(iv)	(v)	(vi)	(vii)
IO_4^- uptake (mol.)	2·00	1·97	2·02	2·03	2·05	2·08	2·10
$H{\cdot}CO_2H$ (mol.)	0·21	0·26	0·20	0·22	0·29	0·29	0·31
After storage for x hr. (x =)...	280	265	260	240	216	193	168
total $H{\cdot}CO_2H$ (mol.)	0·924	0·96	0·93	0·88	0·968	0·92	0·96

(b) *Estimation of formic acid on reaction at* 70°. In similar work (0·1832 millimole of dambonitol, 0·4902 millimole of metaperiodate), samples (5 c.c.) were kept for 4—10 hr. at room temperature, then treated with ethylene glycol and alkali (to neutrality), and heated at 70°. The production of acid was followed as before, the total uptake of alkali corresponding in these cases to 0·96, 0·96, 0·97 mol. of formic acid after about 2 hr. Solutions of the same quantities of periodate, ethylene glycol and methyl-red, even after addition of solid lactol, remained unchanged.

(c) *Recovery of formic acid.* A finally neutral solution from the previous experiment was acidified (Congo-red) by phosphoric acid and transferred with washing into an apparatus similar to Markham's [12] previously standardised with formic acid. The final volume was <10 c.c. as larger volumes give inconsistent results. The solution was steam-distilled for about 16—24 min. and the distillate titrated with standard alkali (phenol-red). A blank determination showed the correction required to be negligible. In three experiments recoveries of 96, 90, and 80% of volatile acid were obtained. That this acid was formic acid was confirmed by evaporating the slightly basified distillate to dryness and heating the residue in a 5% solution (2 c.c.) of mercuric sulphate in sulphuric acid in a stoppered vessel for 1 hr., and then redistilling the mixture : no volatile acid was then present.

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[*Received, July* 18*th*, 1955.]