672. *Reaction of Periodate with Compounds containing Active Methylene Groups.*

By J. L. Bose, A. B. Foster, and R. W. Stephens.

The action of periodate on chloro-, bromo-, and iodo-acetaldehyde has been examined. A convenient source of the halogenoacetaldehydes is by reaction of periodate with the 1,4-dideoxy-1,4-dihalogeno-derivatives of DL-threitol, and synthesis of the latter compounds from *cis*-but-2-ene-1,4-diol is described. A mechanism for the hydroxylation of active methylene groups by periodate is suggested and some supporting evidence is provided.

In addition to cleaving 1,2-diols and related compounds periodate can also cause other reactions.[1-3] Thus, the observation [4] that, in the presence of excess of periodate, malonic acid consumed 3 mol. of oxidant and gave 2 mol. of carbon dioxide led to the suggestion [4] that periodate could hydroxylate active methylene groups, thereby permitting further glycol cleavage. Although numerous reactions in this class have been reported,[4-6] little appears to be known of the mechanism. In seeking further experimental data we investigated the action of periodate on the monohalogenoacetaldehydes.

Although numerous methods are available for the synthesis of chloro- [7] and bromo-acetaldehyde [8] the iodo-analogue [9] is less accessible. A new and convenient method for the preparation of all three compounds was developed in the present work. The halogenoacetaldehyde was generated in the reaction solution by treating the appropriate 1,4-dihalogeno-derivative of DL-butane-2,3-diol (1,4-dideoxy-1,4-dihalogeno-DL-threitol) with periodate. Hatch and Alexander [10] recorded a preparation of chloroacetaldehyde by treatment of 3-chloropropane-1,2-diol with periodate. The dihalogeno-compounds rapidly consumed 1 mol. of oxidant with the release of 2 mol. of the halogenoacetaldehyde. After equimolar amounts of periodate and dihalogeno-compound had reacted, the halogenoacetaldehyde formed could be isolated and characterised as its 2,4-dinitrophenylhydrazone. By using an excess of periodate, the reaction of the halogenoacetaldehyde with the oxidant could be studied. A particular value of the method is that the 1,4-dihalogeno-DL-butane-2,3-diols, which are stable crystalline compounds, may be conveniently stored as precursors of the halogenoacetaldehydes. The 1,4-dihalogeno-compounds may be obtained by the following route. Commercial but-2-ene-1,4-diol was shown to be predominantly *cis* when acidic hydrolysis of the crystalline epoxide obtained on treatment with perbenzoic acid yielded DL-threitol characterised as a di-*O*-benzylidene derivative; the epoxide was therefore 2,3-anhydroerythritol. Addition of bromine to *cis*-but-2-ene-1,4-diol readily yielded

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[1] Bobbitt, *Adv. Carbohydrate Chem.*, 1956, **11**, 1.

[2] Greville and Northcote, *J.*, 1952, 1945.

[3] Foster, Stacey, and Stephens, *J.*, 1959, 2681.

[4] Huebner, Ames, and Bubl, *J. Amer. Chem. Soc.*, 1946, **68**, 1621; Sprinson and Chargaff, *J. Biol. Chem.*, 1946, **164**, 433.

[5] Schwarz and MacDougall, *J.*, 1956, 3065.

[6] Wolfrom and Bobbitt, *J. Amer. Chem. Soc.*, 1956, **78**, 2489 and references cited therein.

[7] Fritsch and Schumacher, *Annalen*, 1894, **279**, 301; Glinsky, *Z. angew. Chem.*, 1867, 678; Reisse, *Annalen*, 1890, **257**, 331; Ohta and Imamura, *Reports Govt. Chem. Ind. Res. Inst., Tokyo*, 1953, **48**, 311 (*Chem. Abs.*, 1955, **49**, 15,730); Malinovskiĭ, *J. Gen. Chem.* (*U.S.S.R.*), 1939, **9**, 832 (*Chem. Abs.*, 1940, **34**, 375); Crane, Forrest, Stephenson, and Waters, *J.*, 1946, 827; Guinot and Tabuteau, *Compt. rend.*, 1950, **231**, 234; Shchukina, *Zhur. obshchei Khim.*, 1948, **18**, 1653 (*Chem. Abs.*, 1949, **43**, 2575); Weygand, Eberhardt, Linden, Schäffer, and Eigen, *Angew. Chem.*, 1953, **65**, 525.

[8] Mauguin, *Compt. rend.*, 1908, **147**, 748; *Ann. Chim.* (*France*), 1911, **22**, 364; Fischer and Landsteiner, *Ber.*, 1892, **25**, 2549; Hibbert and Hallonquist, *Canad. J. Res.*, 1931, **5**, 428; Stepanow, Preobrashenski, and Schtschukina, *Ber.*, 1926, **59**, 2533; Yanovskaya and Terent'ev, *Zhur. obshchei Khim.*, 1952, **22**, 1598 (*Chem. Abs.*, 1953, **47**, 9258).

[9] Chautard, *Ann. Chim. Phys.*, 1839, **16**, 145; Glinsky, *Z. angew. Chem.*, 1868, 618.

[10] Hatch and Alexander, *J. Amer. Chem. Soc.*, 1945, **67**, 688.

a *threo*-2,3-dibromide which was converted into 1,2:3,4-dianhydro-DL-threitol (DL-*threo*-1,2:3,4-diepoxybutane) by treatment with sodium hydroxide. When the diepoxide was treated with hydriodic acid in aqueous tetrahydrofuran at —10°, 1,4-dideoxy-1,4-di-iodo-DL-threitol was obtained in high yield. By using the appropriate acid the 1,4-dibromo- and 1,4-dichloro-analogues were also easily prepared in satisfactory yield. The location of the halogen atoms on the terminal positions in these compounds would be expected by analogy with reactions of related compounds;[11] it was proved by their rapid consumption of 1 mol. of periodate with the formation of halogenoacetaldehyde.

Previous work[3] has shown that alkyl iodides react with periodate according to reaction (1). Similar reactions with iodoacetaldehyde [reaction (2) starting from 1,4-di-deoxy-1,4-di-iodo-DL-threitol] would require 9 mol. of oxidant with the liberation of 4 mol. acid and 1 mol. of formaldehyde. In the presence of excess of periodate the di-iodo-compound rapidly consumed 1 mol. of oxidant and thereafter uptake of periodate was slow. The time of half-oxidation of iodoacetaldehyde was 140 hr. [*i.e.*, after consumption of 5 mol. oxidant on the assumption that equation (2) operates]. After 2016 hr. 10·66 mol. of oxidant had been consumed; from a plot of the results, the latter part of the curve indicated a very slow oxidation, and extrapolation to zero time gave an uptake of *ca.* 9 mol. of oxidant for the principal reaction pathway. However, formaldehyde could not be detected during the reaction and only 25% of the acidity predicted by reaction (2) developed. Loss of formaldehyde by oxidation is unlikely, since it is known[3] to survive long periods in conditions represented by reaction (4). Formaldehyde would not be an expected product if hydroxylation occurred [reaction (3)] but in this case the required consumption of oxidant (11 mol.) and liberation of acid (6 ml.) are much greater than the observed values.

$$\mathrm{R{\cdot}CH_2I + 3IO_4^- \longrightarrow R{\cdot}CH_2{\cdot}OH + 4IO_3^- + H^+} \quad . \; . \; . \; . \; . \; . \; . \quad (1)$$

$$\mathrm{[CH(OH){\cdot}CH_2I]_2 \xrightarrow{IO_4^-} 2CHO{\cdot}CH_2I \xrightarrow{6IO_4^-} 2CHO{\cdot}CH_2{\cdot}OH + 2H^+}$$
$$\mathrm{\xrightarrow{2IO_4^-} 2H{\cdot}CO_2H + 2H{\cdot}CHO} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (2)$$

$$\mathrm{[CH(OH){\cdot}CH_2I]_2 \xrightarrow{IO_4^-} 2CHO{\cdot}CH_2I \xrightarrow{2IO_4^-} 2[CHO{\cdot}CHI{\cdot}OH]}$$
$$\mathrm{\longrightarrow 2CHO{\cdot}CHO + 2HI \xrightarrow{8IO_4^-} 4H{\cdot}CO_2H + 2H^+ + 2IO_3^-} \quad . \quad (3)$$

$$\mathrm{R{\cdot}CH(OH){\cdot}CH_2I \xrightarrow{4IO_4^-} R{\cdot}CHO + H{\cdot}CHO + IO_3^- + H^+} \quad . \; . \; . \; . \quad (4)$$

The results obtained with bromo- and chloro-acetaldehyde do not clarify the situation. Thus, after 2016 hr. bromoacetaldehyde had consumed 0·7 mol. of oxidant and liberated 0·43 mol. of acid, and chloroacetaldehyde had consumed 0·59 mol. of oxidant and liberated 0·375 mol. of acid. In view of the extreme slowness of these reactions they were not followed to completion. It may be noted also that, whilst ethyl bromoacetate reacted with periodate with the liberation of bromine, alkyl bromides such as 1,2-dibromoethane and 6-bromo-6-deoxy-1,3:2,4-di-*O*-ethylidene-D-glucitol[3] did not react. Although the precise mechanism of the periodate–halogenoacetaldehyde reaction cannot be deduced from the preceding results, it appears not to involve hydroxylation of the methylene group.

In their detailed study of the reaction with periodate of compounds containing active methylene groups, Huebner, Ames, and Bubl[4] observed that, although a wide range of compounds reacted, there were certain notable exceptions, *e.g.*, diethyl malonate, ethyl acetoacetate and cyanoacetic acid. Acetylacetone was also reported[4] to be resistant to periodate but Wolfrom and Bobbitt[6] found it to be slowly oxidised, as were also 1-phenyl-butane-1,3-dione and 1,3-diphenylpropane-1,3-dione.

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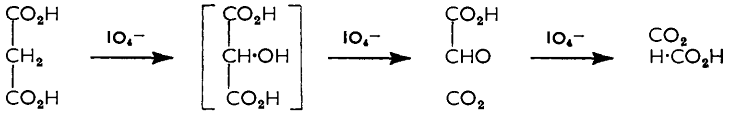
[11] Foster and Overend, *J.*, 1951, 1132; Wiggins and Wood, *J.*, 1950, 1566.

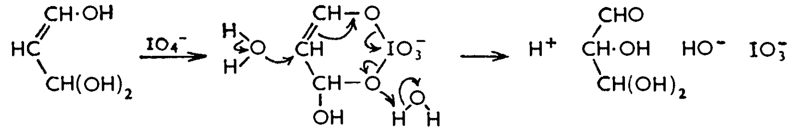
In the presence of excess of periodate, malonic acid was considered[4] to react by the following route:



By comparison of the rate of the overall oxidation with those of tartronic and glyoxylic acid, intermediates in the above sequence, it was inferred that the hydroxylation stage was rate-determining. An initial hydroxylation stage is also strongly indicated in the periodate oxidation of benzyloxymalondialdehyde[5] and cyclohexane-1,3-dione.[6]

From the results of Huebner *et al.*,[4] the influence of R in compounds of the type $R\cdot CH_2\cdot CO_2H$ in promoting attack by periodate follows the sequence $CO_2H > Ac > CO_2Et > CN \gtrsim 0$. Relative activating influences have been determined in other ways. Thus by studying the coupling reaction of *p*-nitrobenzenediazonium fluoroborate with compounds containing active methylene groups Hünig and Boes[12] obtained, *inter alia*, the sequence $Ac > CN > CO_2Et > CO_2H$ for the relative activating abilities of the respective groups. From the ionisation constants of acids[13] $R\cdot CH_2\cdot CO_2H$ the sequence $CN > CO_2H > CO_2Et > Ac$ is obtained, which reflects the ability of these groups to enhance the ionisation of the respective acids. Neither of the last two sequences shows any notable relation to the first, which suggests that a different mechanism operates in each case.

That ethyl acetoacetate, cyanoacetic acid and diethyl malonate are unaffected by periodate whereas acetoacetic acid, ethyl hydrogen malonate, and malonic acid undergo hydroxylation may be explained if this is assumed to require formation of a cyclic intermediate. With malondialdehyde as an example, hydroxylation could result from the breakdown of the six-membered cyclic complex (II) formed between periodate and the hydrated enol form (I) of the dialdehyde, to yield tartronic aldehyde (III) which may react further with periodate by normal glycol cleavage. The reaction sequence (I ⟶ II ⟶ III) involves the IO_4^- ion but it is possible that reaction may proceed through hydrated forms of the ion.[14,15] In general, the presence of an active methylene group will not be the sole factor which determines the occurrence of oxidation. Instead, the structural requirements for complex formation, and hence oxidation, will be the presence on 1,3-carbon atoms of hydroxyl groups, one of which must be provided by enolisation. It will be shown later that reaction will proceed if the non-enolic hydroxyl group is replaced by an amino-group. Thus in the compounds noted which contain an active methylene group but do not react with periodate, enolisation is possible but a cyclic complex cannot be formed. The postulated reaction sequence may be used to explain other observations; thus, the initial product (IV) of the reaction of 2-(1,4-anhydro-D-*xylo*-2,3,4,5-tetrahydroxybutyl)benzimidazole which reacts[4] further with periodate may do so through a complex of the type (V) in which an NH group is involved in complex formation. In a study of the reaction of cyclohexane-1,3-dione with periodate Wolfrom and Bobbitt[6] concluded that the annexed reaction sequence occurred. Whilst the initial stage may be explained in



(I) (II) (III)

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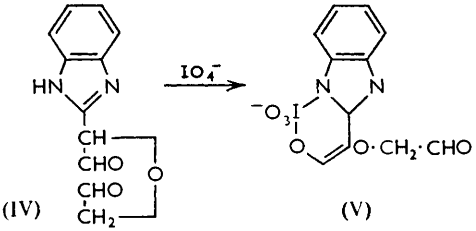
[12] Hünig and Boes, *Annalen*, 1953, **579**, 28.

[13] " Physikalisch–Chemische Tablellen," Springer, Berlin, 1936, Suppl. 3, Vol. III, pp. 2109 *et seq.*

[14] Crouthamel, Hayes, and Martin, *J. Amer. Chem. Soc.*, 1951, **73**, 82.

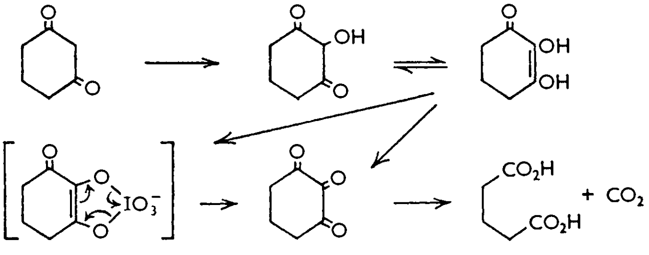
[15] Buist and Bunton, *J.*, 1954, 1406.

terms of the reaction sequence (I ⟶ II ⟶ III) the second stage may also be explained in terms of the formation and decomposition of an intermediate cyclic complex (VI).



(IV) (V)

The operation of the reaction mechanism as suggested in this paper implies that, for example, 3-hydroxybutyraldehyde (aldol), β-hydroxy- and β-amino-propionic acid ought to be oxidised by periodate. Reaction was in fact observed to occur slowly at pH 4—5 with aldol and at pH 2—2·5 with these acids; formaldehyde was produced from the acids. β-Propionolactone was not attacked by periodate. Failure to recognise these reactions before may have been due to their slowness, coupled with the possibility



(VI)

that reaction of substituted compounds of the type R·CH(OH)·CH(OR′)·CHO and R·CH(OH)·CH(OR′)·CO_2H, encountered in the periodate oxidation of carbohydrates, may be retarded (cf. Huebner *et al.*[4]) by the presence of OR′ and/or by involvement of the hydroxyl and aldehyde groups in internal hemiacetal formation with the appropriate functional groups in R.

The observation [3] that β-iodopropionic acid consumed 5—6 mols. of periodate with the release of formaldehyde and development of acidity may now be explained in terms of an initial reaction as shown in equation (1) followed by reaction of the type (I ⟶ II ⟶ III), yielding glyceric acid which undergoes [4] further glycol cleavage.

Wolfrom and Bobbitt [6] have shown that carbocyclic 1,3-diketones react much more rapidly with periodate than do the corresponding acyclic compounds, which implies that, in terms of the reaction mechanism suggested in this paper, cyclic-complex formation in these cases must be greatly facilitated.

The influence of stereochemical variations on the rate of oxidation of 1,2-diols [1,16] strongly indicates a path involving a 5-membered cyclic intermediate. Isolation of such a complex intact presents a problem since in general it will decompose rapidly to the products of oxidation. By analogy, the formation of a 6-membered cyclic complex from periodate and a 1,3-diol may be reasonably expected since the minimum O–O distances obtainable without deformation of bond angles in, for example, propane-1,2- and -1,3-diol are similar (2·49 and 2·51 Å respectively [17]). A 6-membered cylic complex of a simple 1,3-diol would not be expected to decompose. It is of interest that Barker and Shaw [18] have suggested

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[16] Brimacombe, Foster, Stacey, and Whiffen, *Tetrahedron*, 1958, **4**, 351; Wasserman in "Steric Effects in Organic Chemistry," Academic Press, New York, 1956; Schwarz, *J.*, 1957, 276.

[17] Barker, Bourne, and Whiffen, *J.*, 1952, 3865.

[18] Barker and Shaw, *Proc. Chem. Soc.*, 1957, **259**; *J.*, 1959, 584.

that a relatively stable terdentate complex may be formed between periodate and a 1,2,3-triol of suitable stereochemistry.

Buist and Bunton [15] found that when an excess of ethylene glycol was added to aqueous periodic acid at pH 2 or 5 there was an immediate drop in pH followed by slower changes. This would be expected if the periodate complex was a stronger acid than periodic acid itself. We have found that the addition of numerous 1,3-diols to aqueous periodic acid at pH of 1·86, 2·6, or 3·57 caused no detectable change in pH. However, significant pH changes resulted when 1,3-diols were added to aqueous sodium metaperiodate (pH 4—5). Surprisingly perhaps, butane-1,4-diol and *cis*-but-2-ene-1,4-diol also lowered the pH and in fact the latter diol effected the greatest change of all the diols examined and also slowly consumed oxidant. Pentane-1,5-diol and hexane-1,6-diol caused no pH change. It thus seems possible that periodate can form complexes with 1,3-diols.

EXPERIMENTAL

2,3-*Anhydroerythritol.*—To a solution [19] of perbenzoic acid in chloroform (330 ml.) at −5° *cis*-but-2-ene-1,4-diol (11·426 g., b. p. 100—102°/0·6—0·7 mm., n^{20} 1·4790) was added and the mixture stored at −5°. A crystalline precipitate slowly separated during 14 hr. and after 4 days the reaction was complete as shown by determination of unchanged perbenzoic acid.[19] The precipitate was collected, washed with chloroform (3 × 100 ml.), and dried *in vacuo*, yielding 2,3-*anhydroerythritol* (8·86 g., 66%), m. p. 54·5—56°. Recrystallisation from acetone–ether at −15° afforded hygroscopic crystals, m. p. 57·5—58·5° (Found: C, 46·3; H, 7·7. $C_4H_8O_3$ requires C, 46·2; H, 7·7%).

2,3-Anhydroerythritol reacted slowly, if at all, with bromine water. The consumption of oxidant in a solution (100 ml.) of the anhydro-compound (0·684 mmol.) in 0·0625M-sodium metaperiodate was as follows:

Time (min.)	44	125	356	1276
Consumption of periodiate (mol.)	0·124	0·185	0·215	0·365

Hydrolysis of 2,3-*Anhydroerythritol.*—A solution of the anhydro-compound (2 g.) in 0·1N-sulphuric acid (8 ml.) was boiled under reflux for 1 hr. and then neutralised with barium carbonate. After removal of insoluble inorganic material the filtrate was evaporated to yield a syrup (2·3 g., 98%) which was dissolved in ethanol and treated with charcoal. DL-Threitol was obtained which, after recrystallisation from ethanol, had m. p. 59—64°; Griner [20] records m. p. 72°.

The product (0·684 mmol.) rapidly consumed 3·02 mol. of 0·0625M-sodium metaperiodate.

The product (0·96 g.), by the methods of Hockett [21] and Lucas and Baumgarten,[22] gave a di-*O*-benzylidene derivative (1·92 g., 81%), m. p. 221—223° after three recrystallisations from benzene (Found: C, 72·6; H, 6·3. Calc. for $C_{18}H_{18}O_4$: C, 72·5; H, 6·0%). Hockett [21] gives m. p. 220—222° for di-*O*-benzylidene-D-threitol; Lucas and Baumgarten [22] give m. p. 221—223° for the L-isomer. Di-*O*-benzylidene-erythritol is reported [22] to have m. p. 201°.

1,2:3,4-*Dianhydro*-DL-*threitol.*—A mixture of *cis*-but-2-ene-1,4-diol (158 ml.) and ether (300 ml.) was shaken whilst bromine was cautiously added (cf. Prevost [23]). The olefin dissolved gradually. After 1 hr. a slight excess of bromine had been added and the mixture was stored overnight at room temperature, then washed with aqueous sodium thiosulphate and water. Evaporation of the dried ($MgSO_4$) ethereal solution yielded a syrup (443 g., 80%), presumably 2,3-dibromo-2,3-dideoxy-DL-threitol.

The dibromo-compound (55 g.) in dry ether (100 ml.) was treated with potassium hydroxide (30 g.) previously powdered under ether (cf. Prevost,[23] Griner,[20] and Przybytek [24]). After

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[19] Braun, *Org. Synth.*, Coll. Vol. I, 1932, p. 431.

[20] Griner, *Compt. rend.*, 1893, **117**, 554; cf. Thiele, *Annalen*, 1899, **308**, 341.

[21] Hockett, *J. Amer. Chem. Soc.*, 1935, **57**, 2260.

[22] Lucas and Baumgarten, *ibid.*, 1941, **63**, 1653.

[23] Prevost, *Compt. rend.*, 1926, **183**, 1292.

[24] Przybytek, *Ber.*, 1884, **17**, 1091.

30 min. the mixture was boiled under reflux for a further 30 min., then filtered and concentrated. Distillation of the residue gave 1,2:3,4-dianhydro-DL-threitol (5 g., 26%), b. p. 62°/29 mm., 142°/~760 mm., n^{20} 1·4365; Przybytek[24] gives b. p. 138°/767 mm., n^{20} 1·4400.

Action of Hydrogen Halides on 1,2:3,4-*Dianhydro*-DL-*threitol*.—The following general procedure was adopted.[3,25] The diepoxide (*ca.*, 2 g.) in tetrahydrofuran (100 ml.) at −15° was treated with a slight excess of 56% hydriodic acid, 45·5% hydrobromic acid, or 10N-hydrochloric acid at such a rate that the temperature did not exceed 0°. After storage at −5° for *ca.* 40 hr. solid sodium thiosulphate and potassium carbonate were added to remove free iodine and excess of acid. Sufficient water was then added to form two phases. The organic layer was separated, combined with two ether-extracts of the aqueous layer, dried ($MgSO_4$), and evaporated. The following compounds were thus obtained.

(i) 1,4-*Dideoxy*-1,4-*di-iodo*-DL-*threitol* (79%), m. p. 96—97° after recrystallisation from benzene (Found: C, 14·4; H, 2·2; I, 74·1. $C_4H_8O_2I_2$ requires C, 14·0; H, 2·3; I, 74·4%). Nesmayanov and Lutsenko[26] report m. p. 109° for a 1,4-di-iodobutane-2,3-diol formed by reaction of iodine with the 1,4-bischloromercuributane-2,3-diol (obtained by the treatment of butadiene sequentially with mercuric acetate, potassium chloride, and sodium hydroxide).

The di-iodo-compound (0·51 g.) in dry pyridine (7 ml.) was treated with toluene-*p*-sulphonyl chloride (1·71 g.) in pyridine (3 ml.) for 6 hr. at room temperature. Longer reaction times decreased the yield. The mixture was diluted with sodium hydrogen carbonate solution, then acidified with dilute hydrochloric acid and extracted several times with chloroform. The combined extracts were washed successively with dilute hydrochloric acid and sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated. Recrystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave 1,4-*dideoxy*-1,4-*di-iodo*-2,3-*di*-O-*toluene*-p-*sulphonyl*-DL-*threitol* (0·24 g., 25%), m. p. 139—140° (Found: C, 33·0; H, 2·9; I, 39·0; S, 9·85. $C_{18}H_{20}O_6I_2S_2$ requires C, 33·2; H, 3·1; I, 39·1; S, 9·8%).

(ii) 1,4-Dibromo-1,4-dideoxy-DL-threitol (87%), m. p. 79—81° after recrystallisation from benzene (Found: C, 19·2; H, 3·4; Br, 64·4. Calc. for $C_4H_8O_2Br_2$: C, 19·4; H, 3·2; Br, 64·5%). Griner[20] gives m. p. 83° for the compound prepared by hydroxylation of 1,4-dibromobut-2-ene with permanganate.

(iii) 1,4-Dichloro-1,4-dideoxy-DL-threitol (87%), m. p. 72—73° (from benzene) (Found: C, 30·4; H, 5·0; Cl, 44·9. $C_4H_8O_2Cl_2$ requires C, 30·2; H, 5·1; Cl, 44·7%). Schalit[27] gives m. p. 126—126·5° for the *erythro*-compound obtained by the action of fuming hydrochloric acid at 100° on erythritol. Kilmer *et al.*[28] give m. p. 62—63° for the product, presumably the *threo*-compound, obtained by hydroxylation of 1,4-dichlorobut-2-ene with permanganate.

Action of Periodate on the 1,4-*Dideoxy*-1,4-*dihalogeno-derivatives of* DL-*Threitol*.—(*a*) 1,4-Dideoxy-1,4-di-iodo-DL-threitol (0·47 g.) was added to 0·25M-sodium metaperiodate (6 ml.). The iodo-compound, which is sparingly soluble in water, dissolved within 2 min., and after 5 min. the solution was extracted ten times with ether. The combined and dried ($MgSO_4$) extracts were concentrated (removal of all the solvent caused decomposition of the residue) and treated with an excess (*ca.* 200 ml.) of an acidified (HCl) saturated solution of 2,4-dinitrophenylhydrazine in ethanol. There was an immediate precipitate (0·35 g., 37%) of, presumably, *iodoacetaldehyde* 2,4-*dinitrophenylhydrazone*, m. p. 147—148° (from ethanol) (Found: C, 28·7; H, 2·25; N, 16·5. $C_8H_7O_4N_4I$ requires C, 27·4; H, 2·0; N, 16·0%).

By the same procedure 1,4-dibromo-1,4-dideoxy-DL-threitol gave bromoacetaldehyde 2,4-dinitrophenylhydrazone, m. p. 155—156° (from ethanol) (Found: C, 32·0; H, 2·3; N, 18·6. Calc. for $C_8H_7O_4N_4Br$: C, 31·7; H, 2·3; N, 18·5%). Newbold[29] gives m. p. 155—157°; Heilbron *et al.*[30] give m. p. 150°.

Similarly 1,4-dichloro-1,4-dideoxy-DL-threitol gave chloroacetaldehyde 2,4-dinitrophenylhydrazone, m. p. 154—155° (from ethanol) (Found: C, 37·35; H, 3·0; N, 22·0. Calc. for $C_8H_7O_4N_4Cl$: C, 37·1; H, 2·7; N, 21·7%). Crane *et al.*[31] give m. p. 155°.

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[25] Lucas and Garner, *J. Amer. Chem. Soc.*, 1950, **72**, 2145.

[26] Nesmayanov and Lutsenko, *Bull. Acad. Sci. U.R.S.S. Classe Sci. chim.*, 1942, 366 (*Chem. Abs.*, 1945, **39**, 1637).

[27] Schalit, *Chem. Zentr.*, 1931, **102**, I, 2602.

[28] Kilmers, Armstrong, Brown, and du Vigneaud, *J. Biol. Chem.*, 1947, **145**, 495.

[29] Newbold, *J.*, 1950, 3346.

[30] Heilbron, Jones, and O'Sullivan, *J.*, 1946, 866.

[31] Crane, Forrest, Stephenson, and Waters, *J.*, 1946, 827.

The dichloro- and dibromo-DL-threitol derivatives were water-soluble and the derived halogenoacetaldehydes were much more stable than was the iodo-derivative. The 2,4-dinitrophenylhydrazones of chloro- and bromo-acetaldehyde were not formed readily. Heating to 80° for 10—15 min. accelerated the formation of chloroacetaldehyde 2,4-dinitrophenylhydrazone but resulted in replacement of bromine by chlorine in an attempt to prepare bromoacetaldehyde 2,4-dinitrophenylhydrazone. No depression of m. p. occurred with mixtures of chloro- and bromo-acetaldehyde 2,4-dinitrophenylhydrazones but their infrared spectra (potassium chloride discs) showed marked differences.

(*b*) Aqueous 0·075M-sodium metaperiodate solutions (100 ml.) severally containing 1,4-dichloro-1,4-dideoxy-DL-threitol (0·1088 g.), 1,4-dibromo-analogue (0·1696 g.), and 1,4-di-iodo-analogue (0·2342 g.) were stored at room temperature in the dark. The consumption of periodate was followed by essentially the method of Jackson [32] and was as shown in Table 1. Determination of formaldehyde by chromotropic acid [33] after 550 and 1375 hr. indicated that none had been formed. The hydrogen ion liberated after 1350 hr. was as follows: di-iodo-compound 1·09, di-bromo-compound 0·85, dichloro-compound 0·75 g.-ion per mole.

TABLE 1. *Consumption of periodate by the* 1,4-*dideoxy*-1,4-*dihalogeno*-DL-*threitols.*

Time (hr.)	3	17	45	72	142	196	305	545	838	1349	2016
Consumption of periodate (mol.):											
di-iodo-	1·8	2·19	2·91	3·80	5·22	5·92	6·84	8·44	9·26	9·97	10·66
dibromo ...	1·11	1·17	—	1·24	1·33	1·35	1·37	1·70	1·89	2·03	2·41
dichloro ...	1·04	1·08	1·10	1·14	1·17	1·19	1·25	1·46	1·58	1·70	2·18

Miscellaneous Periodate Oxidations.—Aqueous 0·0625M-sodium metaperiodate solutions (100 ml.) severally containing sodium β-hydroxypropionate [prepared by titration of β-propionolactone (0·05 g.) with 4N-sodium hydroxide] and β-aminopropionic acid (0·0626 g.) were prepared; the pH of the solutions were 5·7 and 5·1. Duplicate solutions were also prepared of which the pH was adjusted to 2·0—2·5. All the solutions were stored at 33° in the dark. Periodate was not consumed in the solutions at *ca.* pH 5 and was as follows in the solutions at pH 2·0—2·5:

Time (days)	Consumption of periodate (mol.)		Formaldehyde liberation (mol.)	
	A	*B*	*A*	*B*
3·15	—	0·04	—	0·02
10·15	0·02	0·12	0·006	0·03
75·0	0·25	0·76	—	—

A, β-Aminopropionic acid; *B*, β-hydroxypropionic acid.

Schwarz and MacDougall [5] have found that the determination of periodate, in the presence of benzyloxymalondialdehyde and related compounds, by titration with arsenite of the iodine liberated after addition of sodium hydrogen carbonate and iodide, gives unreliable results. Anomalous results were not encountered with Jackson's method [32] in its applications in this paper.

In a separate experiment a solution of aldol (1·4 mmoles) in 0·0625M-sodium metaperiodate was set aside at room temperature; the solution had pH 4—5. The consumption of oxidant was as follows: [32]

Time (days)	2	4	7
Consumption of periodate (mol.)	0·07	0·10	0·13

Influence of Certain 1,3-, 1,4-, 1,5-, *and* 1,6-*Diols on the* pH *of Aqueous Periodic Acid.*—Most of the diols listed in the Table were obtained by purification of commercial samples. In the case of propane-1,3-diol and butane-1,3-diol the samples were contaminated with appreciable amounts of impurities which consumed periodate. The diols were purified by dissolution in

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[32] Jackson, *Organic Reactions*, 1944, **2**, 341.
[33] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.

water and treatment with a calculated excess of sodium metaperiodate for 30 min. at room temperature. After one extraction with benzene, the aqueous solution was continuously extracted with ether for 48 hr., the ether extract concentrated, and the residue distilled. The initial sample of propane-1,3-diol also contained a water-insoluble impurity which was removed by a single ether-extraction of the aqueous solution before the periodate oxidation stage. Pentane-2,4-diol, which presumably contains a mixture of DL- and *meso*-forms, was obtained by hydrogenation of acetylacetone and contained a trace of carbonyl compound as shown by the weak absorption at 1700 cm.$^{-1}$. The cyclohexane-1,3-diols were gifts from Dr. W. Rigby of Birkbeck College. The physical constants recorded in the Table are in reasonable agreement with values in the literature. With one exception, the purified diols did not react with periodate or contain acidic products; a 0·02713M-solution of *cis*-but-2-ene-1,4-diol in 0·06132M-sodium metaperiodate at 39° showed the following oxidant consumption: 48 hr. 0·083 mol., 120 hr. 0·253 mol., 502 hr. 0·65 mol.

The pH changes were measured as follows: separate aqueous solutions *A* and *B*, of 0·0255M-sodium metaperiodate which were also respectively *ca.* 0·025M and *ca.* 0·1M with respect to diol, were prepared and stored in the dark at room temperature for 48 hr. The pH of the solutions was then determined by using an E.I.L. direct reading pH meter (Model 23A) calibrated against potassium hydrogen phthalate (pH 4). The arithmetical difference between the pH's of solution *A* and *B* and 0·0255M-sodium metaperiodate are expressed respectively as ΔpH (*A*) and ΔpH (*B*), and are recorded in Table 2. The values represent the average of several determinations. A negative value of ΔpH indicates a depression of the pH.

TABLE 2. *Physical constants and* ΔpH *values for some diols.*

	B. p./mm.[a] or m. p.	n^{20}	ΔpH (*A*)	ΔpH (*B*)
Propane-1,3-diol	72—74°/0·15	1·4388	−0·22	−0·49
Butane-1,3-diol	85—86°/1	1·4395	−0·06	−0·14
Pentane-2,4-diol	76—77°/0·7—0·8	1·4339	−0·57	−0·89
2,2-Dimethylpropane-1,3-diol	129—131°	—	−0·04	−0·04
Pentaerythritol	255—257°	—	−0·23	−0·36
Butane-1,4-diol	91—92°/0·4—0·5	1·4459	−0·10	−0·27
cis-But-2-ene-1,4-diol	96—99°/0·4—0·6	1·4771	−0·92[b]	−1·92
Pentane-1,5-diol	100°/0·3—0·4	1·4510	−0·00	+0·02
Hexane-1,6-diol		—	−0·02	−0·04
Cyclohexane-*cis*-1,3-diol	86°	—	−0·04	+0·08
Cyclohexane-*trans*-1,3-diol	117°	—	−0·06	−0·05

[a] Vapour temperature given. [b] Determined after 5 min.

The pH's of aqueous periodic acid solutions 0·025M (pH 1·86), 0·0025M (pH 2·61), and 0·00025M (pH 3·57) were not significantly changed when the solutions were also *ca.* 0·025M and *ca.* 0·1M with respect to pentaerythritol. There was also no significant effect in 0·00025M-periodic acid solutions which were also *ca.* 0·025M with respect to, 2,2-dimethylpropane-1,3-diol, butane-1,3-diol, butane-1,4-diol, *cis*-but-2-ene-1,4-diol, propane-1,3-diol, and pentane-1,5-diol.

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