Organic Chemistry of Periodates

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1 Introduction

Malaprade's observation[1] that mannitol is destroyed by periodic acid, and Fleury's closer definition of the reaction as a specific oxidative fission of 1,2-diols,[2] launched periodic acid and its salts on a distinguished career among the oxidising agents of organic chemistry. Closely related fissions of α-ketols, α-diketones, and α-amino-alcohols having been discovered in the 1930's, the reagent became an indispensable tool for the structure determination of the most varied natural products, particularly the carbohydrates and more recently the nucleic acids.

The reviews by Jackson[3] and by Bobbitt[4] fully describe these developments, while more recent applications in the carbohydrate and nucleic acid fields will be found in standard works.[5,6] Malangeau's review[7] is limited in scope and is inaccessible. The well-established theory and practice of oxidation with periodates, particularly in carbohydrate chemistry, is described in practical manuals.[8] Only a brief outline, including recent innovations will be attempted here.

In the last decade, the organic chemistry of periodate has grown mainly in two directions. The classical glycol cleavage has been studied in detail and a consistent picture of its mechanism is emerging. This has shed light on the oxidation of simple sugars where detailed re-examination of the reactions has revealed some of the intermediates.

On the other hand, several new well-defined reactions have come to light which extend the use of the reagent in organic chemistry. This Review is devoted principally to these two aspects.

The term 'oxidation' will refer to reaction with periodic acid or its salts unless otherwise qualified.

[1] L. Malaprade, *Bull. Soc. chim. France*, 1928, 683.
[2] P. Fleury and J. Lange, *Compt. rend.*, 1932, **195**, 1395.
[3] E. L. Jackson, *Org. Reactions*, 1944, **2**, 341.
[4] J. M. Bobbitt, *Adv. Carbohydrate Chem.*, 1956, **11**, 1.
[5] W. Pigman (ed.) 'The Carbohydrates', Academic Press, Ohio, 1956; E. Percival, 'Structural Carbohydrate Chemistry', J. Garnett-Miller, London, 1962.
[6] A. M. Michelson, 'Chemistry of the Nucleosides and Nucleotides', Academic Press, London, 1963; see also P. R. Whitfield, *Biochim. Biophys. Acta*, 1965, **108**, 202, and references therein.
[7] P. Malangeau, *Mises au Point de la Chimie Analytique pure et appliqueé et de l'Analyse bromatologique*, 1961, **9**, 81.
[8] (*a*) G. F. Smith, 'Analytical Applications of Periodic Acid and Iodic Acid', G. F. Smith Chemical Co., Ohio, 1950; (*b*) J. R. Dyer, *Methods Biochem. Analysis*, 1956, **3**, 111; (*c*) R. D. Guthrie, 'Methods in Carbohydrate Chemistry', ed. R. L. Whistler and M. L. Wolfrom, Academic Press, London, 1962, p. 432 *et seq.*

Methods.—Periodate oxidation lends itself particularly to analytical experiments which are often followed by preparative oxidations. Periodic acid and its sodium and potassium salts are the usual reagents.

In analytical experiments, mixtures containing excess of 0·1—0·01M-periodate are allowed to react at room temperature or below, along with a blank, and for long reaction times should be kept in the dark. The photochemistry of periodate solutions, which slowly form ozone in daylight, has been studied.[4,8b]

Organic solvents can be added but may retard some reactions.[9] Tetraethylammonium periodate, which is highly soluble in water and considerably soluble also in several organic solvents including chloroform, may be of value in overcoming solubility problems.[10] The choice of pH depends on the reductant.[4,8b]

The reaction is usually followed by estimation of the remaining periodate in aliquot portions withdrawn at intervals from the mixture and the blank. The various iodometric titrations are described in the above reviews.[8] Methods will also be found there for the estimation of small-molecular oxidation products such as formaldehyde, formic acid, carbon dioxide, and ammonia.

The elegant methods of polarography[11] have been extended to periodate reactions, and in favourable cases[11a] permit simultaneous estimation of organic products. Periodate can also be estimated by its absorption at 223 mμ[8c] or, in more concentrated solution, at 260 mμ.[12]

When oxidations are carried out on a preparative scale,[8b] it may be necessary to remove periodate and iodate ions by precipitation or by ion-exchange, if the organic products cannot be extracted. Excess of reagent is sometimes destroyed by adding ethylene glycol or pinacol, etc.

Several simple compounds frequently used as solvents or appearing as oxidation products are hardly attacked by periodate in the dark though more appreciably in sunlight.[13] They include methanol, ethanol, and their derived aldehydes and acids.

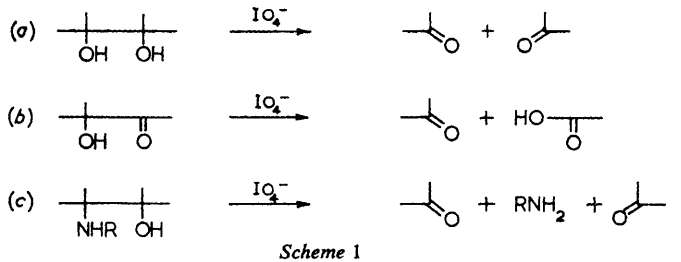
The limited solubility of the commonly used periodates, their high molecular weight, and the frequent appearance of iodine are the principal drawbacks to their preparative use.

2 Glycol Fission and Related Reactions

Introduction.—The oxidative cleavage of vicinal diols is the classical and most widely used reaction of periodate. Oxidation is fast at room temperature except for heavily substituted diols, aldehydes and ketones being formed (*a*; Scheme 1). Analogous cleavage occurs more slowly with α-hydroxy-carbonyl[2,14] and α-dicarbonyl compounds,[14] in which the carbonyl groups appear as carboxyl

[9] R. D. Guthrie, *Chem. and Ind.*, 1960, 691.
[10] A. K. Qureshi and B. Sklarz, *J. Chem. Soc.* (*C*), 1966, 412.
[11] (*a*) P. Zuman and J. Krupicka, *Coll. Czech. Chem. Comm.*, 1958, **23**, 598; (*b*) P. Zuman, 'Organic Polarography', Pergamon, Oxford, 1964.
[12] J. S. Dixon and D. Lipkin, *Analyt. Chem.*, 1954, **26**, 1092.
[13] F. S. H. Head and G. Hughes, *J. Chem. Soc.*, 1952, 2046.
[14] P. W. Clutterbuck and F. Reuter, *J. Chem. Soc.*, 1935, 1467.

functions in the products (*b*). α-Hydroxy- and α-keto-acids are oxidised rather slowly,[15,16] with some exceptions such as glycollic and glyoxylic acids.[15]



Scheme 1

α-Amino-alcohols and α-diamines are likewise oxidised to carbonyl fragments (*c*), unless one of the amino-groups is tertiary or acylated.[17,18] These points are discussed in detail later (p. 13).

All these reactions are two-electron oxidations, requiring one molecule of periodate, in which the iodine atom is reduced from the +7 to the +5 valency state with the formation of iodate ions.

Lead tetra-acetate has long been used as a glycol-cleaving reagent.[19] It is used in glacial acetic acid or in other organic solvents and oxidises also α-hydroxy- and α-keto-acids, and many other structures.[20] It is thus a useful complement to, rather than 'a serious competitor'[19a] of periodate. Iodosobenzene diacetate[21] resembles lead tetra-acetate as does sodium bismuthate,[22] which can be used also in aqueous acid solution. Chromium trioxide has been used for the cleavage of di-tertiary glycols,[23a] and the mechanism has been studied.[23b]

Mechanism.—A mechanism for the periodate oxidation of glycols suggested as early as 1933 by Criegee[24] involved the formation of a cyclic periodate complex, in analogy with lead tetra-acetate. Much subsequent work has borne out and amplified this idea. The evidence consists of direct observations on the complexes and, more extensively, of kinetic evidence.

The interaction of periodic acid with glycols in water has been observed spectrometrically by an increase in the absorbance of the periodate ion at

[15] D. B. Sprinson and E. Chagraff, *J. Biol. Chem.*, 1946, **164**, 433.
[16] J. E. Courtois and M. Guernet, *Ann. pharm. franc.*, 1958, **16**, 119.
[17] B. H. Nicolet and L. A. Shinn, *J. Amer. Chem. Soc.*, 1939, **61**, 1615.
[18] P. F. Fleury, J. E. Courtois, and M. Grandchamp, *Bull. Soc. chim. France*, 1949, 88.
[19] (*a*) R. Criegee, L. Kraft, and B. Rank, *Annalen*, 1933, **507**, 159; (*b*) A. S. Perlin, *Adv. Carbohydrate Chem.*, 1959, **14**, 9.
[20] R. Criegee, *Angew. Chem.*, 1958, **70**, 173.
[21] L. K. Dyall and K. H. Pausacker, *J. Chem. Soc.*, 1958, 3950 and refs. therein.
[22] W. Rigby, *J. Chem. Soc.*, 1950, 1907.
[23] (*a*) M. Uskovic, M. Gut, E. N. Trachtenberg, W. Klyne, and R. I. Dorfmann, *J. Amer. Chem. Soc.*, 1960, **82**, 4965; (*b*) J. Rocek and F. Westheimer, *J. Amer. Chem. Soc.*, 1962, **84**, 2241.
[24] R. Criegee, *Sitzungsberichte der Gesellschaft für die Beöfrderung der gesamten Wissenschaften, Marburg*, 1934, **69**, 25 (*Chem. Abs.*, 1935, **29**, 6820).

222·5 mμ,[25] while increased absorbance at 226 mμ in isopropyl alcohol also suggests some interaction.[26]

A fall in pH has been observed on addition of ethylene glycol,[27] other vicinal diols,[28] and certain 1,3-diols[29] to periodate solutions. Malaprade[30] had already observed this effect and deduced the formation of an 'addition compound', but as to its rôle in the mechanism of the oxidation, he could only speculate.

Investigating the periodate oxidation of some cyclic monosaccharide compounds and cycloalkane polyols, Barker and Shaw[31] found that several of these compounds rapidly took up one molecule of the reagent, which reappeared slowly after the titrations, while considerable amounts of substrate (ribose) were recovered. All these compounds had a 1,2,3-*cis*-triol system capable of existing in a favoured diaxial-monoequatorial conformation, from which a terdentate periodate ester (I) was thought to be formed. The other polyols took up periodate rapidly *with* oxidation.

The terdentate complex from 1,2-*O*-isopropylidene-α-D-glucofuranose has been studied by nuclear magnetic resonance (n.m.r.).[32] Its stability in alkaline solution is such that the monosaccharide is not oxidised. Probably the triesters cannot break down directly to oxidation products,[32,33] and any oxidation involves prior hydrolysis to the diester. Despite this stability the terdentate esters have not been isolated. The cyclic diesters are much less stable, and the principal evidence for their structure and function in glycol fission comes from kinetic studies.[34]

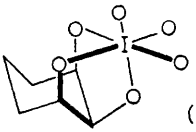
Early experiments had shown that the oxidation of ethylene glycol and of pinacol have different kinetic forms.[35] A two-stage reaction course (*d*) was later suggested[27,36] in which the glycol (G) reacts reversibly with periodate (P) to give an intermediate (X) which breaks down to the products. The rate constants

$$(d) \qquad G + P \underset{k_b}{\overset{k_a}{\rightleftharpoons}} X \xrightarrow{k} \text{products}$$

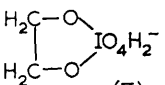
k_a, k_b, and k and the equilibrium constant K for formation of X have been evaluated for a series of simple glycols in an elegant set of studies by Bunton and his colleagues.

Taking the complex equilibria of ionisation and hydration of periodate[37] into account, they showed that the complex X undergoing breakdown must

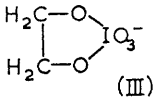
[25] G. J. Buist, C. A. Bunton, and J. H. Miles, *J. Chem. Soc.*, 1957, 4575.
[26] J. Kläning and M. C. R. Symons, *J. Chem. Soc.*, 1960, 977.
[27] G. J. Buist and C. A. Bunton, *J. Chem Soc.*, 1954, 1406.
[28] G. J. Buist, C. A. Bunton, and J. H. Miles, *J. Chem. Soc.*, 1957, 4567.
[29] J. L. Bose, A. B. Foster, and R. W. Stephens, *J. Chem. Soc.*, 1959, 3314.
[30] L. Malaprade, *Bull. Soc. chim. France*, 1934, 883.
[31] G. R. Barker and D. F. Shaw, *J. Chem. Soc.*, 1959, 584.
[32] A. S. Perlin and E. von Rudloff, *Canad, J. Chem.*, 1965, **43**, 2071.
[33] T. P. Nevell, *Chem. and Ind.*, 1959, 567.
[34] C. A. Bunton, *Ann. Reports*, 1959, **56**, 185.
[35] C. C. Price and H. Kroll, *J. Amer. Chem. Soc.*, 1938, **60**, 2726; C. C. Price and M. Knell, *ibid.*, 1942, **64**, 552.
[36] F. R. Duke and V. C. Bulgrin, *J. Amer. Chem. Soc.*, 1954, **76**, 3803.
[37] C. E. Crouthamel, A. M. Hayes, and D. S. Martin, *J. Amer. Chem. Soc.*, 1951, **73**, 82.



(I)



(II)



(III)

be a mono-anion written as (II) or its dehydrated form (III).[27] The complex is a stronger acid than periodic acid (cf. borate and tellurate complexes). The stability of X is subject to electronic and steric influences. K increased in going from ethane- through propane-1,2- to (-)-butane-2,3-diol, *i.e.*, with increasing methyl substitution, and consequent electron availability at oxygen, but the sharp drop in the equilibrium constant for *meso*-butane-2,3-diol is a steric effect.[28] A model (Fig. 1) based on atomic dimensions was suggested, in which methyl groups interfere sterically with the octahedral periodate oxygen atoms when placed at the hindered positions H,H′ but not at the free positions F,F′.

The rate of formation k_a was determined spectrometrically for some diols of the series and decreased with increasing substitution for steric reasons. Under certain conditions, the initial esterification was relatively slow, followed by fast cyclisation.[25]

The rate of collapse of X was also estimated, and increased with methyl substitution, so that steric crowding is probably the dominant factor, although electronic effects (hyperconjugation) may also operate.[28]

The importance of this work lay in the separate evaluation of the various constants for the two reactions steps. With the help of these, the difference in over-all kinetics between ethylene glycol and pinacol could be explained. In the former and other lightly substituted diols, K is large, *i.e.*, the intermediate accumulates, and its collapse (k) is rate-determining. The rate of oxidation is greatest near neutrality when the concentration of mono-anion is maximal, but decreases at higher pH where the stable dianion is formed but cannot break down.

For hindered diols such as pinacol, K is small and formation of the complex appears to be rate-determining (k_a), leading to overall second-order kinetics. The influence of pH is also more complex, and earlier reports are in conflict.[35,38] According to a detailed study by Bunton and his colleagues the oxidation of pinacol is subject to general acid–base catalysis of the ring-closing step[39] ammonia being a good catalyst.[40]

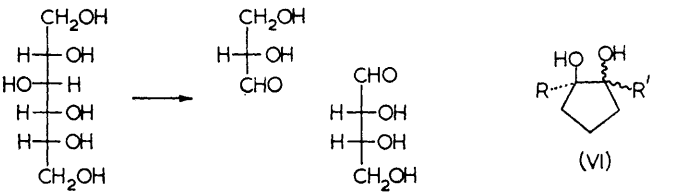
2-Methylbutane-2,3-diol lies on the mechanistic borderline with kinetics which depart from first order between pH 4 and 5, and can be interpreted *only* in terms of an intermediate X.[41]

Acyclic *threo*-diols are very generally oxidised more quickly than the *erythro*-

[38] S. Senent and P. Escudero, *Anales real Soc. espaň. Fis. Quim.*, 1961, **57,B**, 153; *Chem. Abs.*, 1961, **55**, 21761.
[39] G. J. Buist, C. A. Bunton and J. Lornas, *J. Chem. Soc.* (*B*), 1966, 1094, 1099.
[40] C. A. Bunton and M. D. Carr, *J. Chem. Soc.*, 1963, 5854 (p. 5860).
[41] G. J. Buist and C. A. Bunton, *J. Chem. Soc.*, 1957, 4580.

isomer, and relative configurations have been assigned on this basis.[42] Polyols are likewise oxidised first at a *threo*-diol group, glucitol (V) for instance giving glyceraldehyde and D-erythrose when oxidised with limited amounts of periodate.[43] A more recent study has revealed the detailed sequence of oxidation of all the diol pairs in [^{14}C]glucitol [(3,4) > (2,3) > (4,5) > (5,6) > (1,2)].[44] A neat rationalisation of these results was possible in terms of the cyclic complex (IV).

Studies with cyclic 1,2-diols have further clarified the structure of the complex.[45a] *cis*- and *trans*-Cyclopentanediols (VI; R = R′ = H or CH_3) undergo second-order ('pinacol-type') oxidation which is faster for the *cis* compounds. The *trans*-diol (VI; R = R′ = CH_3) is not attacked at all owing to severe crowding in the complex.



cis-Cyclohexane-1,2-diols, are oxidised faster than the *trans*- (diequatorial) isomers and the *trans*-diaxial diol group is not oxidised.[46] In a detailed analysis of the 'ethylene glycol' kinetics of *cis*- and *trans*-cyclohexanediols, Bunton and

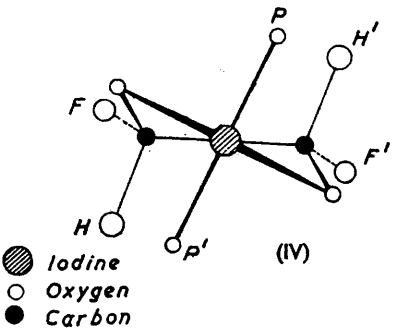


FIG. 1. *Model of the intermediate complex* (*two oxygen atoms omitted*). [Reproduced by permission from ref. 28]

[42] P. Zuman, J. Sicher, J. Krupicka, and M. Svoboda, *Coll. Czech. Chem. Comm.*, 1958, **23**, 1237.
[43] J. C. P. Schwartz, *J. Chem. Soc.*, 1957, 276; J. E. Courtois and M. Guernet, *Bull. Soc. chim. France*, 1957, 1388.
[44] D. H. Hutson and H. Weigel, *J. Chem. Soc.*, 1961, 1546.
[45] (*a*) V. C. Bulgrin and G. Dahlgren, *J. Amer. Chem. Soc.*, 1958, **80**, 3883; (*b*) C. A. Bunton and M. D. Carr, *J. Chem. Soc.*, 1963, 770.
[46] J. Honeyman and C. J. G. Shaw, *J. Chem. Soc.*, 1959, 2454.

his colleagues[47] showed that the *trans*-fused complex is actually *more* stable than the *cis*-fused, at least at pH 9, and that the higher overall oxidation rate of the *cis*-diol is due to the faster breakdown of the *cis*-fused complex (VIII). The flexibility of the five-membered ester ring is such that the *trans*-diequatorial junction with the cyclohexane ring is preferred (VII; Fig. 2). At the same time

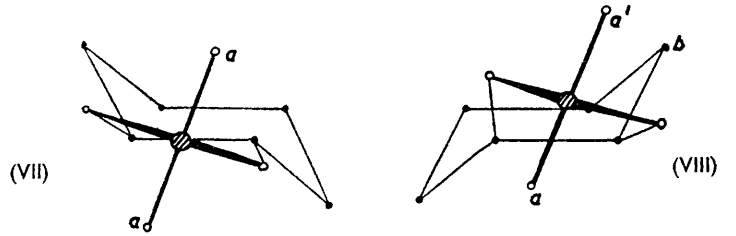


FIG. 2. (VII) *Intermediate complex of the* trans-*diol (equational conformation); bonds joining oxygen atoms 'a' to iodine are in the plane of the paper.*

(VIII) *Intermediate complex of the* cis-*diol; bonds joining oxygen atoms 'a', 'a'' to iodine are out of the plane of the paper, 'a'' being away from the observer.*

In both models, two of the oxygen atoms joined to iodine are omitted.

[Reproduced by permission from ref. 47]

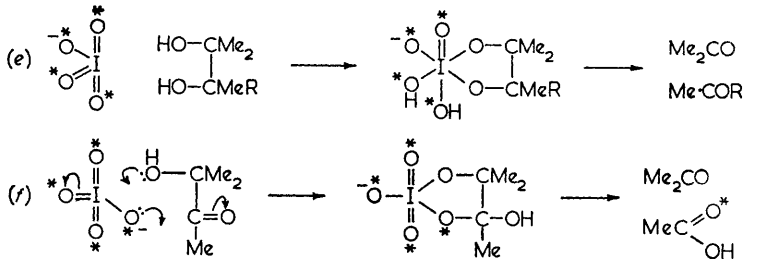
there is less non-bonding interaction between the periodate oxygen and ring-carbon atoms. Methyl groups increase these interactions and lead to second-order kinetics.[45b] α-Glucopyranose, with a *cis*-diol function at C(1)–C(2), is oxidised at this position appreciably more quickly than the β-anomer.[48]

Rigid *trans*-diaxial diols such as *trans*-decalin-9,10-diol,[49a] are not oxidised; a cyclic intermediate is clearly impossible. Ditertiary alcohols of this type are cleaved by lead tetra-acetate,[49b,50] an observation which among others prompted the suggestion by Levesley, Waters, and Wright[51] that monoesters undergo breakdown in glycol fission. This is certainly excluded for periodate since the monoester of an *erythro*-diol or of a *trans*-diaxial cyclic diol should then favour cleavage by *trans* elimination, which is contrary to observations.[52] The stereochemical requirements of lead tetra-acetate differ somewhat from those of periodate,[50] as seen in the differing initial action on sucrose.[53]

The oxidative cleavage of α-diketones has received relatively little attention. Shiner and Wasmuth[54] have shown that it is base-catalysed and of second-order, and have postulated a cyclic intermediate formed by nucleophilic attack of the various periodate anions on the carbonyl groups. The glycol-periodate esters arise from electrophilic attack on the diols.

[47] G. J. Buist, C. A. Bunton, and J. H. Miles, *J. Chem. Soc.*, 1959, 743.
[48] S. J. Angyal and J. E. Klavins, *Austral. J. Chem.*, 1961, **14**, 577.
[49] S. J. Angyal and R. J. Young, *J. Amer. Chem. Soc.*, 1959, **81**, (*a*) 5251; (*b*) 5467.
[50] R. Criegee, E. Höger, G. Huber, P. Kruck, F. Marktscheffel, and H. Schellenberger, *Annalen*, 1956, **599**, 81.
[51] P. Levesley, W. A. Waters, and A. N. Wright, *J. Chem. Soc.*, 1956, 840.
[52] K. B. Wiberg and K. A. Saegebarth, *J. Amer. Chem. Soc.*, 1957, **79**, 2822.
[53] A. K. Mitra and A. S. Perlin, *Canad. J. Chem.*, 1959, **37**, 2047.
[54] V. J. Shiner and C. R. Wasmuth, *J. Amer. Chem. Soc.*, 1959, **81**, 37.

Support for these views has come from isotopic labelling experiments.[55] When pinacol and 2-methylpropane-1,2-diol were oxidised in ^{18}O-enriched water, no label was found in the acetone. Thus oxygen atoms of periodate (which exchange rapidly with water[56]) do not become linked to carbon (*e*; Scheme 2). Experiments with [^{18}O]biacetyl and with methylacetoin were more difficult to interpret, but showed that here periodate oxygen atoms were being linked to carbon. The



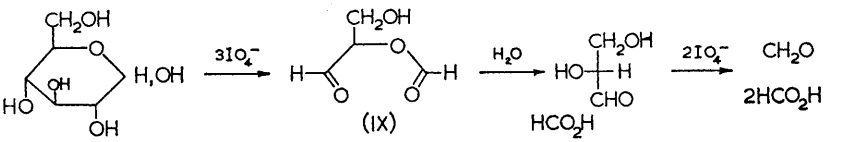
Scheme 2

mixed nucleophilic and electrophilic rôles of the reagent were strikingly observed with methylacetoin, for the acetic acid produced was labelled while the acetone was not (*f*).

The breakdown of the cyclic intermediates in glycol oxidation with periodate and chromate[23b] have been discussed from a theoretical viewpoint.[57] Stable glycol chelates have been obtained with some antimony (v) compounds, which on pyrolysis give the glycol fission products.[58]

Contrary to an earlier suggestion, glycol oxidation does not involve free radicals, methyl methacrylate not being polymerised in the reaction mixture.[59] The graft-polymerisation of acrylonitrile on cellulose which is undergoing periodate oxidation is thus surprising, but may be due to secondary free-radical reaction of the many aldehyde groups which do in fact terminate polymerisation.[60] A study of glycol fission by electron spin resonance is lacking.

Intermediates in the Oxidation of Polyols.—Because of the importance of periodate oxidation in the carbohydrate field, the intermediates arising in the oxidation of various polyols have been examined in detail. We have already referred to the preferential cleavage of certain bonds for steric reason (p. 8).



[55] C. A. Bunton and V. J. Shiner, *J. Chem. Soc.*, 1960, 1593.
[56] Cf. M. Anbar and S. Guttmann, *J. Amer. Chem. Soc.*, 1963, **83**, 781.
[57] M. C. R. Symons, *J. Chem. Soc.*, 1963, 4331.
[58] F. Nerdel, J. Buddrus, and K. Höher, *Chem. Ber.*, 1964, **97**, 124.
[59] H. Tanabe, *Chem. Pharm. Bull.* (*Tokyo*), 1960, **8**, 365 (*Chem. Abs.*, 1961, **55**, 10307).
[60] T. Toda, *J. Polymer Sci.*, 1962, **58**, 411.

In the complete degradation of glucose, five molecules of the reagent are required and formic acid (five molecules) and formaldehyde (one molecule) are formed, but the reaction does not proceed at a uniform speed. At pH 3–5, distinct stages in the uptake of reagent and liberation of fragments were observed,[61,62] and β-formylglyceraldehyde (IX) was isolated from the reaction mixture.[63] Glucose is oxidised mainly in the pyranose form, but exists to about 15% in the acyclic and furanose forms, as estimated from the *initial* release of formaldehyde by oxidation of the 5,6-bond.[62] The formyl ester (IX) is relatively stable at pH 3·6 but is quickly hydrolysed at pH 7 where the oxidation is smooth and complete.

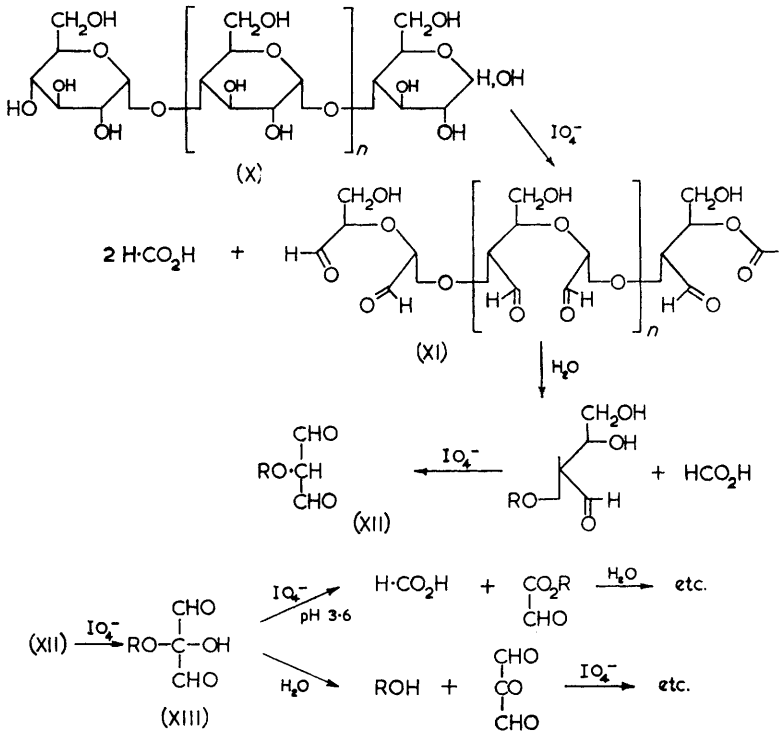
Consideration of these esters can be useful in structural studies. Amylose consists of largely unbranched chains of 1,4-α-linked glucose units (X). Periodate oxidation (Scheme 3) releases one molecule of formic acid from each terminal residue by direct fission, and a further molecule by subsequent hydrolysis of the formyl ester at the reducing end. The total amount thus represents one unbranched molecule of amylose, whose length can then be calculated, given the sample weight. Conflicting results were obtained as to the release of the third molecule of formic acid from a simple model compound, maltose (X; $n = 0$).[64] To avoid the uncertainty, Wolff *et al.*,[65] working with a corn amylose, first estimated the formic acid released immediately and then, after destroying excess of periodate, hydrolysed the intermediate ester (XI) and estimated the additional formic acid. This procedure gave a separate estimate of the number of reducing residues in the amylose molecule which was thus shown to consist on average of two branches.

The chemistry of the polyaldehydes produced in the oxidation of polysaccharides has been reviewed.[66]

Carbohydrates tend to reduce more periodate than expected from mere glycol fission.[67] The new reaction was shown to be a hydroxylation of CH-groups, activated by adjacent carbonyl groups,[68] and is discussed further later (p. 15).

An α-alkoxy-malondialdehyde moiety (XII) arises from the 4-*O*-substituted terminal residue of polysaccharides such as (X). The activated CH-group of the largely enolised dialdehyde (XII) is hydroxylated by periodate to give a hemiacetal (XIII). The formation and breakdown of such intermediates has been studied with model compounds (XII; R = CH_3 or $C_6H_5{\cdot}CH_2$).[69] At pH 3·6, where (XIII) is most stable to hydrolysis, oxidative cleavage predominates,

[61] F. S. H. Head, *Chem. and Ind.*, 1958, 360; S. A. Warsi and W. S. Whelan, *ibid.*, p. 71.
[62] L. Hough, T. J. Taylor, G. H. S. Thomas, and B. M. Woods, *J. Chem. Soc.*, 1958, 1212.
[63] C. Schöpf and H. Wild, *Chem. Ber.*, 1954, **87**, 1571.
[64] K. H. Meyer and P. Rathgeb, *Helv. Chim. Acta*, 1943, **31**, 1545; A. L. Potter and W. Z. Hassid, *J. Amer. Chem. Soc.*, 1948, **70**, 3489.
[65] I. A. Wolff, B. T. Hofreiter, P. R. Watson, W. L. Deatherage, and M. M. MacMasters, *J. Amer. Chem. Soc.*, 1955, **77**, 1654.
[66] R. D. Guthrie, *Adv. Carbohydrate Chem.*, 1961, **16**, 105.
[67] T. G. Halsall, E. L. Hirst, and J. K. N. Jones, *J. Chem. Soc.*, 1947, 1427.
[68] C. F. Huebner, S. R. Ames, and E. C. Bubl, *J. Amer. Chem. Soc.*, 1946, **68**, 1621.
[69] (*a*) J. C. P. Schwartz and M. MacDougall, *J. Chem. Soc* , 1956, 3065. (*b*) M. Cantley, L. Hough, and A. O. Pittet, *Chem. and Ind.*, 1959, 1126, 1253.



Scheme 3

giving formic acid and an ester which is slowly hydrolysed further and oxidised. At other pH's hydrolysis of (XIII) occurs, followed by oxidation of mesoxalaldehyde.[70]

In the later stages of carbohydrate oxidation, the above hydrolyses and hydroxylations, varying independently with pH, are superimposed to produce a complicated pattern of reactions. This has been resolved for some simple mono- and di-saccharides by kinetic estimation of the various fragments at different acidities.[70,71]

Under the acidic conditions used in early studies, over-oxidation was found to be associated with the liberation of iodine.[67] A method for the detection and estimation of 1,4-links in polysaccharides was even devised on the basis of this fact.[72] It has since been shown that sodium iodate in acid solution oxidises benzyloxymalondialdehyde, the iodide ion formed being re-oxidised to iodine.[69a]

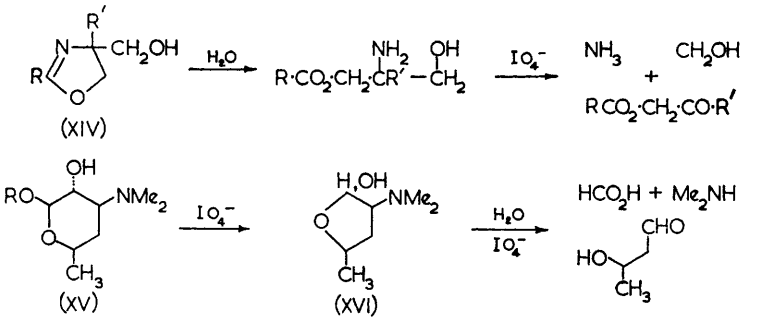
Over-oxidation is usually undesirable since it confuses the number of true

[70] M. Cantley, L. Hough, and A. O. Pittet, *J. Chem. Soc.*, 1963, 2527.
[71] L. Hough and B. M. Woods, *Chem. and Ind.*, 1957, 1421; F. S. H. Head and G. Hughes, *J. Chem. Soc.*, 1954, 603.
[72] K. Ahlborg, *Svensk Kem. Tidskr.*, 1942, **54**, 205; *Chem. Abs.*, 1944, **38**, 4254.

glycol-cleavage steps from which structural deductions are most easily made. Low temperatures (5°c)[73] and reduced concentrations of periodate[8b] have been recommended to minimise it.

In oxidation mixtures exposed to sunlight less specific hydroxylations involving singly-activated CH-groups can occur, and oxidations of polyols should therefore be carried out in the dark.[74]

Amino-alcohols.—The periodate cleavage of *N*-primary and *N*-secondary α-amino-alcohols[17,18] (p. 5) is fastest at pH 7–8 and is suppressed in mildly acid solution. (The oxidation of hydroxy-amino-acids is discussed separately below.)



Scheme 4

4-Hydroxymethyloxazolines (XIV) are oxidised in a two-stage reaction (Scheme 4).[75] Acid-catalysed ring opening produces an α-amino-alcohol which is cleaved in slightly alkaline solution.

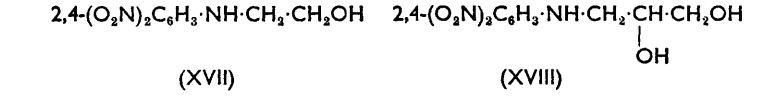
The tertiary amino-group does not prevent cleavage entirely.[18] Oxidation of desosamine (XV; R = H) gave in turn the tetrose (XVI) and acetaldol, and the methyl acetal (XV; R = CH_3) also took up one molecule of the reagent.[76] However, erythromycin and erythralosamine, parent glycosides of (XV), gave[77] the *N*-oxide (p. 23).

An electron-withdrawing substituent on nitrogen, such as the acetyl[17] or 2,4-dinitrophenyl group,[78] retards the cleavage, which can however proceed in the latter case if there is a second hydroxyl group vicinal to the first. Thus the arylaminoethanol (XVII) resists oxidation but the 3-arylaminopropane-1,2-diol (XVIII) is cleaved giving 2,4 dinitroaniline.[78]

Studies on the oxidation of 2-amino- and 2-acetylamino-2-deoxyglucose

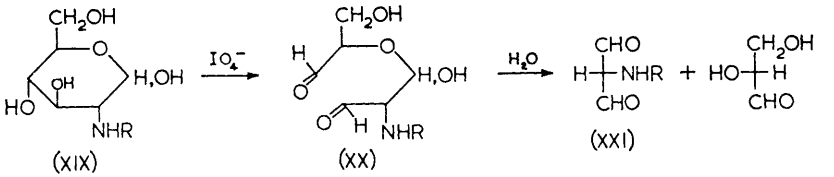
[73] Ref. 16 in M. Cantley *et al.*, ref. 70.
[74] F. S. H. Head, *J. Text. Inst.*, 1953, **44**, T209; *Chem. Abs.*, 1953, **47**, 8378.
[75] H. L. Wehrmeister, *J. Org. Chem.*, 1961, **26**, 3821.
[76] R. K. Clarke, *Antiobiotics and Chemotherapy*, 1953, **3**, 663.
[77] E. H. Flynn, M. V. Sigal, jun., P. F. Wiley, and K. Gerzon, *J. Amer. Chem. Soc.*, 1954, **76**, 3121.
[78] K. Hattori, H. Harada, and Y. Hirata, *Bull. Chem. Soc., Japan*, 1962, **35**, 312.

(XIX; R = H or Ac) (Scheme 5) and the corresponding methyl glucosides confirmed that *N*-acetylation prevents the aminoalcohol cleavage.[79,80] The subsequent reactions, involving hydrolysis of (XX) and the hydroxylation of



(XVII) (XVIII)

aminomalondialdehyde derivatives (XXI; R = H or Ac), have been elucidated.[81]

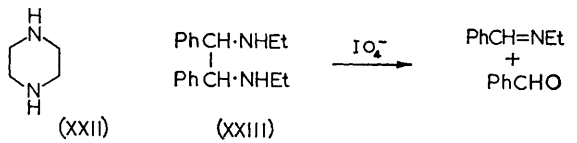


Scheme 5

There have been few studies on the kinetics and mechanism of the fission. It is accelerated by increasing pH and probably involves the unprotonated amine.[82,83] With rare exceptions, only second-order kinetics have been observed[84] which permit of no deduction as to an intermediate. The kinetic form may be due to the very dilute solutions used by the Czech workers.[28,36] Evidence for a cyclic intermediate is again stereochemical.

In a series of acyclic α-amino-alcohols, the *threo*-isomers were consistently oxidised more quickly than the *erythro*-compounds. This difference was enhanced by *N*-methylation, which, when followed by periodate oxidation at pH 6·5–7·0, was recommended as a method for establishing the relative configurations of diasteroisomeric α-amino-alcohols.[84] *N*-Benzylation retarded the oxidation of the *threo*-compounds to such an extent that the usual order could be reversed. These effects are interestingly rationalised by the authors in terms of hydrogen bonding.[84]

cis-2-Aminocyclopentanol is oxidised somewhat more quickly than the *trans* isomer, but the difference is much smaller than for the corresponding diols,[82] and the order is reversed in the aminocyclohexanols.[84] Differences in hydrogen bonding presumably contribute to these effects.



(XXII) (XXIII)

[70] R. J. Jeanloz and E. Forchielli, *J. Biol. Chem.*, 1951, **188**, 361.
[80] L. Hough and M. I. Taba, *J. Chem. Soc.*, 1956, 2042.
[81] M. Cantley and L. Hough, *J. Chem. Soc.*, 1963, 2711.
[82] G. E. McCasland and D. A. Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5164.
[83] G. Dahlgren and J. M. Hodson, *J. Phys. Chem.*, 1964, **68**, 416.
[84] J. Kovar, J. Jary, and K. Blaha, *Coll. Czech. Chem. Comm.*, 1963, **28**, 2199.

α-Diamines.—Periodate oxidation is similar to that of α-amino-alcohols with regard to rate and pH.[18] Piperazine (XXII) gave, besides ammonia and formaldehyde, a little formic acid,[85] while benzaldehyde and benzylidene-ethylamine were formed from the diamine (XXIII).[86] The second product is probably the precursor of the aldehyde.

3 Oxidation of Enolic Compounds

Activated CH-Groups and Enols.—The hydroxylation of malondialdehyde intermediates in the oxidation of sugars has already been mentioned. A study[68] with a series of acyclic model compounds (XXIV) showed that one of the

$$R^1{\cdot}CO{\cdot}CHR^2{\cdot}CO{\cdot}R^3 \xrightarrow{IO_4^-} R^1{\cdot}CO.\underset{\displaystyle OH}{CR^2}{\cdot}CO{\cdot}R^3 \xrightarrow{IO_4^-} \text{etc.}$$

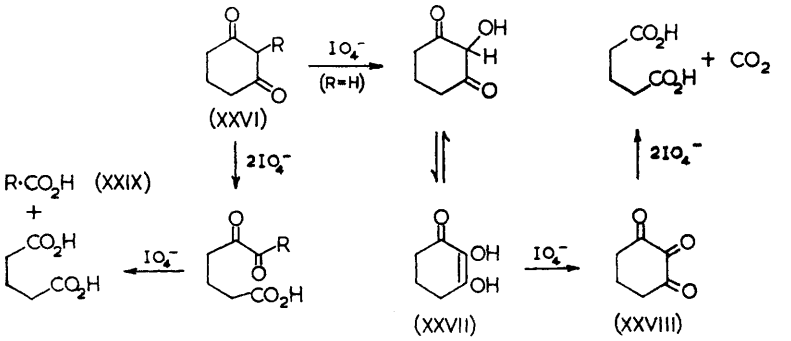
(XXIV) (XXV)

activating groups must be an aldehyde or carboxyl function (R^1 = H or OH) but that there is no oxidation with a keto-group (as in acetylacetone) or a cyano-group (as in cyanoacetic acid). The intermediate (XXV) undergoes normal cleavage giving ultimately formic acid (R^1 = H) or carbon dioxide (R^1 = OH) and other expected fragments depending on R^2 and R^3 (alkyl, alkoxyl or hydrogen). Further hydroxylation of (XXV) competes with the slower cleavage when R^1 = OH, malonic acid giving some oxalic acid, and for alkoxymalondialdehydes, hydrolysis of the hemiacetal (XXV; R^2 = OAlk) can occur (p. 12).

Cyclic β-diketones are oxidised smoothly.[87] The reductone (XXVII) (p. 17) and the triketone (XXVIII) were oxidised (Scheme 6) just as readily as 1,3-cyclohexanedione (XXVI; R = H) and are the probable intermediates. Predictably, 2-alkyldiketones gave a carboxylic acid (XXIX) instead of carbon dioxide, and 2-dialkylketones were not oxidised.

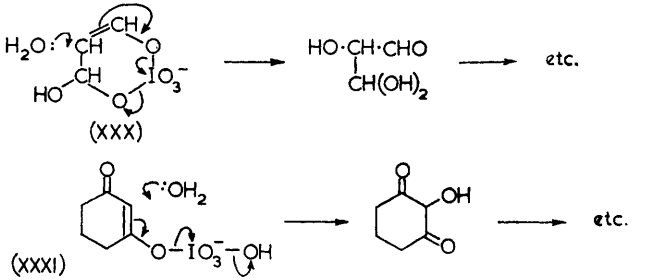
One of the activating groups may be an aromatic[88] or heteroaromatic[89] ring as in benzyl ketones (slow oxidation)[88] and in riboflavin,[89b] and rapid hydroxylation probably occurs also in the β-dinitrone (LXXV, p. 25).[86] The mechanism of hydroxylation is unknown. Enolisation cannot be the sole factor, as pointed out by Bose, *et al.*,[90] since some weakly enolised compounds such as malonic acid are readily oxidised, while certain strongly enolised compounds (*e.g.*, acetylacetone) are hardly attacked. The cyclic mechanism (XXX) suggested for malondialdehyde and its largely enolised derivatives[90] cannot be extended readily to malonic acid or, for steric reasons, to cyclohexanedione.

[85] A. Wickstrom and A. Valseth, *Ann. pharm. franc.*, 1954, **12**, 777.
[86] V. M. Clark, B. Sklarz, and Sir A. R. Todd, *J. Chem. Soc.*, 1959, 2123.
[87] M. L. Wolfrom and J. M. Bobbitt, *J. Amer. Chem. Soc.*, 1956, **78**, 2849.
[88] H. Felkin, *Bull. Soc. chim. France*, 1951, 915.
[89] (*a*) C. F. Huebner, R. Lohmar, R. J. Dimler, S. Moore, and K. P. Link, *J. Biol. Chem.*, 1945, **159**, 503; L. J. Haynes, N. A. Hughes, G. W. Kenner, and Sir A. R. Todd, *J. Chem. Soc.*, 1957, 3727; (*b*) H. S. Forrest and A. R. Todd, *J. Chem. Soc.*, 1950, 3295.
[90] J. L. Bose, A. B. Foster, and R. W. Stephens, *J. Chem. Soc.*, 1959, 3314.

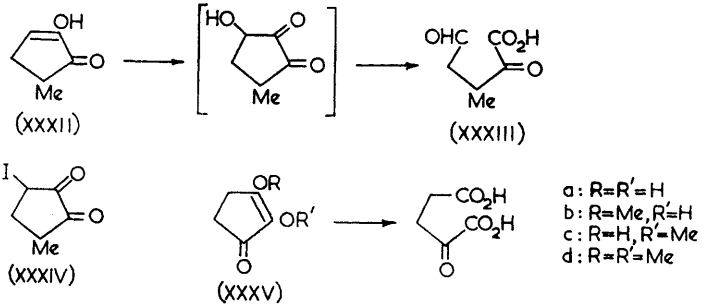


Scheme 6

A transient malonic-periodic acid anhydride can be envisaged in which enolisation is promoted, but there is no precedent or evidence for this at present. As shown experimentally for catechol (p. 19), a labile enol–periodate complex



may be formed from the enolised cyclic β-diketone, and written hypothetically as (XXXI). The contrasting resistance of the acyclic diketones is perhaps related



to the anomalous properties of their enols.[91] However, the above discussion must remain speculative without further experimental evidence.

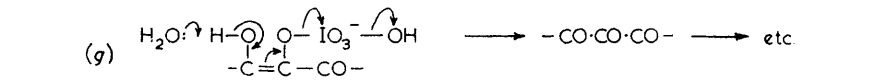
[91] G. S. Hammond in 'Steric Effects in Organic Chemistry' ed. M. S. Newman, Wiley, New York, 1956, p. 452.

Free radicals were not detected in the oxidation of malonic acid.[92] However, a study of the hydroxylation by electron spin resonance would be valuable.

Methylcyclopentane-2,3-dione, which exists largely as the enol (XXXII), in an exothermic oxidation afforded acidic products, one of which was probably (XXXIII), presumably *via* hydroxylation as above and cleavage.[93] The iodo-compound (XXXIV) was isolated when limited amounts of periodate were used.

Reductones.—The reductone structure -C(:O)·C(OH) = C(OH)- is oxidised rapidly, and the triketone subsequently cleaved, as in triose reductone[93,94] and in (XXVII, p. 15).[15,87]

The dimethyl ether (XXXVd) of reductic acid was not oxidised, but the parent reductone (XXXVa) and the monomethyl ethers (XXXVb) and (XXXVc) gave α-oxoglutaric acid.[93] Iodine was formed under the acid conditions. This recalls the behaviour of the enolic α-alkoxymalondialdehydes already mentioned, to which the monoethers (XXXVb and c) are in fact related structurally.



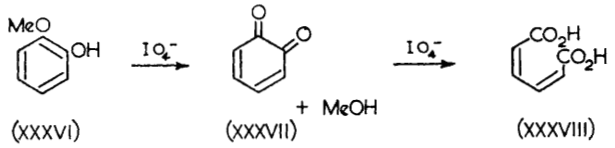
As in the oxidation of catechol, the reductone oxidation probably proceeds by removal of the second enolic proton, rather than by attack of water on carbon (*g*). Other mechanisms are suggested by Hesse and Mix.[93]

Phenols.—Several research groups concerned with lignin chemistry have studied the oxidation of phenolic compounds by periodate.[95] They confined themselves to recording the uptake of the reagent and did not isolate products from the often coloured solutions. In a recent set of elegant studies, Adler and his colleagues have described the complex products which can arise and the essentially simple reactions leading to them.[96–100]

Adler's oxidations were carried out with sodium periodate in aqueous or 80% acetic acid solution. The phenols studied were of two types: the dihydric phenols with their mono-ethers, and some methylphenols.

The study was prompted by the observation that methanol is formed rapidly and quantitatively in the periodate oxidation of guaiacol (XXXVI), and an estimation of guaiacol residues in lignin was based on this.[96] The red solution

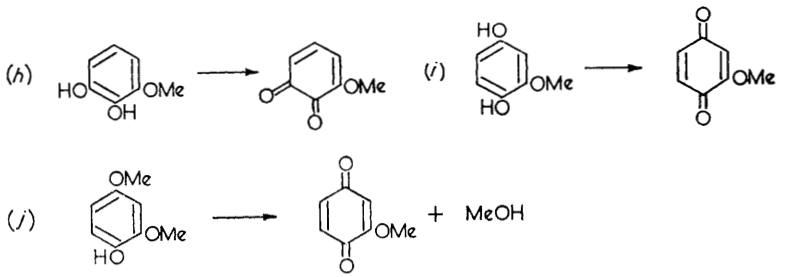
[92] M. C. R. Symons, *J. Chem. Soc.*, 1955, 2794.
[93] G. Hesse and K. Mix, *Chem. Ber.*, 1959, **92**, 2427.
[94] J. C. P. Schwartz, *Chem. and Ind.*, 1955, 1588.
[95] J. P. Feifer, M. A. Smith, and B. R. Willeford, *J. Org. Chem.*, 1959, **24**, 90, and refs. therein.
[96] E. Adler and S. Hernestam, *Acta Chem. Scand.*, 1955, **9**, 319.
[97] E. Adler and R. Magnusson, *Acta Chem. Scand.*, 1959, **13**, 505.
[98] (*a*) E. Adler, R. Magnusson, B. Berggren, and H. Thomelius, *Acta Chem. Scand.*, 1960, **14**, 515; (*b*) E. Adler and B. Berggren, *Acta. Chem. Scand.*, 1960, **14**, p. 529; (*c*) E. Adler, R. Magnusson, and B. Berggren, *Acta. Chem. Scand.*, 1960, **14**, p. 539.
[99] E. Adler, I. Falkenberg, and B. Smith, *Acta Chem. Scand.*, 1962, **16**, 529.
[100] (*a*) E. Adler, L. Junghahn, U. Lindberg, B. Berggren, and G. Westin, *Acta Chem. Scand.*, 1960, **14**, 1261; (*b*) E. Adler, J. Dahlen, and G. Westin, *Acta. Chem Scand.*, 160, **14**, p. 1580.



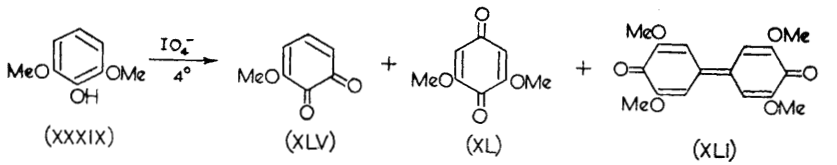
from the oxidation of (XXXVI) gave *o*-benzoquinone (XXXVII) and *cis-cis*-muconic acid (XXXVIII), obviously derived by further cleavage of the quinone.[97] The reaction is general for catechol and quinol ethers, the latter yielding *p*-benzoquinone, but resorcinol monomethyl ether is attacked only very slowly giving methoxy-*p*-quinone.

The quinones are also formed in the very fast oxidation of catechol and quinol themselves.

The relative facility of these various reactions is apparent from the major products in the following cases when two pathways are possible. Simple dehydrogenation is preferred to demethylation (*h*, *i*), and the latter reaction is faster for *para*- than for *ortho*- placed groups (*j*).[97]

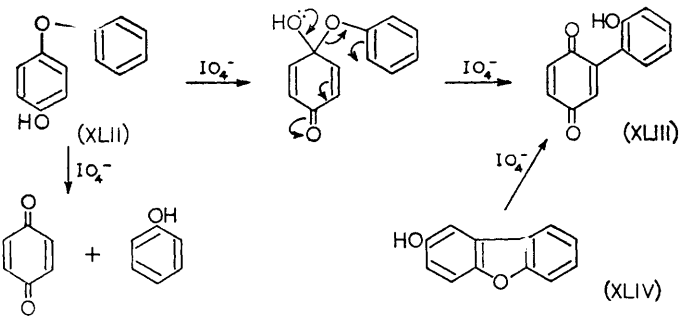


Sodium bismuthate also demethylated guaiacol, but lead tetra-acetate and Fremy's salt gave 2-methoxy-*p*-benzoquinone. *para*-Hydroxylation by periodate was observed in the by-products (XL) and (XLI) (coerulignone) of the oxidation of 2,6-dimethoxyphenol (XXXIX),[98a] but the mechanism is probably ionic.



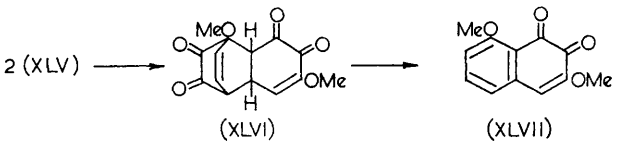
Besides the expected reaction, a rearrangement occurred (Scheme 7) in the oxidation of the phenyl ether (XLII), with the formation of a biphenyl (XLIII), formed also by the normal oxidation of 2-hydroxydibenzofuran (XLIV).[97]

Dimeric products were obtained in concentrated solution and at room temperature from the oxidation of (XXXIX). 3,8-Dimethoxy-1,2-naphthaquinone



Scheme 7

(XLVII)[98c] was formed together with small amounts of an isomer. Adler showed that the Diels–Alder dimer (XLVI) of 3-methoxy-*o*-quinone (XLV) was oxidised by periodate to (XLVII) in a pathway involving diketone fission and decarboxylation.[98b]



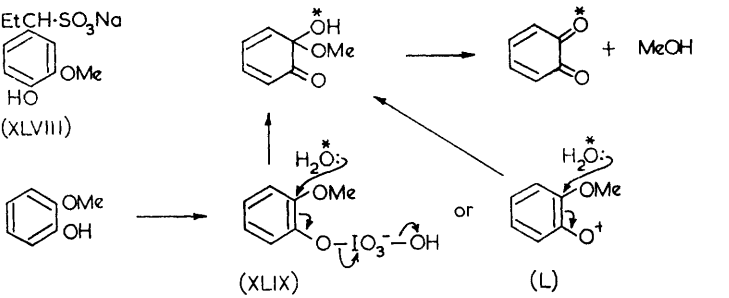
The details of the mechanism by which the dihydric phenols and their ethers are oxidised are not yet understood. Kinetic studies by the stopped-flow method have revealed for catechol the second-order formation of an intermediate, which breaks down by a first-order reaction, but no intermediate was detected for guaiacol.[101] The oxidation of quinol is of the second order.[102]

Using ^{18}O-labelled water, Adler, Falkenberg, and Smith[99] demonstrated a difference between the oxidation mechanism of the dihydric phenols and their monoethers.

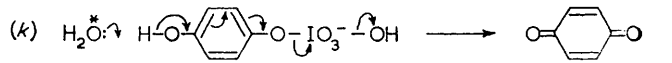
The water-soluble guaiacol derivative (XLVIII) was oxidised with sodium periodate in ^{18}O-enriched water, but the liberated methanol contained no label. The *o*- and *p*-benzoquinones isolated from similar oxidation of the monomethyl ethers were 50% labelled. Since the quinones did not exchange ^{18}O with water at the experimental pH (3–4) the label must have entered during the oxidation, envisaged as the attack of water on a periodate ester (XLIX) or a transient cation (L). Attack by water at the methyl carbon would have given labelled methanol.

When catechol and quinol were oxidised in $H_2{}^{18}O$ the quinones obtained were not labelled. Here the water molecule removes the hydroxylic proton rather than attacking at carbon (*k*).

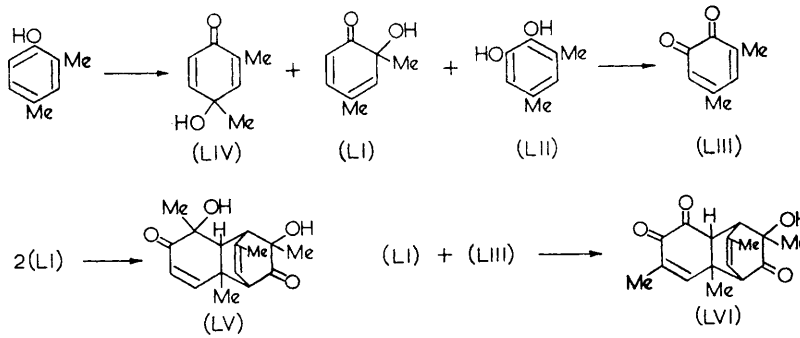
[101] E. T. Kaiser and S. W. Weidman, *Tetrahedron Letters*, 1965, 497.
[102] E. T. Kaiser and S. W. Weidman, *J. Amer. Chem. Soc.*, 1964, **86**, 4354.



The periodate oxidation of alkylphenols is surprisingly fast, leading to various products of *ortho-* and *para*-hydroxylation which have been elucidated by Adler and his group.[100]



Phenol itself is only very slowly attacked.[97] The oxidation of 2,4-dimethylphenol illustrates the various reactions that have been found to occur. Dimeric products (LV and LVI) arise from the *o*-quinol (LI) itself, and from its Diels–



Adler addition to the *o*-quinone (LIII). The latter arises from the oxidation of (LII), the alternative *ortho*-hydroxylation product.[100a] The *p*-quinols, *e.g.*, (LIV), which are minor products, do not dimerise.[100b] The reaction of oestrogens with periodate, reported without details, may involve hydroxylation of the steroid at C(10).[103]

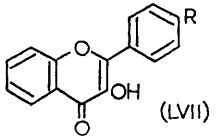
The mechanism is probably analogous to that of the first hydroxylation step in the oxidation of guaiacol [cf. (XLIX or L)].

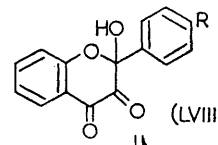
Other hydroxylations of phenols have been reviewed.[104]

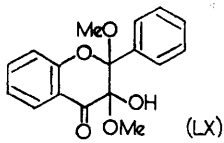
Flavanols.—The flavanols (LVII; R = H or OCH_3) were oxidised by periodic acid in aqueous dimethylformamide to give a tautomeric mixture of the 2-

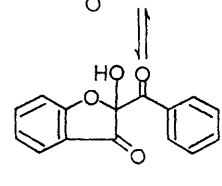
[103] R. A. Harkness and K. Fotherby, *Experentia*, 1961, **5**, 253.
[104] J. D. Loudon, *Progr. Org. Chem.*, 1961, **5**, 46; W. A. Waters, *ibid.*, p. 35.

hydroxyflavandiones (LVIII; R = H or OCH_3).[105] In methanol the methoxy-analogue of (LVIII; R = H) was obtained as its methyl hemiacetal (LX).[106]

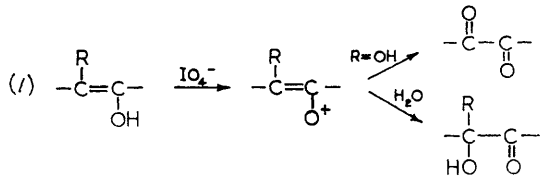






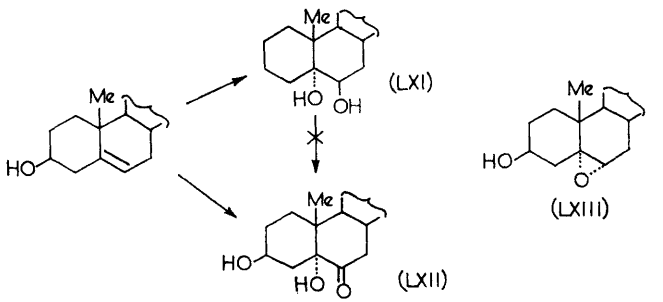


Smith has pointed out the analogy of this oxidation with that of phenols and reductones. In those reactions and in the oxidation of simple enols one may consider the attack of water on a transient cation or enol-periodate ester (*I*). If R is a hydroxyl group, a diketone is formed by loss of a proton; otherwise *C*-hydroxylation occurs. In either case, further reactions may ensue as illustrated throughout this section.



4 Other Functional Groups

Alcohols, Olefins, and Epoxides.—Methanol and ethanol are attacked only in the light.[13] A selective oxidation of the 11β-OH group in steroids to the 11-ketone has been reported, and at higher concentrations of periodic acid, 3α-, and 17β-16β-hydroxyl groups are also attacked.[103]



Scheme 8

[105] M. A. Smith, *J. Org. Chem.*, 1963, **28**, 933.
[106] M. A. Smith, R. A. Webb, and L. J. Cline, *J. Org. Chem.*, 1965, **30**, 995.

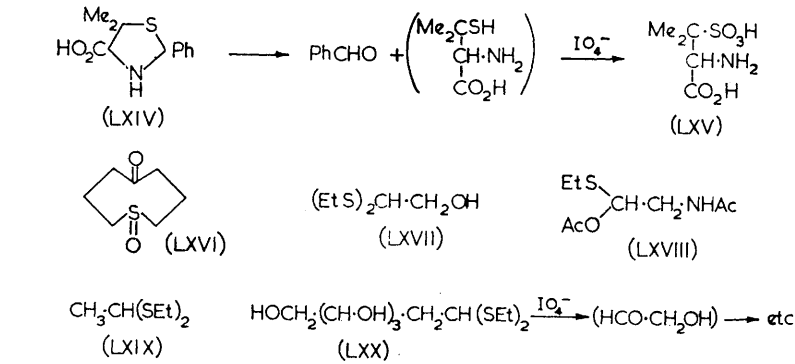
Olefins are inert to periodate, at least at room temperature, and steroids again provide the only well-established exception.[107] With a three-fold excess of periodic acid, cholesterol (Scheme 8) gave 3β,5α,6β-cholestanetriol (LXI), while with ten-fold excess, the 6-ketone (LXII) was also formed. The triol is not an intermediate, being unaffected under the conditions (*trans*-diaxial *vic*-glycol!). The epoxide (LXIII) was presumed to be involved. With the high concentration of periodic acid, acid-catalysed ring-opening by periodate ion cannot be excluded, the periodate ester then collapsing to the ketone. A simple hydrolysis of epoxides catalysed by periodic acid was reported earlier by Fieser and Rajagopalan.[108]

Styrene and stilbene oxides were reported (without details) to take up periodate slowly.[88]

Sulphur Compounds.—The oxidation of sulphur compounds with periodate was studied by Sykes and Todd in connection with the penicillin problem.[109] Thiols are oxidised, *via* disulphides, to sulphonic acids, though the second stage is effected also by iodic acid. Thus spontaneous hydrolysis of the thiazolidine (LXIV) gave a thiol, oxidation of which gave penicillaminic acid (LXV). A periodate estimation of penicillin has been described.[110]

Thioethers (sulphides) are oxidised to sulphoxides. Thus, excellent yields of (LXVI) were obtained by oxidation of the sulphide at 0°, although other oxidising agents failed.[111] At higher temperatures, sulphones are formed.[111,112]

Although there was no cleavage of 2-aminoethanethiol, it has been observed for thioethers. The ethanol derivatives (LXVII) and (LXVIII) were both oxidised



[107] R. P. Graber, C. S. Snoddy, H. B. Arnold, and N. L. Wendler, *J. Org. Chem.*, 1956, **21**, 1517.
[108] L. Feiser and S. Rajagopalan, *J. Amer. Chem. Soc.*, 1949, **71**, 3938.
[109] P. Sykes and A. R. Todd in 'The Chemistry of Penicillin', ed. H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton, 1949, p. 927.
[110] L. Mazor and M. K. Papay, *Acta Chim. Acad. Sci. Hung.*, 1961, **26**, 473; *Chem. Abs.*, 1961, **55**, 20330.
[111] N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, 1962, **27**, 282.
[112] W. A. Bonner and R. W. Drisko, *J. Amer. Chem. Soc.*, 1951, **73**, 3699.

by sodium periodate, the former alone yielding formaldehyde. Detailed study of the oxidation of thio-derivatives of sugars and amino-sugars showed that cleavage of the group R-S-C-C-X can occur when X is OH, NH_2, or NHAc.[113] In all the examples adduced, the carbon atom adjacent to C–X actually carries *two* thioether groups or one together with a second electronegative function, as in (LXVIII). The importance of this is seen in the remarkable cleavage of the acetaldehyde derivative (LXIX) to give methanol, and of 2-deoxyglucose diethyl-(but not dibenzyl-)dithioacetal (LXX) to give, as an intermediate, glycolaldehyde.[113] The fate of the sulphur-bearing fragment was not reported and the reaction merits further study.

Amines.—Formation of an *N*-oxide from a tertiary amino-group was observed with erythromycin (p. 13),[77] and has been found for *N*-(2-hydroxyethyl)- and *N*-propyl-piperidine.[114] Triphenylphosphine readily gave the oxide.[114] Complexes apparently formed between potassium periodate and some primary and secondary aliphatic amines[115] merit further study in connection with the mechanism of these reactions.

A new pattern of periodate oxidation thus emerges, summarised by the expression $R_nZ \rightarrow R_nZ\text{–}O$, where Z is N, P, or S. Its scope and utility, particularly for the first two classes, remains to be studied.

Mono- and di-alkylanilines, toluidines, and, more slowly, halogenoanilines are oxidised.[78,116] The rate of the extensive oxidation of phenylenediamines decreases in the order *meta* > *ortho* > *para*,[117] in contrast to the phenols (p. 18). Electron-withdrawing groups such as -CHO, $-COCH_3$,[117] and $-NO_2$[78,116] retard or suppress the oxidation, particularly when placed *ortho* or *para* to the amino-group.

Reaction products have been studied only for aniline, and vary considerably with pH. Emeraldine is formed at pH 1,[118] various amino- and anilino-quinoneimines and anils at pH 4·5,[119] and unidentified products at pH 9. Free radicals are involved.[120]

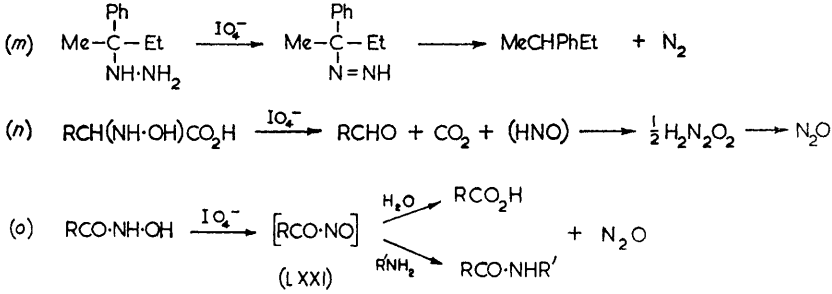
Hydrazine Derivatives.—Hydrazobenzene is rapidly oxidised by periodate to azobenzene.[117] Monoalkylhydrazines give nitrogen and alkanes in good yield[121a] *via* an alkyldi-imine (m), the mechanism and stereochemistry of whose breakdown depends on the amount of base present. The reaction has been used in a synthesis of 3-deoxyglucose derivatives,[121b] and an improved preparation of

[113] L. Hough and M. I. Taha, *J. Chem. Soc.*, 1957, 3994.
[114] B. Sklarz and A. K. Qureshi, unpublished observations.
[115] K. L. Jaura, K. K. Tewari, and R. L. Kaushik, *J. Indian Chem. Soc.*, 1963, **40**, 1008.
[116] J. Kawashiro, *J. Pharm. Soc. Japan*, 1953, **73**, 943 (*Chem. Abs.*, 1954, **43**, 10630).
[117] H. Tanabe, *J. Pharm. Soc. Japan*, 1956, **76**, 1023 (*Chem. Abs.*, 1957, **51**, 2598).
[118] H. Tanabe, *J. Pharm. Soc. Japan*, 1958, **78**, 410 (*Chem. Abs.*, 1958, **52**, 14562).
[119] H. Tanabe, *Chem. Pharm. Bull.* (*Tokyo*), 1958, **6**, 645 (*Chem. Abs.*, 1960, **54**, 16417), and refs. therein.
[120] H. Tanabe, *Chem. Pharm. Bull.* (*Tokyo*), 1959, **7**, 177, 316; (*Chem. Abs.*, 1960, **54**, 22425).
[121] (*a*) D. J. Cram and J. S. Bradshaw, *J. Amer. Chem. Soc.*, 1963, **85**, 1108; (*b*) D. M. Brown and G. H. Jones, *Chem. Comm.*, 1965, 561.

nicotinaldehyde by the periodate oxidation of nicotinic acid hydrazide at 0° is a related reaction.[122] Strongly acid solutions of various hydrazine derivatives have been titrated with potassium periodate.[123]

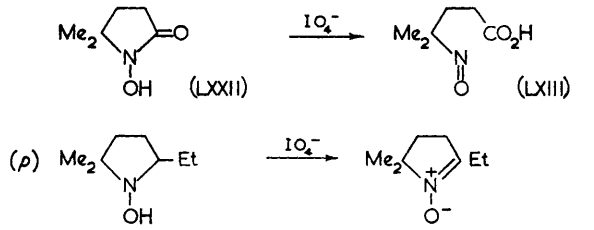
Hydroxylamine Derivatives.—Hydroxylamine is instantly oxidised by sodium periodate with formation of nitrous oxide and iodine.[124] Analogous oxidation of phenylhydroxylamine[117] and methylhydroxylamine[125] gave the nitroso-compound, in the latter instance as the *cis*-dimer without tautomerisation to the oxime. Such oxidation proceeds also in chloroform with tetraethylammonium periodate.[10] However, α-hydroxyamino-acids undergo instantaneous oxidative decarboxylation (*n*).[126]

Primary hydroxamic acids are oxidised to nitrous oxide and the parent acid (*o*).[125] The formation in fair yields of amides in the presence of primary amines[127]



points to the existence of an acylating intermediate,[124] assumed to be (LXXI).[127] *N*-Alkylhydroxamic acids, *e.g.*, (LXXII)[86] similarly give the acid or amide,[127] together with a nitroso-compound,[86,125] *e.g.*, (LXXIII).

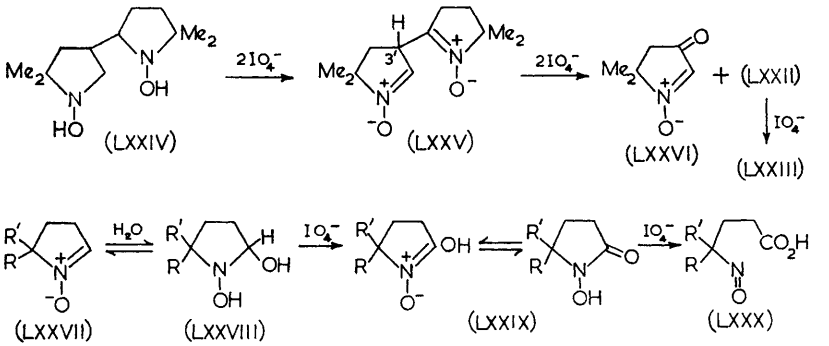
N-Hydroxypyrrolidines with an α-hydrogen atom are rapidly oxidised to the nitrone (*p*).[10,86] This reaction is also seen in the first two stages of the oxidative



[122] H. N. Wingfield, W. R. Harlan, and H. R. Hanmer, *J. Amer. Chem. Soc.*, 1952, **74**, 5796.
[123] B. Singh and S. S. Sahota, *J. Sci. Ind. Res. India*, 1958, **17,B**, 386 (*Chem. Abs.*, 1959, **53**, 7863).
[124] T. F. Emery and J. B. Neilands, *J. Org. Chem.*, 1962, **27**, 1075.
[125] T. F. Emery and J. B. Neilands, *J. Amer. Chem. Soc.*, 1960, **82**, 4903.
[126] G. A. Snow, *J. Chem. Soc.*, 1954, 2588; J. B. Neilands and P. Azari, *Acta Chem. Scand.*, 1963, **17**, S190.
[127] B. Sklarz and A. F. Al-Sayyab, *J. Chem. Soc.*, 1964, 1318.

degradation of the 2,3′-bispyrrolidinyl (LXXIV) to the nitroso-acid (LXXIII) and the keto-nitrone (LXXVI).[86] Hydroxylation at the activated C(3′) is a probable step in the sequence.

Several Δ^1-pyrroline 1-oxides unsubstituted at C(2) (LXXVII) were cleaved smoothly by sodium periodate at the double bond, with formation of a nitroso- and a carboxyl group (LXXX).[10] There is indirect evidence for a reaction path



via the hydrate (LXXVIII) and the hydroxamic acid (LXXIX). In agreement with this, the nitrone-acid (LXXVII; R = CH_3, R′ = CO_2H) gave lævulaldehyde, presumably *via* oxidative decarboxylation of the α-hydroxyamino-acid (LXXVIII; R = CH_3, R′ = CO_2H).[10] The oxidation of Δ^1-pyrroline to pyrrolidone may be of similar nature.

Amino-acids and Peptides.—Several studies on the periodate oxidation of amino-acids have been recorded,[128–132] usually as preliminaries to the oxidation of proteins. In a recent and extensive survey,[132] the periodate uptake and formation of carbon dioxide at various pH's were measured. Products have only occasionally been identified.

Cleavage of the α-amino-acid function is extremely slow (cf. α-hydroxy-acids) but is promoted by higher temperature [129] and pH, [132] and by *N*-alkylation.[132] Thus proline is oxidised even at pH 2·2 to Δ^1-pyrroline[130,133] which is oxidised further at pH 7·2 to give 2-pyrrolidone[130] (cf. this page).

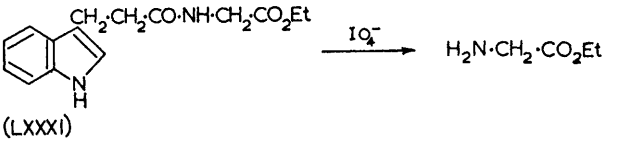
Expectedly, the polyamide chain of peptides is not susceptible to periodate, and oxidation occurs only at the side-chains of certain constituent amino-acids.

Free serine, threonine, and hydroxyproline[130] undergo normal cleavage permitting their estimation,[134] followed by extensive further oxidation. In peptides, they are cleaved only when in the *N*-terminal position, when the

[128] P. Desnuelle, S. Antonin, and A. Casal, *Bull. Soc. Chim. biol.*, 1947, **29**, 694.
[129] K. Arakawa, *J. Biochem. (Japan)*, 1957, **44**, 217.
[130] P. D. Bragg and L. Hough, *J. Chem. Soc.*, 1958, 4050.
[131] H. Hormann, K. Hannig, and G. Fries, *Z. physiol. Chem.*, 1959, **315**, 109.
[132] J. R. Clamp and L. Hough, *Biochem. J.*, 1965, **94**, 17.
[133] L. Skursky, *Z. Naturforsch.*, 1959, **14b**, 473.
[134] See ref. 132 for collected references.

amino-group is free.[135] Thus, brief treatment of corticotropin with periodate destroyed the *N*-terminal serine, and the borohydride-reduced product had altered biological properties.[136]

In yet other amino-acids, oxidation of the side-chain is independent of the α-amino-group. Hydroxylysine undergoes normal fission,[137] cysteine and cystine are oxidised to the sulphonic acid, cysteic acid,[109] and the methionine residue of peptides gives the sulphone.[138]

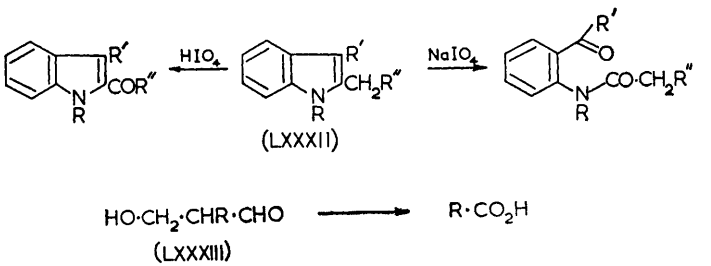


(LXXXI)

Tryptophan, tyrosine (a phenol), and histidine are extensively oxidised to unknown coloured products. The slow dissolution of collagen in aqueous periodate[138] probably involves a specific cleavage at tyrosine of the type reviewed by Witkop,[139] and the cleavage of the model amide (LXXXI) to give ethyl glycinate is also of this type.[139b]

Recently, substituted indoles (LXXXII; R = H or Me) have been shown to undergo mild, rapid, and specific oxidations, the products depending on the acidity.[140] Sodium periodate cleaves the 2,3-double bond of 3-alkylindoles (LXXXII; R′ = H) giving *ortho*-acyl-*N*-acylanilines. Periodic acid leaves this bond intact but oxidises an alkyl methylene group attached at the 2-position to a carbonyl group (Scheme 9).

A recent analysis[131] of the effect of periodate treatment on the amino-acid composition of procollagen confirms that oxidation occurs largely at the amino-acids of the last type, and is in consonance with earlier, less refined studies on ovalbumin,[128] ribonuclease,[141a] chymotrypsin,[141b] and lysozyme.[142]



Scheme 9

[135] S. Fujii, K. Arakawa, and N. Aoyagi, *J. Biochem.* (*Japan*), 1957, **47**, 471.
[136] H. B. F. Dixon, *Biochem. J.*, 1962, **83**, 91.
[137] D. D. van Slyke, A. Hiller, and D. A. MacFayden, *J. Biol. Chem.*, 1941, **141**, 681.
[138] H. Zahn and L. Zurn, *Z. Naturforsch.*, 1957, **12,B**, 788.
[139] B. Witkop, *Adv. Protein Chem.*, 1961, **16**, (*a*) 221; (*b*) 252.
[140] L. J. Dolby and D. L. Booth, *J. Amer. Chem. Soc.*, 1966, **88**, 1049.
[141] (*a*) W. F. Goebel and G. E. Perlman, *J. Exp. Med.*, 1949, **89**, 479; (*b*) E. F. Jansen, A. L. Curl, and A. K. Balls, *J. Biol. Chem.*, 1951, **189**, 671.
[142] L. Maekawa and M. Kushibe, *Bull. Chem. Soc. Japan*, 1954, **27**, 277.

Miscellaneous Reactions.—The oxidation of the mixed aldols (LXXXIII; R = C_4H_9 or C_6H_{13}) proceeds readily in cold aqueous dioxan containing bicarbonate, the acids RCO_2H being formed.[143a] The reaction is comparable with the hydroxylation of other activated CH-compounds (p. 15). Cameron and his co-workers have suggested the intervention of free radicals arising from impurities in the dioxan. They observed two hydroxylations in the aphid pigment series which required the presence of benzoyl peroxide and thus involve free radicals.[143b] However their phenolic-quinonoid substrates are not strictly comparable with aldol (LXXXIII) and β-diketones (XXIV, XXVI), and in their conditions (periodate in refluxing aqueous dioxan) the specificity of the reagent is lost, even acetone being oxidised.[143c]

Glucose polymethyl ethers are appreciably oxidised.[143d] Iodine is liberated slowly from primary alkyl iodides. Prior hydrolysis appears to be promoted by the periodate ion (cf. p. 22) which oxidises the liberated iodide ion.[144]

Periodic acid has been used in a potentiometric estimation of uric acid,[145] and dilute sodium periodate in the detection of ferrocene derivatives on paper chromatograms.[146]

5 Periodate as a Co-oxidant

A mild, specific reagent for the oxidative fission of olefinic double bonds was developed by Lemieux and von Rudloff.[147] It consists of aqueous sodium periodate and potassium permanganate at pH 7·7 in a molar ratio of about 60:1. Intermediate aldehydes are oxidised further to acids which, with ketones, are the oxidation products. Permanganate first oxidises the olefin to the two ketols which are cleaved by periodate. The latter also reoxidises Mn^{V} to Mn^{VII} at this pH, so that the process amounts to a permanganate-catalysed oxidation by periodate.

The reagent has been particularly valuable in the analysis of oils and fats, butanol or pyridine being used as co-solvents.[148] The fragment acids from an unsaturated lipid are esterified in situ and identified by gas–liquid chromatography.[149] This method should also be useful in the oxidative degradation of terpenes,[150] steroids,[151] etc.

The action of the reagent on various functional groups has been examined to define its specificity.[152] For example, oxidation of isolated alcoholic groups

[143] (*a*) A. J. Birch, D. W. Cameron, Y. Harada, and R. W. Rickards, *J. Chem. Soc.*, 1959, 889; (*b*) D. W. Cameron, R. I. T. Cromartie, Y. K. Hamied, E. Haslam, D. G. I. Kingston, Lord Todd, and J. C. Watkins, *ibid.*, 1965, 6923; (*c*) P. Fleury and R. Boisson, *Compt. Rend.*, 1939, **208**, 1509; (*d*) G. D. Greville and D. H. Northcote, *J. Chem. Soc.*, 1952, 1945.
[144] A. B. Foster, M. Stacey, and R. W. Stephens, *J. Chem. Soc.*, 1959, 2681.
[145] A. Berka, *Analyt. Chim. Acta*, 1961, **25**, 434.
[146] A. N. de Belder, E. J. Bourne, and J. B. Pridham, *Chem. and Ind.*, 1959, 996.
[147] R. U. Lemieux and E. von Rudloff, *Canad. J. Chem.*, 1955, **33**, 1701.
[148] E. von Rudloff, *Canad. J. Chem.*, 1956, **34**, 1413.
[149] T. C. L. Chang and C. C. Sweeney, *J. Lipid Res.*, 1962, **3**, 170.
[150] R. U. Lemieux and E. von Rudloff, *Canad. J. Chem.*, 1955, **33**, 1710, 1714; 1965, **43**, 2660.
[151] M. E. Wall and S. Serota, *J. Org. Chem.*, 1959, **24**, 741.
[152] E. von Rudloff, *Canad. J. Chem.*, 1965, **43**, 1784.

is slow, but activating groups accelerated the oxidation (benzyl alcohol giving benzoic acid) and may lead to further degradation, as with allyl and tetrahydrofurfuryl alcohols. Aldehydes are oxidised smoothly to acids, some β-dicarbonyl compounds, not attacked by periodate alone, are oxidised, and acyclic ethers also suffer a slow oxidation. By the effective use of very small quantities of permanganate, greater selectivity is achieved than is normally associated with this reagent.

Disubstituted olefins are oxidised cleanly by a mixture (210:1 molar) of sodium periodate and osmium tetroxide in aqueous dioxan, but with more substitution, oxidation is slow.[153] Aldehydes can be isolated. The method is thus selective, and effects a valuable economy in the expensive and toxic osmium tetroxide.

A combination of ruthenium tetroxide and sodium periodate (1:15 molar) has been used in the mild oxidation of steroid C(3)- and C(6)- alcohols in neutral conditions.[154]

I thank Professor V. M. Clark for suggesting my first periodate experiment. To Professor L. N. Owen and to Dr. G. J. Buist I am indebted for valuable comments and to Professor C. A. Bunton and the Chemical Society for permission to reproduce diagrams (IV), (VII), and (VIII). The facilities for experiment and study at Cambridge and at Imperial College are gratefully acknowledged.

[153] R. Pappo, D. S. Allen, R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, 1956, **21**, 478.
[154] H. Nakata, *Tetrahedron*, 1963, **19**, 1959.