REVIEWS

New Applications of Periodic Acid and Periodates in Organic and Bio-Organic Chemistry

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Recent applications of periodic acid and periodates to organic and bio-organic chemistry are reviewed. Unique periodate oxidations and synthetic methods employing periodates are discussed.

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Es wird eine Zusammenfassung über neuere Anwendungen von Perjodsäure und ihren Salzen in der organischen und bioorganischen Chemie gegeben. Einige Perjodat-Oxidationen und Synthese-Verfahren mit Hilfe von Perjodaten werden abgehandelt.

One of the trends in modern organic synthesis is the development of selective reagents. In the area of oxidation reactions of organic compounds, the general tendency is to develop new, selective oxidizing agents. An aim of this review is to give a "new look" to the "old" oxidizing agents, namely, paraperiodic acid (H_5JO_6) and sodium metaperiodate ($NaJO_4$). Malaprade[1] was the first to introduce these reagents for glycols, and this discovery rapidly turned into an indispensable analytical tool in structural studies of polyols and carbohydrates. Thereafter periodic acid or periodates have been used extensively for cleavage of 1,2-hydroxy-aldehydes, -ketones, and -acids, 1,2-diketones, 1,2-amino-alcohols and -aldehydes, certain activated methylene groups, and cyclic 1,3-diketones. Very extensive literature references on the subject are presented in some review articles[2–10], a monograph[11], and in periodical reports on carbohydrates[12]. General organic periodate oxidations have been briefly summarized[13] and inorganic and physical aspects of periodates have been reviewed[14].

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The periodate oxidation of ribonucleic acids and their derivatives has been reviewed[15]; periodate oxidation of polynucleotides and subsequent reduction by sodium borohydride is the topic of a further review[16]. Some periodate oxidations in the steroid series have been summarized[17]. The periodate oxidations of enols, phenols, sulfur compounds, amines, hydroxylamines, hydrazines, hydroxamic acids, indoles, amino acids, and peptides have also been reviewed[18].

Some kinetic studies on the mechanism of periodate oxidations have been discussed[19]. The recent synthetic applications of periodates in organic chemistry have been excellently summarized[20,21,22].

Non-Malapradian reactions (different from those due to overoxidation of carbohydrates[11,23,24]) discussed in this survey cover some new oxidation reactions of periodic acid and periodates (salts) for a broad range of organic compounds. The new reactions include oxidation of condensed, aromatic hydrocarbons, nonbenzenoid hydrocarbons, phenols, β-diketones, lipids, terpenes, steroids, bile acids and pigments, amines, derivatives of hydrazine and hydroxylamine, azines, hydroxamic acids, indoles, tryptophan derivatives, and sulfur and selenium compounds; the review also includes organic periodate salts and iodination reactions, periodates as co-oxidants, synthesis of heterocyclic compounds, stereoselective and asymmetric synthesis, and some important bioorganic and organic-analytical aspects of periodates.

Although there is a considerable difference in the reactivity and chemistry of periodic acid (H_5JO_6) and sodium periodate ($NaJO_4$) towards many organic compounds (for example, towards polycyclic, aromatic hydrocarbons or indoles), an aim of this review is to treat them as a single reagent having multiple chemical applications. Some applications of iodic acid and its salts are also surveyed.

It is considered that a brief survey of some of the pertinent properties of paraperiodic acid may be of considerable help in understanding the mechanisms of the new oxidations with periodate and in comprehending the nature of this simple and often surprising reagent. The literature cited covers the period ending October 1972 and some important references for 1973 have been added.

1. Properties of Periodates and Periodate Oxidation Mechanisms

1.1. Some Properties of Periodic Acid and Periodates

Periodic acid is a strong oxidant; the standard potential E° for the periodate-iodate couple in acid solution is about 1.6 V; in alkaline solution, the value is lower ($E^\circ = 0.7$ V)[25]. The oxidizing power of free iodic acid (HJO_3) is only slightly lower than that of periodic acid[26]. Periodic acid ($pK^1 = 1.64$, $pK^2 = 2.3 \times 10^{-2}$, ref.[27,28]) is a weak acid, comparable in strength to metaphosphoric acid or oxalic acid; it is considerably weaker than iodic acid ($pK^1 = 0.72$). In aqueous solution (pH = 0–7), periodic acid exists as an equilibrium mixture between the free acid and its various ions, and a shift in the equilibrium is expected on dilution or on mixing with an organic solvent.

$$H_3JO_6^{2\ominus} \rightleftharpoons H_2JO_6^{3\ominus}$$
$$H_5JO_6 \rightleftharpoons H_4JO_6^{\ominus}$$
$$JO_4^{\ominus} + 2\,H_2O$$

Hence, an aqueous solution of periodic acid may be regarded as an equilibrium mixture of electrophilic and nucleophilic species; their existence in solution was deduced from their chemistry and from labeling experiments[29]. Exchange of oxygen between periodate and water is very rapid[30,31]; for example, the rate constant for the $H_2{}^{17}O$ exchange reaction[31] is 4.5×10^{-3} sec^{-1} (indicative of lability of the J—O bond).

An aqueous solution of periodic acid is, apparently, a mixture of monoanionic species[28,32,33]. However,

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it has been shown[34] that, in alkaline, aqueous solutions of periodate, a dimeric species is formed that is probably of the form $(O_4J—O—JO_4)^{4\ominus}$. Laser Raman spectroscopy has confirmed the existence of a dimeric periodate ion in aqueous solution (4.0 to 6.0 *M* periodic acid)[35].

X-Ray diffraction experiments[36] have shown that the periodate monoanion, $JO_4^{\ominus}$, is tetrahedral (sp^3). The dianion, $H_3JO_6^{2\ominus}$, or the ion $(JO_6)^{5\ominus}$ is octahedral (sp^3d^2)[37-39].

The J—O bonds in the octahedral ion $(JO_6)^{5\ominus}$ (an interatomic distance for J—O of 1.93 Å[37,39]), as shown by Pauling[40], have some double-bond character. The proportion of "double-bond", however, is much smaller, as compared to the J—O bonds in the tetrahedral ion $JO_4^{\ominus}$ (J—O distance of 1.79 Å[37,39]); the bonds in the latter ion are essentially double bonds[40]. Thus, the high lability of the J—O bond in the periodate ion $(JO_6)^{5\ominus}$ may be ascribed to the small, double-bond character of the octahedrally coordinated iodine[31,35,40]. In iodic acid (HJO_3, J—O distance of 1.80 Å[39]), or in its ion $JO_3^{\ominus}$ (J—O distance of 1.82 Å[39]), the bonds are mainly double bonds, thus reflecting the relative stability of the reagent.

1.2. Mechanism of Periodate Oxidation

The mechanism of periodate oxidation is still under active investigation[11]. In oxidative cleavage of 1,2-diols with periodate, the requirements are (i) a covalent link between the oxidant and reductant, and (ii) formation of a bidentate complex as an intermediate which then breaks down to products via a two-electron process[19,41]. By analogy to the reaction pathway known for lead(IV) acetate with 1,2-diols, it was suggested[42] that a cyclic ester intermediate is formed between the periodate and the glycol. However, much of the evidence for the cyclic intermediate containing periodate has come from kinetic studies[43-50] and from other work[51-56]. A six-membered cyclic intermediate was proposed[56] in the hydroxylation of malondialdehyde by periodate; essentially the same mechanism was proposed[57] from kinetic studies of the oxidation of malonic acid by periodate. Convincing evidence[58,59] was obtained for the formation of tridentate complexes between periodate and certain *cis-cis* (1,2,3-*cis*) triols and the steric factors involved in the formation of a cyclic ester intermediate have been studied[19,60]. Those glycols, such as *trans*-9,10-decalindiol and fixed diaxial 1,2-diols (*trans*-cyclopentane- or *trans*-cyclohexane-diols), for which cyclic intermediates are impossible, do not react with periodic acid[61]. The hypothesis of formation of the intermediate coordination complex was based on the fact that the activation energy for the breakdown of the 1,2-diol/periodate complex was 30-40 Kcal·mole lower than would be expected for cleavage of a nonactivated C_δ—H bond with a bond energy (DE_{C-H} = 89-96 Kcal·mole) or a direct, homolytic cleavage of an O—H bond (DE_{O-H} = ~110 Kcal·mole). Formation of a periodate intermediate in high concentration was not, however, found in the periodate oxidation of 1,4-benzenediol (*p*-quinol)[48] or in the oxidative hydrolysis of quinol ester by periodic acid[51]. Contrary to reports[62], a free-radical intermediate was not observed in the

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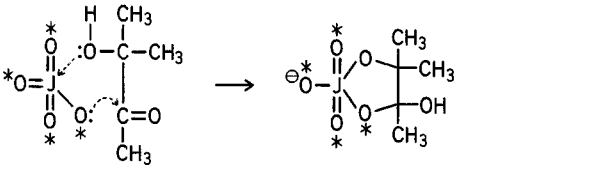
periodate oxidation of 1,2-diols[63], sugar alcohols or inositols[64], or malonic acid (E.S.R. studies)[65]. However, kinetic studies[66] of the oxidation of diethylamine with periodate supported the theory of the formation of an intermediate complex, and the participation of free radicals. Dimerization of pyrene to 1,1′-bipyrene following treatment with periodic acid (discussed in section 2.2) also involves a free-radical intermediate[65,67]. It is now believed that all of the ionic mechanisms found[68] in the oxidation of benzenediols and their mono-ethers with sodium periodate can be partially operative; a paramagnetic intermediate was trapped at 77 °K in periodate oxidations of similar compounds[69]. Low-field, E.S.R. studies of oxidative cleavage of aromatic azines with periodic acid showed that formation of nitrogen may arise through collapse of a dimer complex initially formed between periodate anion and a resonance structure of the azine, for example, benzalazine[35].

This technique, however, failed to obtain any evidence for an intermediate complex between periodate and sugar alcohols, indicating that the alcohol was apparently oxidized by monoanionic periodate species[64].

A molecular-orbital (MO) approach to prediction of a transition state of the chemical reaction for electrocyclic systems[70,71] has been extended to prediction of the pathway in many oxidation reactions, including periodate oxidation[72]. As a result of this approach, cleavage of benzalazine with periodic acid may initially involve, *as a single step*, the addition of $JO_4^{\ominus}$ (or its hydrate) across the conjugated azine system, to give an iodate J(V) complex, and this view is supported from MO symmetry rules[73].

Present knowledge on periodate oxidations supports the view of an initial electrophilic or nucleophilic attack by various periodate anions on a suitable center (nucleophilic or electrophilic, respectively) of an organic molecule; a product of this action can be a cyclic intermediate, or an open-chain periodic ester, or a free radical. Unequivocal support for these views has come from isotopic-labelling studies[29].

When methylacetoin[29] (3-hydroxy-3-methylbutan-2-one, **1**) was oxidized with ^{18}O-labelled periodate, the periodate oxygen atoms were linked to carbon (intermediate **2**), and the acetic acid (**4**) produced was labelled, whereas the acetone (**3**) was not. The mechanism thus involves a nucleophilic attack by the periodate ion on the carbonyl group of **1**, and coordination of the hydroxyl group on the iodine atom of the periodate (an example of a nucleophilic-electrophilic property of the oxidant). This mechanism has been rewritten[18] to indicate more clearly the mode of the periodate attack (Scheme **A**).

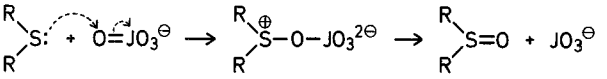


1 **2** **3** **4**

Scheme **A**

The 1,2-diol-periodic esters arise from electrophilic attack of the oxidant on the diols.

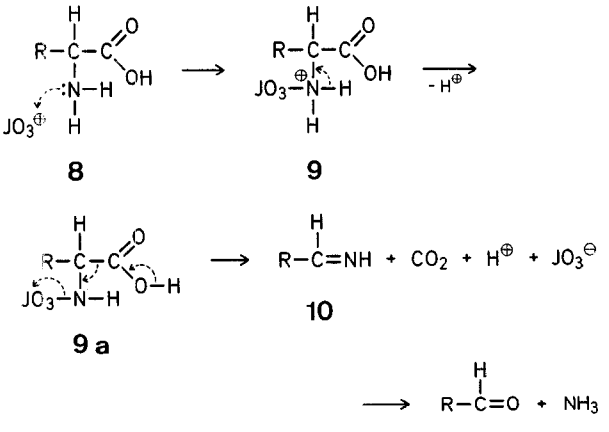
On comparing the quantitative conversion of an organic sulfide (**5**) into sulfoxide **7** by periodate[74], it was suggested[19] that periodate acts as an electrophilic oxidant transferring oxygen to the organic sulfide atom of **5** to give **6** (Scheme **B**).



5 **6** **7**

Scheme **B**

It has been suggested[75] that periodate oxidation of glycine and of the *N*-substituted glycine (e.g. **8**) proceeds by an initial, electrophilic attack of oxidant on nitrogen to give the intermediate **9**; the latter (as **9a**) then decomposes via the imino intermediate **10** to give the aldehyde **11** (Scheme **C**).



8 **9** **9a** **10** **11**

Scheme **C**

[64] A. J. Fatiadi, E.S.R. studies, unpublished observation. On contact with a concentrated solution of periodic acid (5*M*), solid *myo*-inositol reacts violently (exothermic reaction), with copious evolution of iodine.

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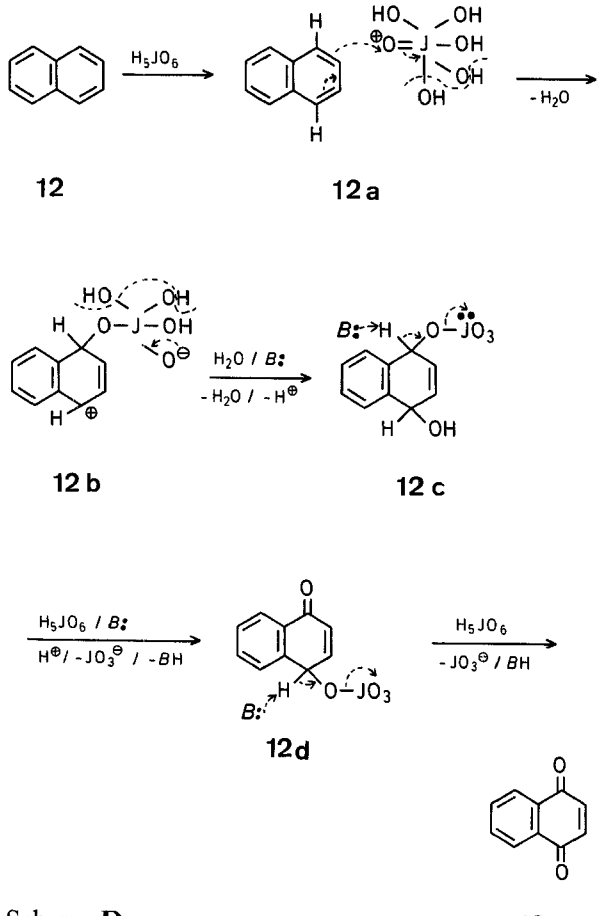
In kinetic studies on the periodate oxidation of glyoxal, pyruvaldehyde, and 2,3-butanedione, the pH-rate behavior was interpreted[76] in terms of a nucleophilic attack on the carbonyl group of the substrate by three forms of periodate, namely, H_5JO_6, $H_4JO_6^{\ominus}$, and $H_3JO_6^{2\ominus}$.

The mechanism for periodate oxidation of naphthalene (**12**) to 1,4-naphthoquinone (**13**) (Scheme **D**), as suggested[65], involves electrophilic attack of periodic acid (hydrated or anhydrous form), as shown in **12a**, on an electron-rich position of **12**[77], with formation of the intermediate **12b**. Addition of water to the cationic carbon of **12b** affords a periodate ester of the 1,4-diol **12c**; a nucleophilic attack (by solvent hydroxide ion or periodate anion) removes the proton, thus facilitating the departure of the iodate ion with its pair of electrons.



12 12a 12b 12c 12d 13

Scheme **D**

A further oxidation with periodic acid via periodate ester intermediate **12d** (compare anthrone **20**⇌**21**) produces dione **13**. E.S.R. studies[65] also support an ionic mechanism in the conversion of **12** into dione **13**; moreover, little or no oxidation of **12** to **13** has been observed in the presence of sodium periodate, indicating that more strongly electrophilic periodate species than those derived from sodium periodate are needed in order to effect the oxidation of **12**.

The kinetics of the periodate oxidation of *p*-hydroxyphenyl phosphate were studied[53] as a model for biological phosphorylation[78]. The authors concluded that reaction can be rationalized by (i) electrophilic attack of the oxidant on the phenolic hydroxyl group, followed by a concerted P—O bond fission, or (ii) formation of the cationic oxygen species, followed by loss of metaphosphate ion, which should react rapidly with water (to give *p*-benzoquinone). No periodate intermediate was observed in this oxidation.

It was suggested[79] that oxidation of alkylenephosphine with periodate may proceed via a cyclic intermediate, to give a diketo derivative, and that the reaction may involve nucleophilic attack of the oxidant on a partially electrophilic phosphorus atom.

A novel mechanism useful in RNA sequence-analysis was proposed[80] for the periodate oxidation of adenosine 5′-phosphate in the presence of methylamine. This mechanism requires the formation of a cyclic enamine, and was used for explaining the formation of both phosphate and adenine, the former by rearrangement of the enamine to a conjugated system, and the latter by periodate oxidation of the enamine (an example of the combined electrophilic-nucleophilic roles of the oxidant). Consequently, the periodate oxidation of an organic compound may be regarded as a function of the electrophilic and nucleophilic roles of the oxidant, and, as noted[65], the oxidizing species involved may depend on the nature of the substrate employed.

2. Condensed Aromatic Compounds

2.1. Periodic Acid, a Novel Oxidant of Polycyclic, Aromatic Hydrocarbons

2.1.1. Scope and Limitations

Results obtained in the original studies[65,81] on the action of periodic acid on a variety of polycyclic, aromatic hydrocarbons revealed that linear and angular polycyclic, aromatic hydrocarbons having the acene structure (anthracene, benz[*a*]anthracene, naphthacene, pentacene, and their analogs[82]) are the

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[82] E. Clar, *Polycyclic Hydrocarbons*, Academic Press, New York, 1964, Vol. 1, pp. 50, 56.

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most reactive; next are the condensed-ring, aromatic compounds having the phene structure (acenaphthene, benzo[*a*]pyrene, pyrene, etc.) and compounds having one, or two, active methylene groups (anthrone, acenaphthene, and fluorene); chrysene and picene are less reactive. Little or no reaction was observed with biphenyl, coronene, fluoranthene, perylene, *p*-terphenyl, and triphenylene. In general, attack by periodic acid is favored at a reactive center, instead of a reactive bond of the aromatic ring in the polycyclic hydrocarbons[65]. These studies showed that the behavior of periodic acid towards polycyclic, aromatic hydrocarbons has a unique, two-fold character: it can produce coupling products through a radical intermediate, or quinones by two-equivalent oxidation.

In the oxidation of polycyclic, aromatic hydrocarbons (and all other suitable organic compounds) with periodic acid, three major factors should be considered: (i) the solvent, (ii) the temperature, and (iii) the proportion of the oxidant. The choice of a solvent appears to be very important, and the effect of various organic solvents (either nucleophilic or electrophilic) on the reactivity of hydrocarbons has been investigated[65]. The relative stability of acetic acid in the presence of periodic acid makes this solvent the most important as a co-solvent, followed by a series of aprotic solvents miscible with water; namely, *N*,*N*-dimethylformamide, *p*-dioxan, acetonitrile, acetone, tetrahydrofuran, methyl sulfoxide, and acetic anhydride. Methyl sulfoxide was used in the periodic acid oxidation of anthracene[65]; however, use of methyl sulfoxide as the co-solvent in the presence of concentrated periodic acid has been reported to be hazardous[83]. A violent reaction occurred when acetic anhydride was used in the oxidation of pyrene with periodic acid, particularly on application of heat. *N*,*N*-Dimethylformamide is a useful co-solvent in the periodic acid oxidation of polycyclic, aromatic hydrocarbons and many other organic substrates, although it slowly interacts with the oxidant[84].

As reported[65,81], perylene is little affected on treatment with periodic acid in the common organic solvents; however, this hydrocarbon can be oxidized when dissolved in concentrated sulfuric acid (to give a deep-purple solution of perylene cation radical) and then treated with aqueous periodic acid to complete discharge of the original purple color[85] (periodic acid has its highest standard potential $H_5JO_6/JO_3^{\oplus}$ couple in 18*M* sulfuric acid: $E^{\circ} = 1.88\,V$[86]).

[83] J. J. M. Rowe, K. B. Gibney, M. T. Yang, G. G. M. Dutton, *J. Amer. Chem. Soc.* **90**, 1924 (1968).

[84] A communication on the product of interaction between DMF and periodic acid (m.p. 84–86°) will be published elsewhere.

[85] A. J. Fatiadi, unpublished results.

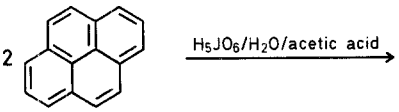
[86] N. S. Astakhina, V. G. Gurevich, *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.* **9**, 724 (1966); *C. A.* **66**, 51 624 (1967).

The use of other acids (phosphoric or perchloric) as co-solvents brings an interesting implication to the periodate oxidation of organic compounds.

To initiate the oxidation of polycyclic, aromatic hydrocarbons with periodic acid, some degree of heating was found to be necessary. In the conversion of pyrene into 1,1′-bipyrene, only mild warming, at 40 to 50°, is needed. The oxidations that result in quinone formation usually require 5 to 10 min of heating at 90 to 130° to start them; then, the temperature must be lowered to 60 to 80° in order to avoid vigorous (sometimes violent) reaction. Oxidative dimerization of pyrene to 1,1′-bipyrene was effected with a 1:1 molar ratio of periodic acid to hydrocarbon. However, in the oxidation of other hydrocarbons to quinones, ~4.2 mol of the oxidant were used per mol of the hydrocarbon.

2.2. Oxidative Dimerization of Pyrene to 1,1′-Bipyrene[67,81]

Pyrene (**14**) is converted into 1,1′-bipyrene (**15**) in 68–72% yield by reaction with periodic acid in aqueous acetic acid.



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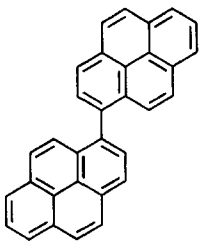

15

The success of this simple synthesis is attributed to the specific ability of the oxidant to associate with pyrene molecules, and to abstract protons to produce acetic acid-solvated radicals capable of dimerization to bipyrene. Similar treatment of fluorene with periodic acid in warm, aqueous acetic acid gave a dimer (1,2-bis[2,2′-biphenylylene]ethylene) in about 10% yield; E.S.R. monitoring revealed the presence of a radical intermediate[65].

Preparation of 1,1′-Bipyrene[67]:

A solution of periodic acid (12 g, 53 mmol) in water (10 ml) and glacial acetic acid (40 ml) at 50° is added to a solution of pyrene (10.1 g, 50 mmol) in glacial acetic acid (300 ml) preheated to 50° in a 500-ml Erlenmeyer flask. The mixture is stirred at 48–51° for 45 min; warm water (3 ml) is then added, and the mixture is stirred for an additional 15 min. The mixture is cooled to about 15–20°, and the crude bipyrene is collected on a Büchner funnel and washed with warm, 90% aqueous acetic acid (2 × 10 ml). The still-wet product is then suspended in a solution of sodium hydrogen sulfite (5 g) and sodium hydrogen sulfite dihydrate (10 g) in 50% aqueous ethanol (200 ml), and the mixture is stirred at 65° for 30 min. The hot suspension is filtered, and the product is washed successively with warm water (50 ml) and warm 95% ethanol (50 ml); yield of crude bipyrene: 6.4–6.8 g. Concentration at 40° of the original filtrate to about 120 ml yields an additional crop, which is collected on a Büchner funnel, and stirred with

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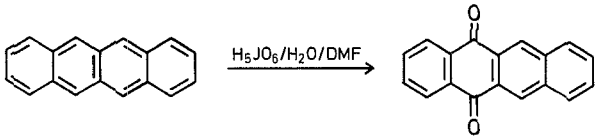
the hydrogen sulfite solution (50 ml) just described: total yield: 7–7.5 g (70–75%); m.p. 310–315°.

The crude bipyrene is purified in the following way. Crude material (2.5 g) is dissolved in hot toluene (425 ml), and the solution is decolorized with carbon (5 g) and rapidly filtered. The product crystallizes out, but is redissolved by heating, giving a deep-blue, fluorescent solution, which is kept overnight at room temperature. Bipyrene crystallizes as light-green lustrous plates; yield: 1.5–1.6 g; m.p. 334–336° (uncorr.). Concentration of the filtrate, and extraction of the filter paper and decolorizing carbon, yields additional material. The total yield of recrystallized bipyrene is 1.7–1.8 g (68–72%).

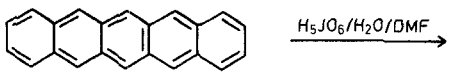
2.3. Oxidation of Polycyclic, Aromatic Hydrocarbons to Quinones[65,81]

On treatment with periodic acid, several polycyclic, aromatic hydrocarbons, particularly those having the acene structure, are oxidized to quinones, and not to dimeric products. This reaction does not occur in the presence of sodium periodate. E.S.R. monitoring indicated that there is no radical participation in the oxidation. A solution of naphthacene (**16**) in *N,N*-dimethylformamide was oxidized with aqueous periodic acid to give naphthacenequinone (**17**) in 80–85% yield.



16 **17**

Similarly, pentacene (**18**) was oxidized to pentacenequinone (**19**) in 81–87% yield.



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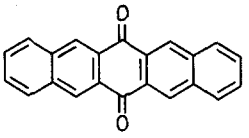
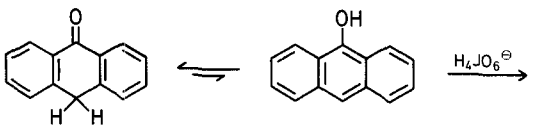
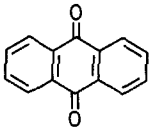


19

The oxidation of anthrone (**20**) with periodic acid, to give anthraquinone (**22**), apparently involves a tautomer (9-anthrol, **21**); the reaction can then proceed via a free radical or a periodic ester intermediate; a concerted process involving both pathways is a strong possibility.



20 **21**

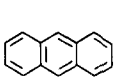
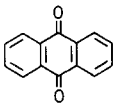
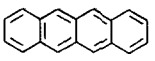
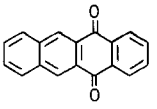
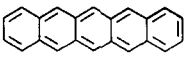
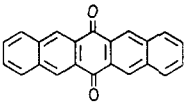
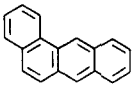
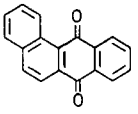
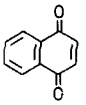
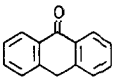
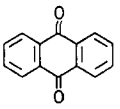
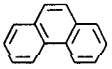
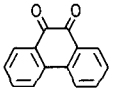


22

Iodic acid in glacial acetic acid, at the boiling point, oxidizes phenanthrene to phenanthrenequinone[87].

Oxidation of Pentacene to 6,13-Pentacenedione[65,81]:
A solution of pentacene (0.28 g, 1 mmol) in DMF (75 ml) is stirred with an aqueous solution of periodic acid (0.92 g, 2 ml, 4 mmol) at 135° for 5 min, and then at 60° for 30 min. The mixture is treated with water (30 ml) and cooled, to yield the quinone; 0.250–0.267 g (81–87%); m.p. 382–384°. Sublimation at 250°/0.05 torr, followed by recrystallization from 1:1 (v/v) *N,N*-dimethylformamide/ethanol, gave light-yellow needles; m.p. 393–395°.

Table 1. Oxidation of Polycyclic, Aromatic Hydrocarbons to Quinones by Periodic Acid[65,81]

Compound	Solvent	Product	Yield (%)
	DMF		91–95
	DMF		80–85
	DMF		81–87
	DMF		78–82
	AcOH		70–76
	AcOH		94
	AcOH		65–70
	*p*-dioxan		50

2.4. *Oxidative Hydrolysis*[85]

On treatment with periodic acid in warm, aqueous acetic acid, 1,6-diacetoxypyrene (**23**) is converted into 1,6-pyrenedione (**24**, 80% yield). The reaction involves simultaneous hydrolysis and oxidation of a 1,6-dihydroxypyrene intermediate. This method can be applied to analogous compounds.

[87] A. G. Williams, *J. Amer. Chem. Soc.* **43**, 1911 (1921).
[88] J. H. Bowie, D. W. Cameron, *J. Chem. Soc.* **1965**, 5651.
[89] D. W. Cameron, R. I. T. Cromartie, Y. K. Hamied, E. Haslam, D. G. I. Kingson, Lord Todd, J. C. Watkins, *J. Chem. Soc.* **1965**, 6923.
D. W. Cameron, Lord Todd in "*Oxidative Coupling of Phenols*", W. I. Taylor, A. R. Buttersby Eds. Marcel Dekker, New York, 1967, pp. 203–241.

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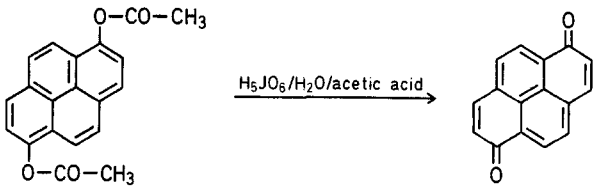
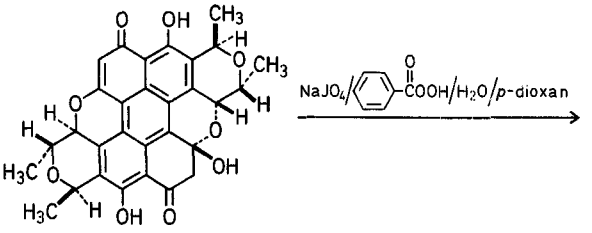


23 24

2.5. Oxidation of Aphid Pigments

In a study of the structure of natural pigments[88,89] of aphids (all of which are polycyclic quinones), chrysoaphin-sl-1 (**25**) was oxidized with sodium periodate/benzoyl peroxide in refluxing aqueous *p*-dioxan to give dihydroxychrysoaphin-sl-1 (**26**) (resembling, in its structure, 4,5-dihydroxy-3,10-perylenequinone[90]) in 50% yield[89]. However, oxidation of **25** without benzoyl peroxide produced **26** in only about 20% yield; hydroxylation of **25** in the presence of benzoyl peroxide may involve free radicals[89].



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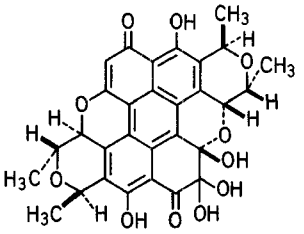


26

3. Nonbenzenoid Aromatics and Cyclopolyenes

3.1. Oxidation of Azulene[91]

The application of periodic acid is being extended to the study of the oxidation of nonbenzenoid, aromatic hydrocarbons.

Oxidation of Azulene:

A solution of azulene (0.64 g, 5 mmol) in acetic acid (40 ml) was stirred with an aqueous solution (10 ml) of periodic acid (2.3 g, 10 mmol) at 20° for 30 min. Water (10 ml) was added, and the black-green precipitate was collected, washed, and dried; yield 0.85 g.

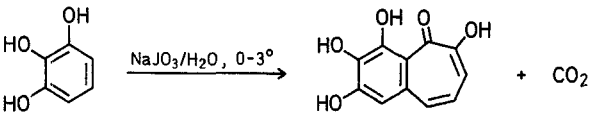
The product (recrystallized from aqueous dimethylformamide and dried at 150°/0.05 torr) is a black, glass-like, amorphous powder which is strongly paramagnetic.

The stability of this radical is shown by the fact that heating of a sample at 485° for 15 min (evolution of iodine) left a residue (Found: C = 93.5%; H = 3.1%, I = 2.9%) that was still paramagnetic.

A polymeric, charge-transfer complex involving iodine appears to be a possible structure of this radical.

3.2. Oxidation of Pyrogallol to the Tropolone Derivative

A most remarkable application of sodium iodate was the preparation of purpurogallin (2,3,4,6-tetrahydroxy-5*H*-benzocyclohepten-5-one) **28** in 65% yield by oxidative cleavage of the cycloaddition intermediate of pyrogallol, **27**; this was accomplished in 1930[92]. Purpurogallin is not formed by phenol coupling of pyrogallol, but is believed to involve a special dimerization of the hydroxy-*o*-quinone followed by elimination and aromatization steps[92].



27 28

3.3. Oxidation of 1,3,5-Cycloheptatriene (Tropilidene)[85]

The oxidation of 1,3,5-cycloheptatriene with sodium periodate proceeds smoothly when catalyzed with osmium(VIII) oxide, ruthenium(VIII) oxide, or a trace of potassium permanganate (in aqueous acetone/dimethylformamide or aqueous dimethylformamide/acetic acid); similarly catalyzed periodate oxidations (or hydroxylations) were observed with cyclooctene, cyclododecene, 1,5-cyclooctadiene, 1,5,9-cyclododecatriene, and squalene.

3.4. Oxidation of Ferrocene

Ferrocene in glacial acetic acid is oxidized immediately when treated with aqueous periodic acid; the precipitated colorless, paramagnetic solid is apparently iron(III) iodate[85].

4. Steroids

Periodate oxidations in the steroid field have been briefly reviewed[17]. Oxidation by periodic acid of the side chain on C-17 in steroids was originally used by Reichstein and coworkers[94,95]; the product of periodate degradation was either a C-17 ketone[94] or hydroxycholanic acid[95].

[90] A. J. Fatiadi, *J. Res. Nat. Bur. Stand.* **72A**, 39 (1968).
[91] A. J. Fatiadi, *Chem. Commun.* **1968**, 456.
[92] T. W. Evans, W. M. Dehn, *J. Amer. Chem. Soc.* **52**, 3674 (1930).
See also A. G. Perkin, A. B. Steven, *J. Chem. Soc.* **83**, 192 (1903).
D. Caunt, W. D. Crow, R. D. Haworth, C. A. Vodoz, *J. Chem. Soc.* **1950**, 1631; *J. Chem. Soc.* **1951**, 1313.
[93] L. Horner, K. H. Weber, W. Durkheimer, *Chem. Ber.* **94**, 2881 (1961) and references therein.
See also J. C. Salfeld, *Angew. Chem.* **69**, 723 (1957).
[94] T. Reichstein, *Helv. Chim. Acta* **20**, 978 (1937).
[95] T. Reichstein, T. C. Meystre, J. V. Euw, *Helv. Chim. Acta* **22**, 1107 (1939).

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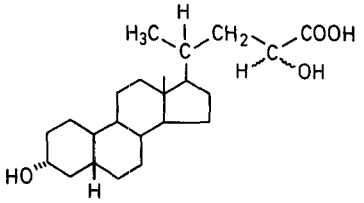
Periodic acid oxidation was also used in a novel process for elimination of the 21-hydroxyl group from the dihydroxyacetone side-chain of cortical steroids by addition of methyl Grignard reagent followed by glycol cleavage[96,97].

New developments and some interesting reactions in this area are summarized next.

4.1. Conversion of α-Hydroxy Bile Acids into Aldehydes: Degradation with Loss of One Carbon Atom

Periodate oxidation was applied[98] for stepwise degradation of the α-hydroxy acid side-chain in bile acids to produce aldehydes, unlike the known Barbier-Wieland degradation that gives an acid[99]. In this way 3α,23-dihydroxycholanic acid (**29**) in water/acetone/acetic acid was oxidized to 3α-hydroxynorcholanal (**30**) in 90% yield. However, replacement of acetone by ethanol as a component in the solvent mixture in a similar periodate oxidation of **29** resulted in formation of a higher oxidation product (norcholanic acid, **31**), thus showing that the product formed depends on the solvent used in the sodium periodate oxidation of bile acids. Likewise, 23-hydroxycholanic acid furnished norcholanal in 90% yield[98].



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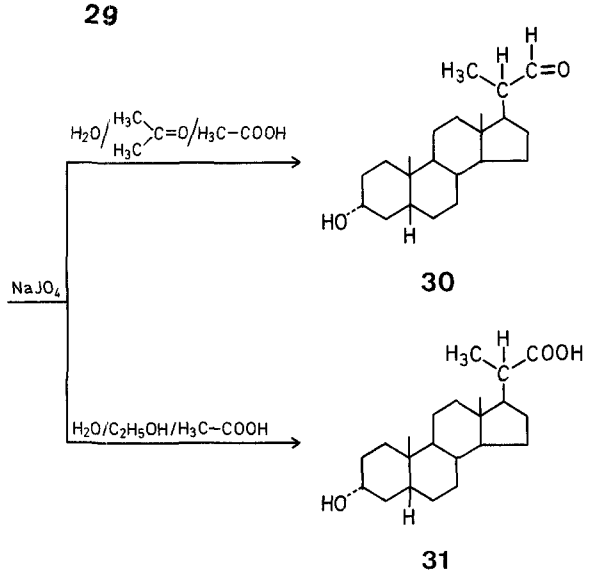

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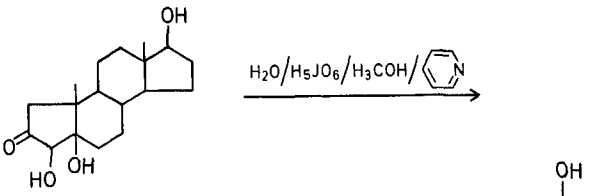
Treatment of the steroid α-hydroxy hemiacetal side-chain with sodium periodate (in acetone/acetic acid/water) causes the loss of one carbon atom with formation of an aldehyde of type **30** in 100% yield (—CH(OH)CH(OH)(OC_2H_5)→CHO)[100].

4.2. Hydroxy Lactones from Cyclic α,β-Dihydroxy Ketones



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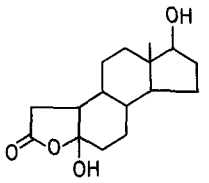

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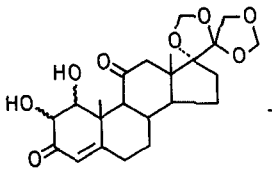
Oxidation of A-Norandrostan-2-one-3β, 5β, 17β-triol (32): Treatment of A-norandrostan-2-one-3β, 5β, 17β-triol (**32**) (1.93 g) in pyridine methanol with aqueous periodic acid for 16.5 h at *room temperature* gave 3-oxa-A-norandrostane-5,17β-diol-2-one (**33**) in about 70% yield (1.14 g)[101].

Treatment of 1,2-dihydroxycortisone derivative (**34**) in aqueous ethanol with sodium periodate gave lactol **35** in 18% yield, and similar treatment of the epoxide of 1,2-dihydroxycortisone derivative (**36**) in aqueous methanol furnished lactol **37** in 51% yield[102]; surprisingly, the epoxide ring was not attacked by the periodate ion.



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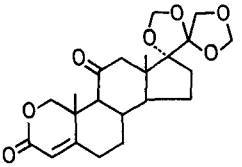

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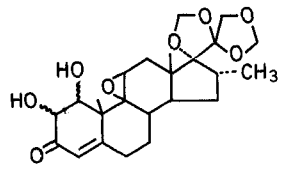

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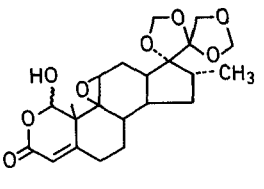

37

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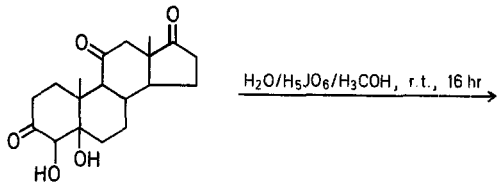
4.3. Keto Acids from Dihydroxy Ketones

Oxidation of the 4,5-dihydroxy-3-ketone **38** with periodic acid in methanol opened up the A ring and gave keto acid **39** in 77% yield[103].



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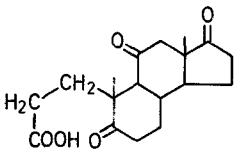
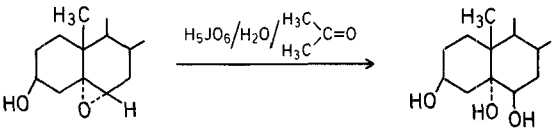


39

4.4. Hydrolysis of an Epoxide Ring

Hydrolysis of an epoxide ring of a steroid was performed with periodic acid (compare, however, the action of sodium periodate on steroid **36**).

Oxidation of Cholesterol α-Oxide (40):
A solution of cholesterol α-oxide (**40**; 1 g) in hot acetone (30 ml) was treated with a solution of periodic acid dihydrate (0.625 g) in water (10 ml). The mixture was refluxed for one hour and cooled, and cholestane-3β, 5α, 6β-triol (**41**) was collected; yield 0.83 g (81%), m.p. 231–232°[104].



40 **41**

4.5. Oxidation of Cholesterol

In general, alkenes are inert to uncatalyzed sodium periodate oxidation, at least at room temperature; however, the cleavage oxidation of certain isolated double bonds and terminal double bonds by periodic acid has been reported[105,509]. Also certain cyclic (conjugated) nonbenzenoid compounds and certain steroids containing a $\Delta^{5,6}$ double bond may respond specifically to the oxidizing action of periodic acid. For example, cholesterol (**42a**) (Scheme **E**) is oxidized with a three-fold excess of the oxidant to give cholestane-3β,5α,6β-triol (**42c**) in 60% yield; with a ten-fold excess of the oxidant, the concomitant formation of 3β,5α-dihydroxycholestan-6-one (**42e**) also occurred[106]. The triol **42c** is not an intermediate, being unaffected under the reaction conditions (*trans*-diaxial *vic*-glycol). The oxidation may involve the 5,6-epoxide derivative (**42b**) as an intermediate, and this possibility is supported by the known cleavage of a steroid epoxide (**40**) by periodic acid[104]. It has also been suggested[106] that, in the presence of an excess of periodic acid, scission of epoxide **42b** may give an intermediate periodic ester **42d** which collapses by α-elimination to the 6-ketone (**42e**) and iodate, in agreement with nonconversion of **42c** into **42e** by periodic acid.

42a **42b** **42c** **42d** **42e**

Scheme E

5. Periodic Acid as a New Oxidant for the Degradation of Bile Pigments. Biliverdine Type of Reaction Intermediate on Oxidation of Bilirubin with Periodic Acid

Treatment of a solution of bilirubin (**43**) in methyl sulfoxide with an aqueous solution of periodic acid, with stirring at 15–20° for 10 min, gives at first a dark-green solid which can be filtered off (prolonged treatment of this solid with periodic acid causes degradation). The solid can be recrystallized from methanol/ether, to give a bluish green, microcrystalline solid (**44**) (45% yield) having a biliverdine type of U.V. absorption; the product contains an iodine atom, and is believed to be a charge-transfer complex[107].

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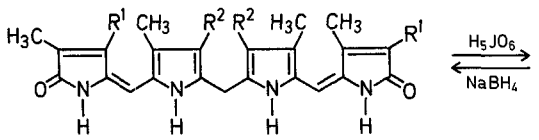

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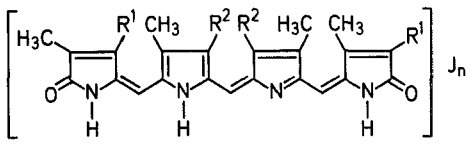


R^1 = $-CH=CH_2$
R^2 = $-CH_2-CH_2-COOH$

44

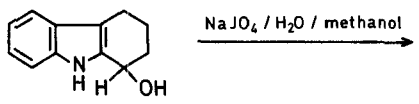
Aqueous periodic acid may be used to degrade such porphyrins as hemin, hematoporphyrin, protoporphyrin, or chlorophyll, as well as such bile pigments as bilirubin (**43**), biliverdine (**44**), urobilin, and other rubins, verdines, and violines. The final degradation products from bile pigments or porphyrins, usually mono-pyrrole derivatives, can be separated, by extraction with ether or ethyl acetate, into an acid fraction and a neutral fraction.

6. Heterocyclic Compounds

6.1. Indole Derivatives

Sodium periodate has been used to cleave 1,2-diol groupings in molecules containing an indole nucleus, without apparent oxidation of the indole ring[108,109]; the cleavage of ethyl indole-3-propanoylglycinate by periodate has been briefly reviewed[110,111].

A study revealed[112] the specificity of sodium periodate and periodic acid toward the mono- or di-substituted indoles. It was found that sodium periodate cleaves the indolic double bond of 2,3-disubstituted indoles to give keto amides in good yield, whereas periodic acid oxidation of 2,3-dimethylindole or of tetrahydrocarbazole affords the corresponding 2-acylindoles. Treatment of 1-hydroxytetrahydrocarbazole (**45**) with sodium periodate gave a hemiacetal of 3-hydroxy-1-aza-8,9-benzcyclononene-2,7-dione (**46**⇄**46a**).



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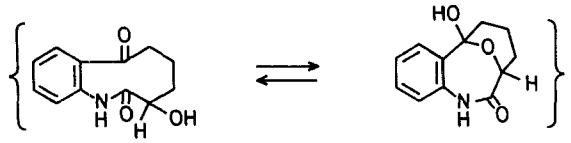


46 46a

Treatment of 2,3-dimethylindole (**47**) with sodium periodate gave *o*-acetamidoacetophenone (**48**), whereas treatment with periodic acid produced 2-formyl-3-methylindole (**49**) (see Tables 2 and 3).

Table 2. Products from the Sodium Periodate Cleavage of Indole Derivatives[112]

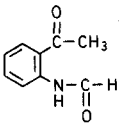
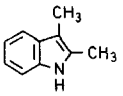
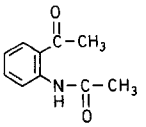
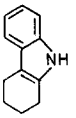
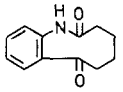
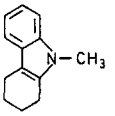
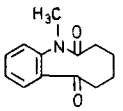
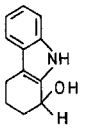
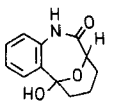
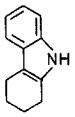
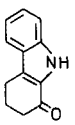
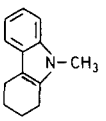
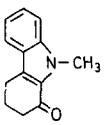
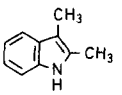
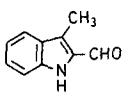
Compound	Product	Yield (%)
		82
		85
		99
		77
		45

Table 3. Products from the Periodic Acid Oxidation of Indole Derivatives[112]

Compound	Product	Yield (%)
		62
		25
		10

[108] E. E. van Tamelen, L. J. Dolby, R. G. Lawton, *Tetrahedron Lett.* **1960**, 30.
[109] J. Barton, J. Harley-Mason, *Chem. Commun.* **1965**, 298.
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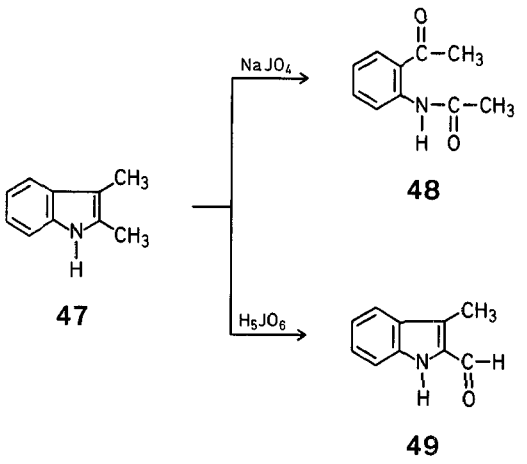
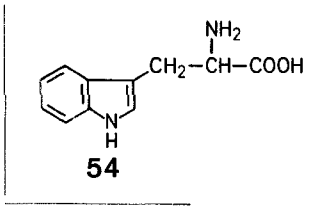


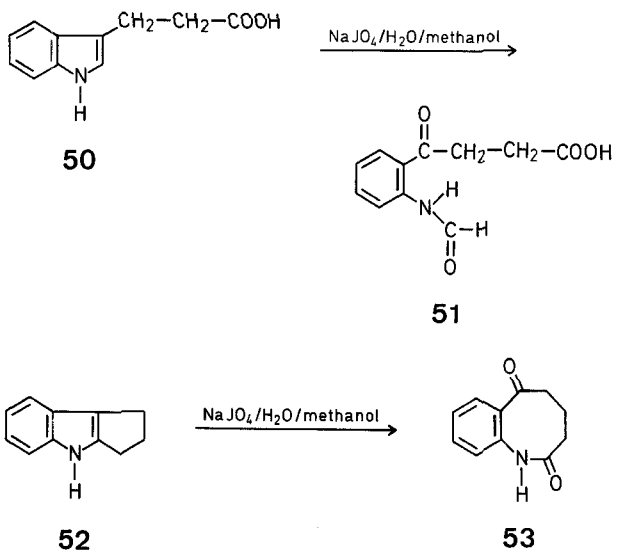
However, oxidation of 2-methylindole with sodium periodate gives a complex mixture from which two indoxyl dimers have been isolated and identified[113,114]. Treatment of 2,3-diphenylindole with sodium periodate gave 2,2-diphenylindoxyl and *o*-benzamidobenzophenone as the major products; and oxidation of tetrahydrocarbazole with methanolic periodic acid gave 11-methoxytetrahydrocarbazolenine[114].

Opening of the heterocyclic ring in 3-alkylindoles or 2,3-alkylindoles[114] by sodium periodate (but not by periodic acid) can partially be explained as due to the nature of the 2,3-double bond in substituted indoles[115]. The periodate ion, which is less electrophilic, hydroxylates the 2,3-double bond and then cleaves the product, whereas the more electrophilic species derived from periodic acid oxidizes the alkyl group attached at C-2 to a carbonyl group.

Cleavage of the indole ring by sodium periodate was also observed in other 3-substituted indole derivatives[116]. Treatment of 3-(3-indolyl)propanoic acid (**50**) with sodium periodate in aqueous methanol gave 4-(2-formamidobenzoyl)propanoic acid (**51**) in 68% yield, and, similarly, the butanoic acid analog (51% yield) and propanoylglycine (35% yield) were



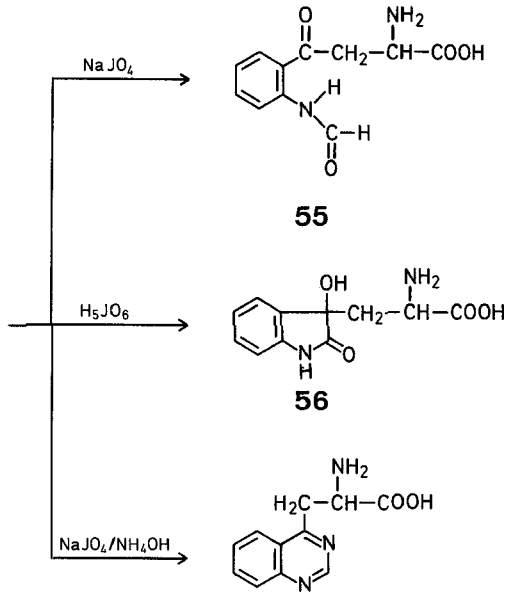
obtained. Cyclopent[*b*]indole (**52**) was oxidized by periodate to lactam **53** (1,2,3,4,5,6-hexahydrobenzazocine-2,6-dione) in 73% yield and 1,2,3,4-tetrahydrocarbazole was similarly converted into the corresponding lactam in 81% yield.



The mechanism of periodate oxidation of 2-substituted indoles may involve a radical intermediate, and an E.S.R. study on this subject would be valuable.

6.2. Tryptophan Derivatives

The behavior of tryptophan toward sodium periodate and periodic acid is analogous to that of 3-substituted indoles. The reaction of L-tryptophan (**54**) in aqueous solution with sodium periodate gives *N*-formylkynurenine (**55**); reaction with periodic acid produces dihydroindolyl-L-alanine (**56**), and reaction with sodium periodate in the presence of ammonia furnishes the quinazoline derivative **57**[116]. Although the yields were low, the reaction is interesting, and warrants further exploration for use in structural studies of proteins and synthesis of new heterocyclic derivatives.



[115] R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, 1970, Chapters 2 and 3.

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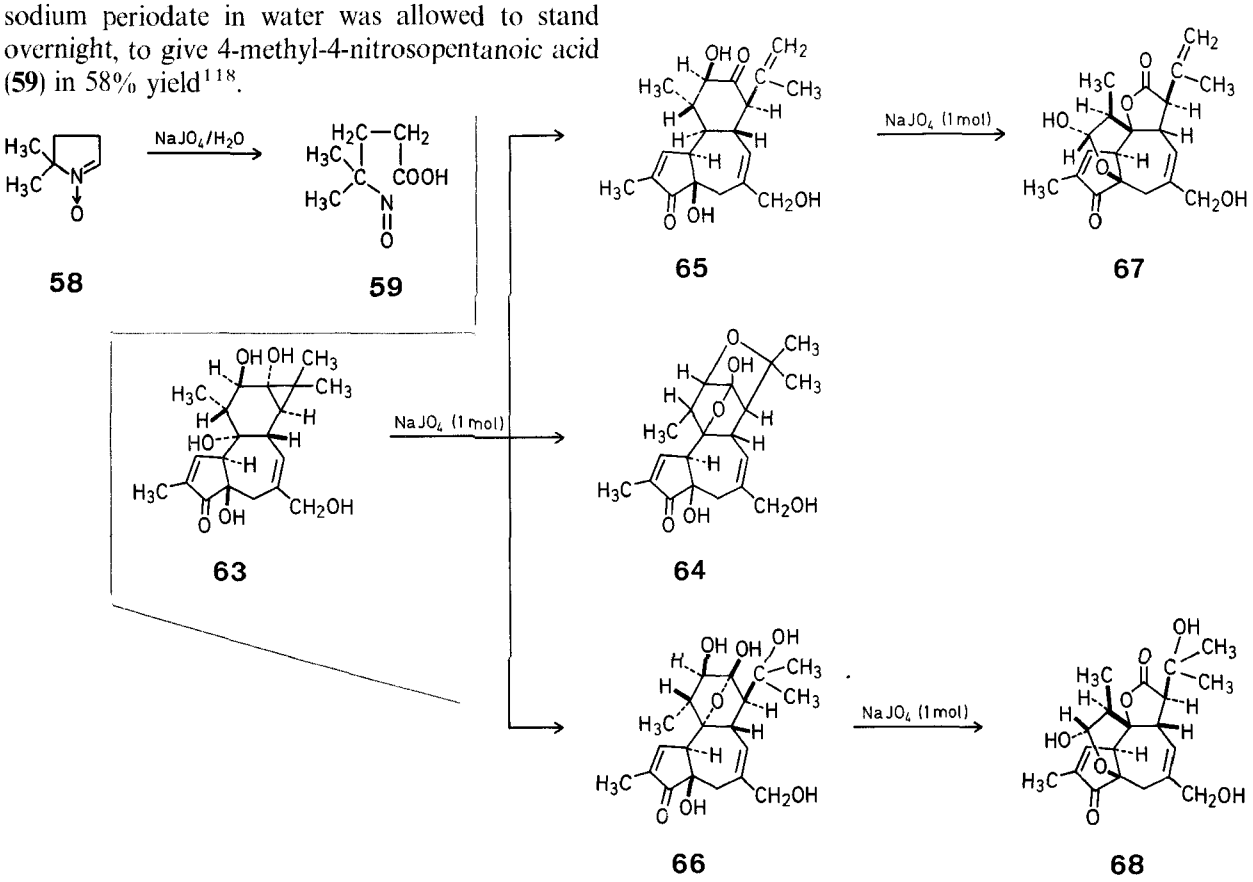
6.3. Isoquinoline Derivatives

Treatment of 1-(α-hydroxybenzyl)-1,2,3,4-tetrahydro-*erythro*- and *threo*-6,7-dimethoxy-isoquinoline with periodic acid in sulfuric acid gives 3,4-dihydro-6,7-dimethoxy-isoquinoline in over 60% yield; similar treatment of 3,4-dihydro-1-benzoyl-isoquinoline gives 3,4-dihydro-6,7-dimethoxy-isocarbostyril[117].

6.4. Nitrosocarboxylic Acids from Cyclic Nitrones

Δ^1-Pyrroline 1-oxides unsubstituted at C-2 are cleaved by sodium periodate at the double bond, with formation of nitrosocarboxylic acids. Thus, 5,5-dimethyl-Δ^1-pyrroline 1-oxide (**58**) mixed with sodium periodate in water was allowed to stand overnight, to give 4-methyl-4-nitrosopentanoic acid (**59**) in 58% yield[118].

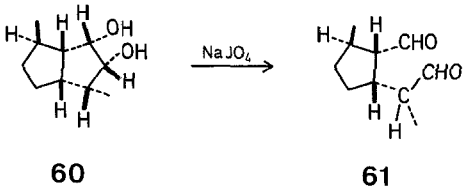


58 59 63 65 67 64 66 68

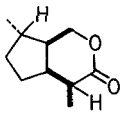
7. Terpenes

Application of periodate oxidation to terpenes, although at present limited to periodate/permanganate oxidation, is receiving more of the momentum desired.

Compound **60** (prepared from D(+)-pulegone) was stereospecifically oxidized[119] with sodium periodate to an enantiomer of iridodial (**61**) shown to be related to natural iridomyrmecin (**62**).



60 61



62

Oxidation of the diterpene phorbol (**63**) with 1 mol of sodium periodate per mol in aqueous solution yielded three main oxidation products, identified as tiglophorbol (**64**), bisdehydrophorbol (**65**), and hydroxybisdehydrophorbol hemiacetal (**66**); treatment of **63** *with 2 mol of sodium periodate per mol gave* **64**, **67**, and hemiacetal **68**[120].

An unusual rearrangement of the diterpene derivative ryanodol (**68a**) has also been observed following treatment with 3 mol of periodate; the isolated product **68b** (trisecoryanodol) has been assigned a dilactal (anhydro) structure[121].

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[123] R. H. Cornforth, J. W. Cornforth, G. Popjak, *Tetrahedron* **18**, 1351 (1962).

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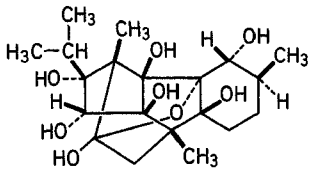
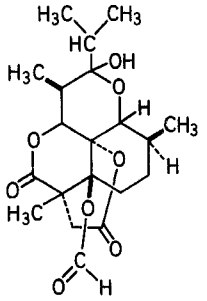
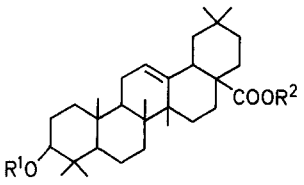


68 a



68 b

Periodate degradation, followed by methylation, of the triterpene clematoside-A′ (**69**), isolated from Siberian pine (*Clematis manshuria Rupr.*), showed that aglycon R^1 is an acylglucoside, and the participating tetrasaccharide is *O*-L-rhamnopyranosyl-(1→4)-*O*-D-glucopyranosyl-(1→4)-*O*-D-glucopyranosyl-(1→6)-D-glucose[122].



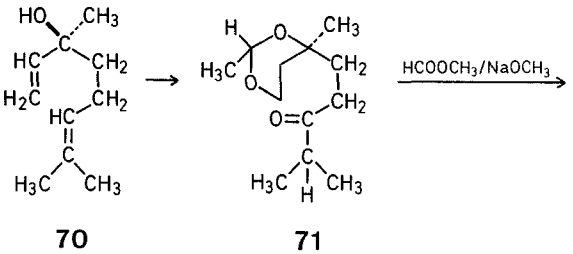
69

$R^2 = H$

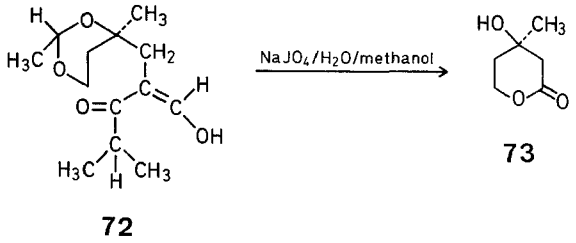
R^1 = D-Glc*p*-(1→4)-D-Xyl*p*-(1→2)-L-Ara*p*-(1→2)-L-Ara*p*-(1→4)-L-Rha*p*→

7.1. Cornforth Ketone Cleavage

In a novel synthesis[123] of *R*-(−)-mevalonolactone (**73**) from *S*(+)-linalool (**70**), this was first converted via a series of steps (hydroboration/oxidation, acetal formation, and chromic acid oxidation) into intermediate **71**; this was condensed with methyl formate to give α-hydroxymethylene ketone (**72**) equivalent



70 **71**



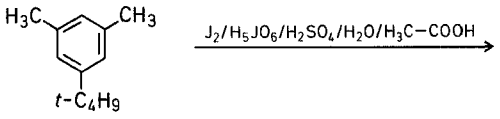
72 **73**

to a cyclic 1,3-diketone that can be cleaved[124] by periodate. Intermediate **72** was not isolated, but was immediately oxidized by addition of aqueous methanolic sodium periodate. The acetal group was hydrolyzed off during the processing, and the product was lactone **73**, isolated in 21% yield from **70**.

8. Aromatic Iodination

8.1. Iodination of Polyalkylbenzenes

Polyalkylbenzenes having bulky groups are not reactive toward iodine alone, but may react in the presence of an oxidizing agent. In a detailed study of agents used in this connection (silver perchlorate, mercury(II) oxide, potassium persulfate, iodic acid, etc.), Japanese investigators[125] found the combination of iodine with periodic acid to be the most satisfactory. Stirring of a mixture of 5-*t*-butyl-1,3-dimethylbenzene (**74**), periodic acid, iodine, and a little sulfuric acid in acetic acid/water at 60–65° produced 4-*t*-butyl-1-iodo-2,6-dimethylbenzene (**75**) in 90% yield.



74

75

8.2. Iodination of Polycyclic and Heterocyclic Aromatic Compounds

Iodine/periodic acid has also been found an efficient iodinating agent with a series of polycyclic and heterocyclic aromatic compounds; in this way, 1-methylnaphthalene was converted into 2-iodo-1-methylnaphthalene in 81% yield[126].

8.3. Iodination of Dimethylaniline

The oxidation of dimethylaniline with iodic acid and iodine in acetic acid afforded, besides *p*-iododimethylaniline, Methyl Violet, *N*-*p*-dimethylaminobenzyl-*N*-methylaniline, and an iodo dye of the Crystal Violet type, which were separated by column chromatography. When *p*-iododimethylaniline was oxidized with iodic acid, the iodo dye was the main product. The oxidation was explained through the formation of an *N*-oxide which then undergoes free-radical transformation[127].

[125] H. Suzuki, K. Hakamura, R. Goto, *Bull. Chem. Soc. Japan* **39**, 129 (1966).
[126] H. Suzuki, Y. Tamura, *Nippon Kagaku Zasshi* **92**, 1021 (1971); *C. A.* **76**, 12665 (1972).
[127] S. Ghosal, *J. Indian Chem. Soc.* **42**, 799 (1965).
[128] A. J. Fatiadi, *Chem. Commun.* **1970**, 11.

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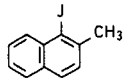
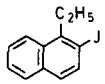
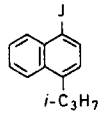
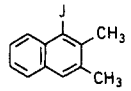
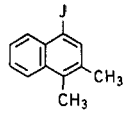
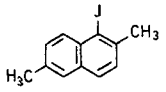
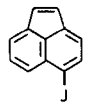
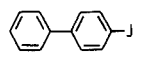
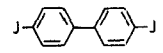
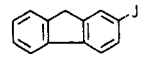
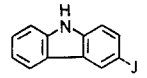
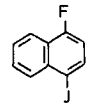
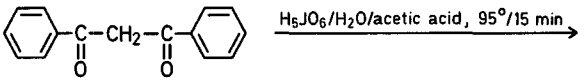
Table 4. Preparation of Polycyclic and Heterocyclic Aromatic Iodo Compounds[126]

Iodo Compound	Yield (%)
	81
	75
	62
	84
	72
	78
	69
	82
	94
	86
	85
	70
	58

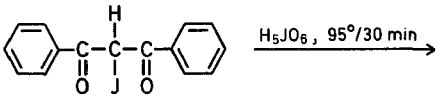
8.4. Iodination of the α-Methylene Group in β-Diketones

Periodic acid was found to iodinate the α-methylene group of β-diketones, including 1,3-diphenyl-1,3-propanedione (**76**), 2,4-pentanedione, 2,4-hexanedione, and hexafluoro-2,4-pentanedione[128].

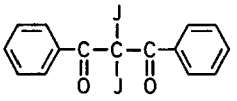
Treatment of **76** in glacial acetic acid with aqueous periodic acid for 15 min at 95°, and then at room temp. for 50 min gave the 2-iodo derivative **77** (43 to 46% yield); when the reaction was performed for 30 min at 95° and then at room temperature, the product was the 2,2-diiodo derivative **78** (19–21% yield).



76



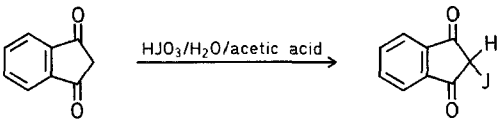
77



78

8.4.1. Conversion of 1,3-dioxoindane into 2-Iodo-1,3-dioxoindane[85]

Iodination of the non-enolizable methylene proton in 1,3-dioxoindane (**79**) can be effected with periodic acid to obtain 2-iodo-1,3-dioxoindane (**80**) in good yield; however, the yield of **80** was even better when iodic acid was used, indicating the lability of the O—J bond in the reagent.



79 **80**

Preparation of 2-Iodo-1,3-dioxoindane[85]:
A solution of 1,3-dioxoindane (0.2 g) in glacial acetic acid (50 ml) was treated with aqueous iodic acid (3*M*, 5 ml); the mixture was stirred at 70–80° for 10 min, diluted with water (50 ml), and kept at room temperature for two hours. Crude product (m.p. 196°, 80% yield) was collected, and recrystallized from warm aqueous acetic acid; white to pale pink crystals; m.p. 198–200°.

Iodination of the ring was observed following the treatment of enolic 1,2-dioxocyclopentane[129] or 3-methyl-1,2-dioxocyclopentane[130] with periodic acid. Oxidation of enolic 1,3-dioxocyclohexane with periodate gave glutaric acid in over 90% yield[124], and similar oxidation of reductone gave α-oxoglutaric acid[130].

8.5. Oxidation and Hydroxylation of Deoxybenzoin[85]

The action of periodic acid and iodic acid on deoxybenzoin, particularly on its methylene group, showed some interesting features. Instead of the iodination expected on treatment with periodic acid in warm aqueous acetic acid, deoxybenzoin was oxidized to benzaldehyde and benzoic acid; iodic acid converted it into benzoin; the latter was, however, little affected by periodic acid at room temperature, but the compound was cleaved on warming. When deoxybenzoin, initially in warm *N*,*N*-dimethylformamide, was

[129] G. Hesse, F. Exner, H. Hertel, *Liebigs Ann. Chem.* **609**, 57 (1957).
[130] G. Hesse, K. Mix, *Chem. Ber.* **92**, 2427 (1959).

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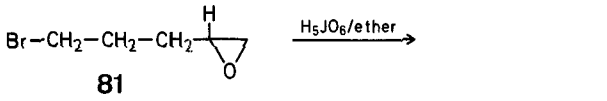
mixed with aqueous periodic acid and kept at room temperature for 48 h, the product was benzil (55 to 65% conversion)[131].

Treatment of benzoin with hot, alkaline sodium iodate gives benzilic acid in good yield[92]; however, treatment of benzilic acid in warm acetic acid with periodic acid produces benzophenone in 90% yield[85].

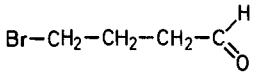
The methylene group in bibenzyl seems to be little affected by periodic acid; the reaction was performed in acetic acid and *N*,*N*-dimethylformamide[85].

8.6. Cleavage with Ethereal Periodic Acid

Periodic acid in ether or tetrahydrofuran can be used to effect hydrolytic cleavage of an epoxide to give an aldehyde or a ketone; the method can be useful for water-insoluble compounds, or where a cleavage product is sensitive to aqueous acid. For example, the extremely water-sensitive 4-bromobutyraldehyde (**82**) was prepared in 80% yield in this way from the epoxide **81**[132].



81



82

The cleavage of tartaric acid esters by ethereal periodic acid is a convenient method for preparation of esters of glyoxylic acid in good yield; in this way, methyl and ethyl glyoxylates were prepared in 76% and 87% yield, respectively[133].

9. Organic Salts of Periodic Acid

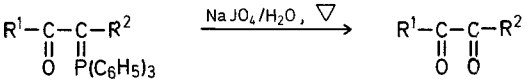
Organic salts of periodic acid could be useful reagents for both nonaqueous and aqueous periodate oxidations; for example, tetraethylaminium periodate $[(C_2H_5)_4N^+JO_4^-]$ has been used as a specific oxidant of hydroxylamines[118]. However, a large-scale preparation of this oxidant led to an explosion[116].

Formation of periodic salts has been observed with certain imino steroids[134], with tertiary bases (pyridine and tribenzylamine), and with some heterocyclic compounds (acridine, adenine, phenazine, or 2,4,5-triphenylimidazole)[85]. These salts are diamagnetic, and usually explode on heating. Benzidine and luminol, following treatment with periodic acid, produced stable free-radicals (E.S.R. measurements); their structure is under study[85].

Organic periodates could also be useful, synthetic intermediates.

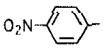
9.1. Dicarbonyl Compounds from Phosphinalkylenes

Treatment of acyl-phosphinalkylenes of type **83** with aqueous sodium periodate under reflux gave dicarbonyl compounds of type **84** in 30–100% yield[79] (Table 5).

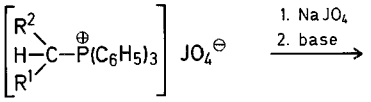


83 **84**

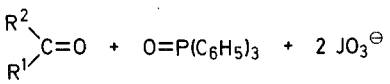
Table 5. Preparation of Dicarbonyl Compounds from Acyl-Phosphinalkylenes[79]

R^1	R^2	Yield (%) of **84**
	H	100
	H	28
H_3C	H	64
H_3C		53
H_3C	n-C_3H_7	33
		76
C_2H_5–O–		100

Treatment of phosphonium periodate of type **85** (R = C_6H_5 or alkyl) with sodium periodate and then with base gave keto derivatives of type **86** in 80–90% yield[79].



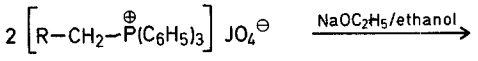
85



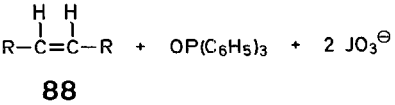
86

9.2. Olefins from Phosphonium Periodates

Treatment of phosphonium periodates of type **87** with ethanolic sodium ethoxide under reflux (under nitrogen) gave olefins of type **88** in 30–90% yield[79] (Table 6).



87



88

[131] On comparable chromic acid oxidation of deoxybenzoin, see K. B. Wiberg, O. Aniline, A. Gatzke, *J. Org. Chem.* **37**, 3229 (1972).
And on ceric ion oxidation of benzoin, see T. L. Ho, *Synthesis* **1972**, 560.

[132] Ref. 20, Vol. 1, p. 817.

[133] T. R. Kelly, T. E. Schmidt, J. G. Haggerty, *Synthesis* **1972**, 544.

[134] W. Nagata, H. Nishimure, *Belg. Patent* 670695 (1966); *C. A.* **65**, 8992 (1966).

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Table 6. Preparation of Olefins from Phosphonium Periodates[79]

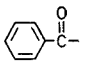
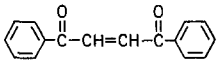
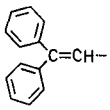
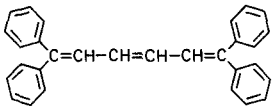
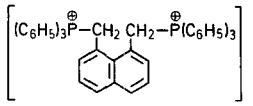
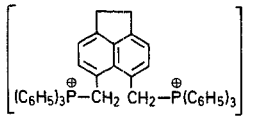
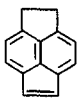
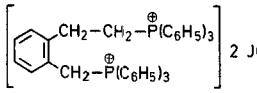
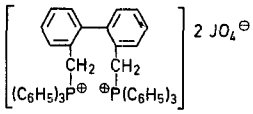
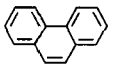
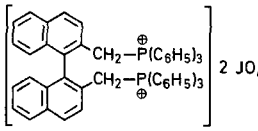
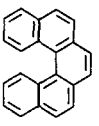
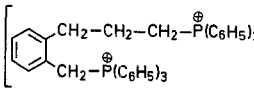
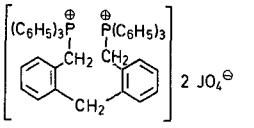
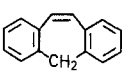
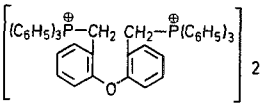
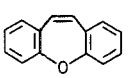
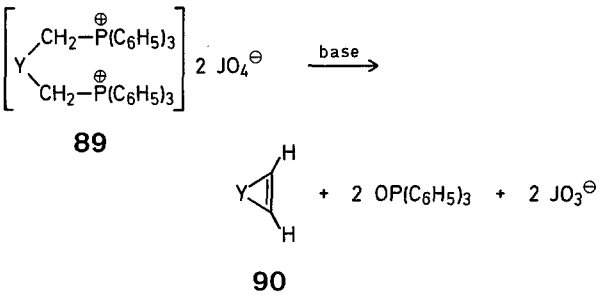
R in **87**	Base	Olefin isolated (**88**)	Yield (%)
$H_3C-C(=O)-$	$NaOC_2H_5$	$H_3C-C(=O)-CH=CH-C(=O)-CH_3$	79
	$NaOC_2H_5$		70
$H_3C-O-C_6H_4-C(=O)-$	$NaOC_2H_5$	$H_3C-O-C_6H_4-C(=O)-CH=CH-C(=O)-C_6H_4-O-CH_3$	88
H_3COOC	$NaOC_2H_5$	H_3COOC, H, $COOCH_3$	83
$H_3C-O-C_6H_4-$	$LiOC_2H_5$	$H_3C-O-C_6H_4-CH=CH-C_6H_4-O-CH_3$	84
$C_6H_5-CH=CH-$	$LiOC_2H_5$	$C_6H_5-CH=CH-CH=CH-CH=CH-C_6H_5$	52
	$NaOC_2H_5$		83
$C_6H_5-CH_2-CH_2-$	$NaNH_2$	$C_6H_5-CH_2-CH_2-CH=CH-CH_2-CH_2-C_6H_5$	33
$n\text{-}C_3H_7$	$NaNH_2$	$n\text{-}C_3H_7-CH=CH-C_3H_7\text{-}n$	13

Table 7. Preparation of Polycyclic Compounds from Bis[phosphinalkylene] Periodates[79]

Starting Material	Base	Product	Yield (%)
	$NaNH_2$		85
	$LiOC_2H_5$		83
	$NaNH_2$		70
	$NaNH_2$		71
	$NaOC_2H_5$		85
	$NaNH_2$		81
	$NaOC_2H_5$		75
	$NaOC_2H_5$		33

9.3. Polycyclic Compounds from Bis[phosphinalkylene] Periodates

Treatment of bis[phosphinalkylene] periodates of type **89** with sodamide in liquid ammonia produced cyclic unsaturated compounds of type **90** in 33–85% yield. This procedure was used in the preparation of a series of polycyclic or condensed, aromatic compounds (Table 7). The yields were best in reactions where the methylene groups were connected to the aromatic ring (Y in **89**)[79].



89 **90**

10. Synthesis of Heterocyclic Compounds

The pathways of formation of cyclic ethers from the periodate cleavage-products of carbohydrates (polyaldehydes and acetals) are known, and the topic has been thoroughly reviewed[7,135]. Recently, it was found[136,137,138] found that the abnormally low periodate consumption by alginate or xylan is the result of intramolecular, hemiacetal formation. Periodate oxidation has also been used in the preparation of five-membered, *N*-heterocyclic compounds, namely, pyrazolone derivatives from glucose phenylosazone[139,140] pyrazole derivatives from osazones[141] from cyclitols, osotriazole derivatives from sugar[142]

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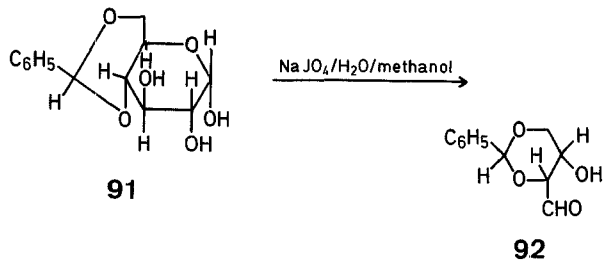
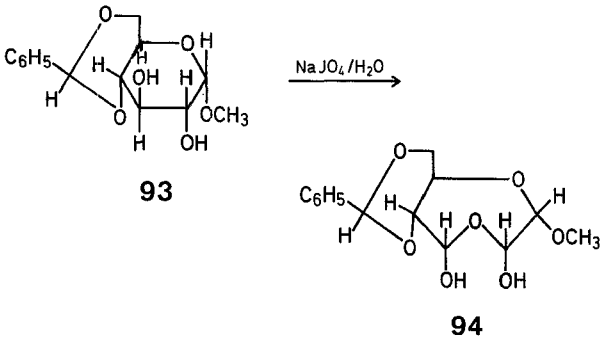
or cyclitol[143,144] osotriazoles, and also benzimidazole derivatives[145] and *C*-glycosyl compounds[146]. An extension of similar periodate oxidations can be a convenient route in the synthesis of new heterocyclic compounds, an addition to other preparations[147], and some of the methods are summarized next.

10.1. Dioxan and Hemialdal Derivatives

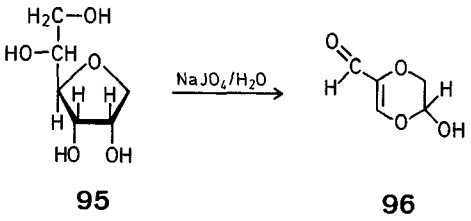
Oxidation of 4,6-*O*-benzylidene-α-D-glucose (**91**) with sodium periodate in aqueous methanol gave the *m*-dioxan derivative **92**[148].



However, oxidation of methyl 4,6-*O*-benzylidene-α-D-glucoside (**93**) with sodium periodate gave compound **94**, to which a hemialdal structure was assigned[7,149]. The open-chain structure for **91** and the pyranoid structure of **93** accounts for the difference in the products obtained on periodate oxidation.

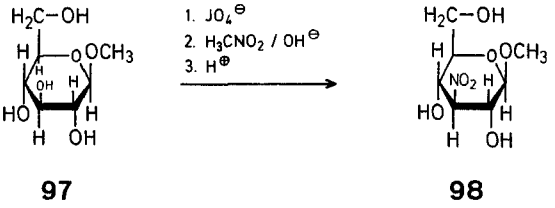


Condensation of hemialdals of type **94** with phenylhydrazine can produce either large heterocyclic rings or new azo-sugars that can be used in preparation of rare amino-sugars[7,150]. An oxepin (a seven-membered cyclic ether) structure has also been assigned[151] to the hemiacetal hydrate **94**. Periodate oxidation of 1,4-anhydro-D-allitol (**95**) gave the crystalline *p*-dioxan derivative **96**; overoxidation that occurred on prolonged treatment of **95** and other carbohydrates with periodate can be explained as being due to the hydroxylation of the double bond in **96**, and subsequent glycol cleavage[152].



10.2. Cyclization of Dialdehydes with Nitromethane

Cyclization of dialdehydes with nitromethane is an important, synthetic route to amino sugars, amino cyclitols, and nucleosides[153] of amino sugars. Such cyclization of the dialdehyde obtained by periodate oxidation of the methyl β-D-glucopyranoside **97** in slightly alkaline solution gives a mixture of three nitrohexosides, from which methyl 3-deoxy-3-nitro-β-D-glucopyranoside **98** was isolated in a yield of 24–56%. Catalytic reduction of **98** gave methyl 3-amino-3-deoxy-β-D-glucopyranoside in 96% yield[153].



10.3. Bicyclic Hemiacetals

The periodate oxidation of 4,4,6,6-tetramethyl-1,2,3-cyclohexanetriol (**99**) in neutral or acidic aqueous

[135] J. F. Stoddart, *Stereochemistry of Carbohydrates*, Wiley-Interscience, New York, 1971, pp. 186–220.
[136] B. Larsen, T. Painter, *Carbohyd. Res.* **10**, 186 (1969).
[137] T. Painter, B. Larsen, *Acta Chem. Scand.* **24**, 813 (1970).
[138] M. F. Ishak, T. Painter, *Acta Chem. Scand.* **25**, 3875 (1971). O. Smidsrød, T. Painter, *Carbohyd. Res.* **26**, 125 (1973).
[139] P. Karrer, K. Pfachler, *Helv. Chim. Acta* **17**, 766 (1934).
[140] E. Chargaff, B. Magasanik, *J. Amer. Chem. Soc.* **69**, 1459 (1947).
[141] B. Magasanik, E. Chargaff, *J. Amer. Chem. Soc.* **70**, 1928 (1948).
[142] H. El Khadem, *Adv. Carbohyd. Chem.* **18**, 99 (1963).
[143] L. Anderson, J. N. Aronson, *J. Org. Chem.* **24**, 1812 (1959).
[144] A. J. Fatiadi, *Carbohyd. Res.* **20**, 179 (1971).
[145] N. K. Richtmyer, *Adv. Carbohyd. Chem.* **6**, 175 (1951).
[146] L. J. Haynes, *Adv. Carbohyd. Chem.* **18**, 227 (1963).
[147] A. R. Katritzky, A. J. Boulton Eds., *Advances in Heterocyclic Chemistry*, Academic Press, New York, Vols. 1–14 (1958–1972).
[148] Z. Fialkiewicz, J. Sokolowski, *Zesz. Nauk. Mat. Fiz. Chem., Wyzsza Szk. Pedagog. Gdánsku* **8**, 235 (1968); *C. A.* **71**, 61721 (1969).
[149] R. D. Guthrie, J. Honeyman, *J. Chem. Soc.* **1959**, 2441.
[150] G. J. F. Chittenden, R. D. Guthrie, J. F. McCarty, *Carbohyd. Res.* **1**, 196 (1965).
B. E. Davison, R. D. Guthrie, D. Murphy, *Carbohyd. Res.* **5**, 449 (1967).
C. B. Barlow, R. D. Guthrie, *Carbohyd. Res.* **10**, 481 (1969); and previous papers in this series.
[151] H. R. Goldschmid, A. S. Perlin, *Can. J. Chem.* **38**, 2280 (1960). On oxepins by periodate oxidation, see T. R. Hollands in *Seven-Membered Heterocyclic Compounds Containing Oxygen and Sulfur*, A. Rosowsky Ed., Wiley-Interscience, New York, 1972, Chapter 8.
[152] B. G. Hudson, R. Barker, *J. Org. Chem.* **32**, 2101 (1967).
[153] F. W. Lichtenthaler, *Methods Carbohyd. Chem.* **6**, 250 (1972); *Angew. Chem.* **76**, 84 (1964); *Angew. Chem. Internat. Edit.* **3**, 211 (1964).
F. W. Lichtenthaler, H. Zinke, *J. Org. Chem.* **37**, 1612 (1972). See also H. H. Baer, *Advan. Carbohyd. Chem. Biochem.* **24**, 67 (1969).
J. Kovář, H. H. Baer, *Canad. J. Chem.* **49**, 3238 (1971).

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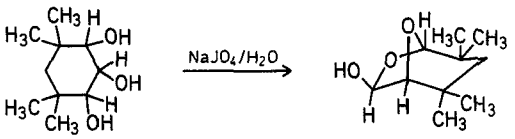
solution did not give the expected 2,2,4,4-tetramethyl-1,5-pentanedial, but *exo*-7-hydroxy-2,2,4,4-tetramethyl-6,8-dioxobicyclo[3.4.1]octane (**100**; 82%), produced by partial oxidation to the hydroxydialdehyde, followed by closure of two intramolecular acetal linkages[154].

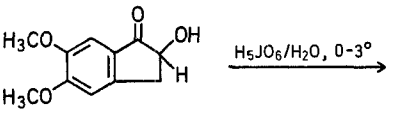


99 **100**

10.4. Isocoumarin Derivatives

Oxidation of 2-hydroxy-indan-1-one derivatives with cold periodic acid produces *o*-carboxyphenylacetaldehydes in high yield[155]; the latter cyclize readily on treatment with warm polyphosphoric acid, and this procedure has been used[156,157] for synthesis of a series of substituted isocoumarins in high yield.

In a typical example, **101** (2-hydroxy-5,6-dimethoxyindane-1-one) was oxidized with periodic acid in water at 0–3°, to give **102** (2-carboxy-4,5-dimethoxyphenylacetaldehyde, 90%); on treatment with warm polyphosphoric acid, **102** gave **103** (6,7-dimethoxyisocumarin, 85%). Similarly, 6-methoxy- (99%), 5,6-dimethoxy- (98%), and 6,7-methylenedioxy- (99%) isocoumarins were synthesized.



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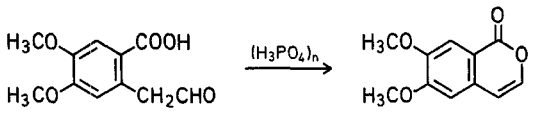
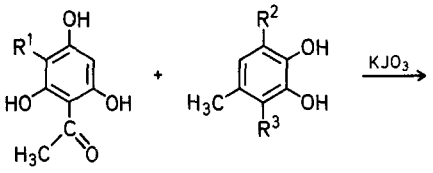


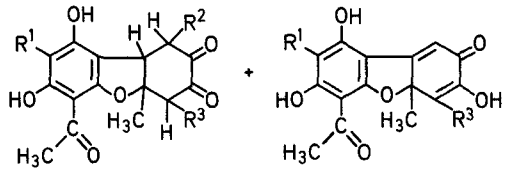
102 **103**

10.5. Dibenzofuran Derivatives

In the presence of potassium iodate, 2,4,6-trihydroxyacetophenone (**104**, $R^1 = H$) and its 3-methyl derivative (**104**, $R^1 = CH_3$) undergo oxidative coupling with mono-, di-, and trimethylpyrocatechols (**105**) that are not substituted in the 4- or 5-position, to give a mixture of 2,3-dioxo-2,3,4,4*a*-dihydrodibenzofurans (**107**). When $R^3 = H$, the dioxo compound **106** is obtained almost exclusively, whereas, when $R^3 = CH_3$, product **107** preponderates[158]. The steps in formation of the furan ring probably involve Michael addition of **104** to an *o*-quinone derived from **105**, re-oxidation of the dihydroxy intermediate to quinone, and an intramolecular, *β*-addition of the hydroxyl group *ortho* to the enone system of the *o*-quinone ring.



104 **105**

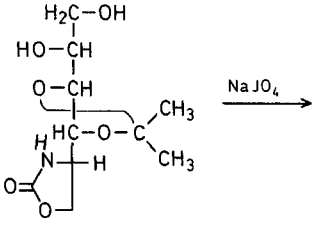


106 **107**

R^1	R^2	R^3	Yield (%) **106**	**107**
H	H	H	60	
CH_3	H	H	56	
H	CH_3	H	47	2.5
CH_3	CH_3	H	47	2.5
H	H	CH_3	7.5	57
CH_3	H	CH_3	5	45
H	CH_3	CH_3	12	68
CH_3	CH_3	CH_3	12	68

10.6. Pyrrolidine Derivatives

Sodium periodate oxidation of 2-amino-1-*O*,2-*N*-carbonyl-2-deoxy-3,4-*O*-isopropylidene-D-glucitol (**108**) gave a dimer (an *s*-trioxane derivative, **109**, 92%); on acid hydrolysis ($H^{\oplus}$ form of resin), the latter produced the pyrrolidino sugar **110**[159]. The preparation of other *N*-ring sugars[160] or other pyrrolidine derivatives (by use of periodate oxidation)[161] has been reviewed.



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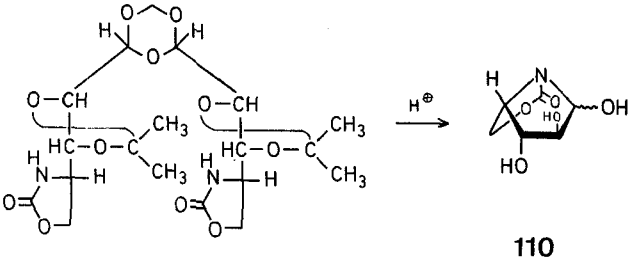

109 **110**

[154] J. S. McConaghy, Jr., J. J. Bloomfield, *J. Chem. Soc. (C)* **1968**, 7.
[155] C. Schöpf, R. Kühne, *Chem. Ber.* **83**, 390 (1950).
[156] N. K. Bose, D. N. Chaudhury, *J. Indian Chem. Soc.* **42**, 211 (1965).
[157] N. Bose, D. N. Chudhury, *J. Indian Chem.* **43**, 411 (1966).
[158] J. C. Overeem, *Rec. Trav. Chim.* **88**, 85 (1969).
J. Raa, J. C. Overeem, *Phytochem.* **1**, 721 (1968).

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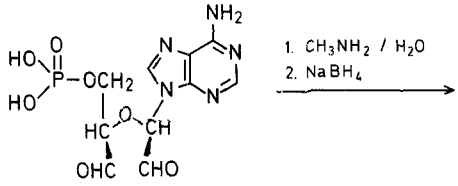
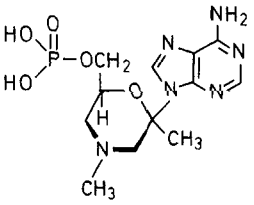
10.7. Morpholine Derivatives

Treatment of dialdehyde **111**, obtained by periodate oxidation of adenosine 5'-phosphate, with methylamine and then with sodium borohydride gave the morpholine derivative **112** [2-(adenin-9-yl)-4-methyl-6-phosphono-oxymethylmorpholine] in 85–90% yield. This condensation reaction was originally studied by Khym[162], but the structure of **112** was proved by Brown and Read[163]. Similar periodate oxidations with 5'-ribonucleotides have also been conducted[164].



111



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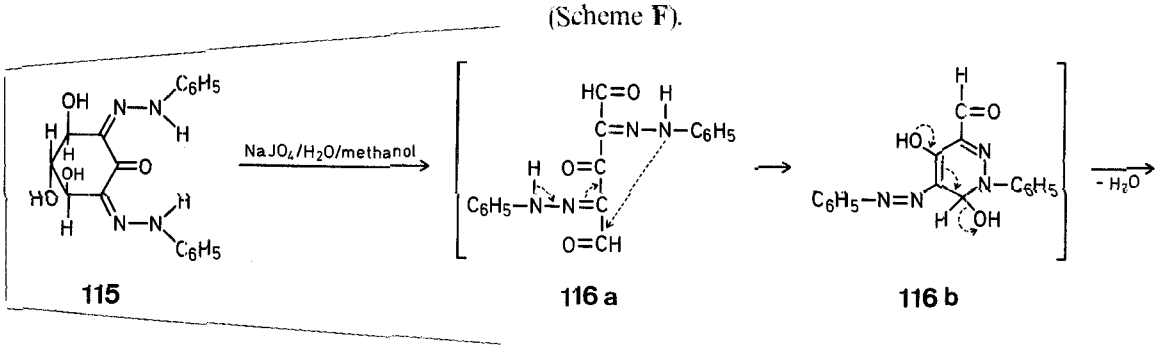
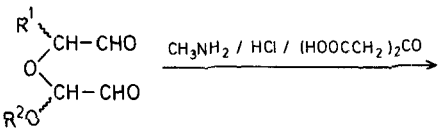


115 **116a** **116b**

10.8. Tropinone Derivatives

The dialdehydes (**113**) obtained by periodate oxidation of glycosides have been used as components in the Robinson-Schöpf condensation (requiring acetonedicarboxylic acid/methylamine hydrochloride) to give tropinone derivatives, analogs of 9-methyl-3-oxagranatan-7-one (**114**) in 30–40% yield[165]. The condensation apparently proceeds via the bis[1-hydroxyalkyl]amine as the reaction intermediate.



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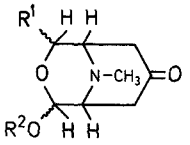
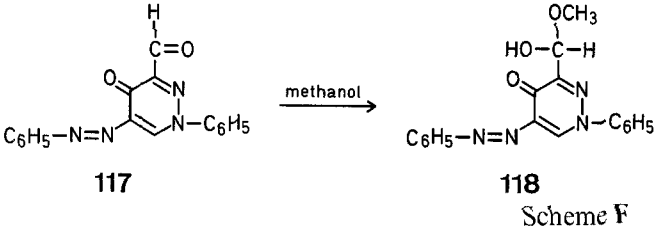


114

$R^1 = H, R^2 = CH_3$;
$R^1 = H, R^2 = -CH_2-C_6H_5$;
$R^1 = R^2 = CH_3$.

10.9. Pyridazine Derivatives

From the periodate oxidation of phenylosazones from cyclitols[140,141], it would be expected that *xylo*-4,5,6-trihydroxy-2-oxo-1,3-bis(phenylhydrazono)cyclohexane (**115**) would, on oxidation with sodium periodate, yield 3-oxo-2,4-bis(phenylhydrazono)glutardialdehyde (**116a**). However, **116a** was not isolated, but, instead, the product was 4-oxo-1-phenyl-5-phenylazo-5-pyridazinecarboxaldehyde (**117**) which, in the presence of methyl alcohol, was isolated as the methyl hemiacetal **118** (60%)[166]. Presumably, **117** was formed by cyclization of **116a** followed by dehydration as illustrated (**116a**→**116b**) (Scheme F).



117 **118**

Scheme F

10.10. Imidazole Derivatives

The products formed by periodate oxidization of polysaccharides react with aqueous ammonia to give imidazoles and 4(5)-substituted imidazoles in low yield[167].

10.11. 4-Oxathiane Derivatives

A new class of sugar derivatives containing two hetero-atoms in a six-membered, cyclic hemi-acetal have been prepared[168]. Oxidation of methyl α-L-rhamnopyranoside (**119**) with sodium periodate, and reduction of the resulting dialdehyde with sodium borohydride, afforded a diol which, on tosylation, gave ditosylate **120**. When the ditosylate **120** was treated with sodium sulfide in boiling methanol,

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159 H. Paulsen, J. Brüning, K. Heyns, *Chem. Ber.* **102**, 459 (1969); **103**, 1621 (1970).

160 H. Paulsen, *Angew. Chem.* **78**, 501 (1966); *Angew. Chem. Internat. Edit.* **5**, 495 (1966).
J. K. N. Jones, W. A. Szarek, *Can. J. Chem.* **42**, 20 (1964).

161 H. El Khadem, *Adv. Carbohyd. Chem.* **25**, 351 (1970).

162 J. X. Khym, *Biochemistry* **2**, 344 (1963).

163 D. M. Brown, A. P. Read, *J. Chem. Soc.* **1965**, 5072.

164 H. C. Neu, L. A. Heppel, *J. Biol. Chem.* **239**, 2927 (1964).

165 R. D. Guthrie, J. F. McCarthy, *J. Chem. Soc. (C)* **1967**, 62.

166 H. S. Isbell, A. J. Fatiadi, *Carbohyd. Res.* **2**, 204 (1966).

167 E. L. Richards, *Aust. J. Chem.* **23**, 1033 (1970).

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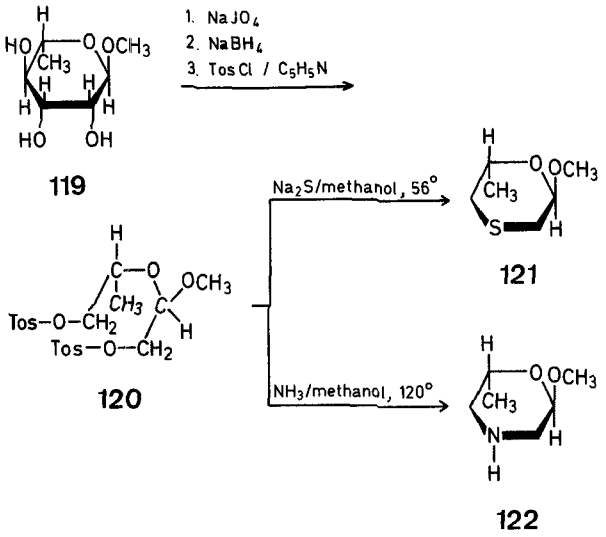
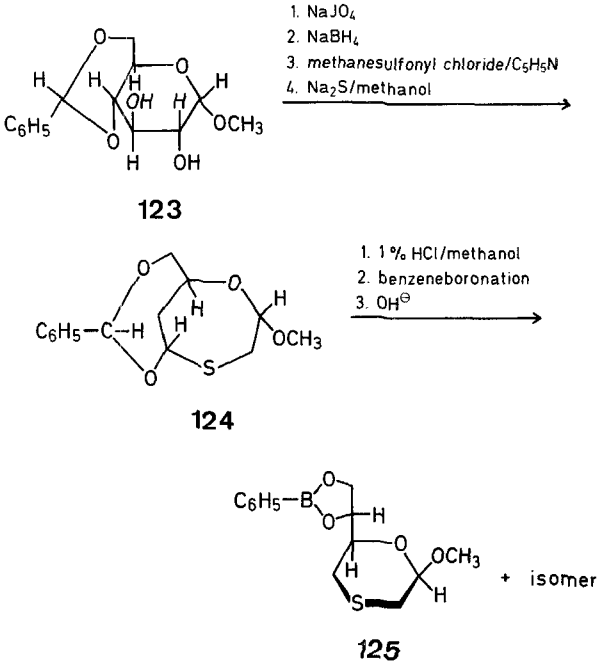
smooth conversion into (2*R*, 6*S*)-2-methoxy-6-methyl-1,4-oxathiane (**121**) occurred; yield 66%[168].

Treatment of the ditosylate **120** *with methanolic* ammonia at 120° gave (2*R*, 6*S*)-2-methoxy-6-methylmorpholine (**122**) in 50% yield.

By treatment of ditosylate **120** with a suitable reagent, it is possible to incorporate some other hetero atoms *(phosphorus, arsenic, or antimony), and, consequently,* to extend the series of unique sugars[169].



Successive treatment of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**123**) with periodate, borohydride, methanesulfonyl chloride/pyridine, and *sodium sulfide/boiling methanol afforded (1R, 3S, 7R, 9R)*-3-methoxy-9-phenyl-2,8,10-trioxa-5-thiabicyclo[5.4.0]undecane (**124**). On treatment with hot 1% methanolic hydrogen chloride, followed by conversion into the benzeneboronate and saponification with Amberlite IRA-400 (OH^-), the latter yielded the 1,4-oxathiane sugar derivative **125** and an isomer in the ratio of ~2:1[170].



11. Stereospecific, Asymmetric Synthesis of Carbohydrates

Stereospecific synthesis in organic chemistry[135,171,172,173,174], and particularly synthesis of stereospecific *vic*-diols[175], is well-known.

Stereospecific synthesis of glycosides and disaccharides is a problem that will be solved in the near future. *Progress in this direction can be envisaged* from current work on stereoselective synthesis in the monosaccharide series.

Periodate oxidation of 1,2-*O*-isopropylidene-α-D-glucofuranose (**126**) gave a dimer (a cyclic acetal) (**127**) *(47%)*[176] *and 1,2-O-isopropylidene-3,5-O-methylene-*(5-hydroxy-α-D-xylofuranose) (**128**) (15%)[177].

When **127** was boiled under reflux with a freshly prepared solution of phenylmagnesium bromide in ether, two compounds were isolated, namely **129** *(1,2-O-isopropylidene-5-C-phenyl-β-L-ido-pentofuranose)* (66%) and **130** (1,2-*O*-isopropylidene-5-*C*-phenyl-α-D-*gluco*-pentofuranose) (25%). Compounds **129** and **130** were prepared by stereospecific, asymmetric synthesis by use of the Grignard reagent, namely, by condensation of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**131**) with phenylmagnesium bromide in ether, followed by hydrogenolysis to remove the benzyl protecting groups. The resulting compounds **130** and **129** were obtained in the ratio of 2:29, thus showing a high degree of *stereoselectivity, to give main compound* **129**, *having* the L-*ido* configuration[178,179]. Inch and coworkers[180,181,182] performed a series of condensation reactions between Grignard reagents and *aldehydo*-aldoses or *keto*-ketoses and obtained similar stereoselectivity in the products.

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[168] K. W. Buck, F. A. Fahim, A. B. Foster, A. R. Perry, M. H. Quadir, J. M. Webber, *Carbohyd. Res.* **2**, 14 (1966).
[169] Personal discussion with Professor A. B. Foster.
[170] A. B. Foster, Q. H. Hasan, D. R. Hawkins, J. M. Webber, *Chem. Commun.* **1968**, 1084.
[171] D. J. Cram, D. R. Kopecky, *J. Amer. Chem. Soc.* **81**, 2737 (1959).
[172] E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962, pp. 81–87.
[173] K. Mislow, M. M. Green, P. Laur, J. T. Mellilo, T. Simmons, A. L. Ternay, *J. Amer. Chem. Soc.* **87**, 1958 (1965).
K. Mislow, Introduction to Stereochemistry, W. A. Benjamin, New York, 1966.
K. Mislow, M. Raban, *Topics in Stereochemistry*, E. L. Eliel and N. L. Allinger Eds., Interscience, New York, 1966, vol. 1, p. 1.
See also K. R. Hanson, *J. Amer. Chem. Soc.* **88**, 273 (1968).
[174] J. D. Morrison, H. S. Mosher, *Asymmetric Organic Reactions*, *Prentice-Hall*, Englewood Cliffs, New Jersey, *1971*, particularly Chapters 1, 2, and 4.
[175] M. A. Khuddus, D. Swern, *Tetrahedron Lett.* **1971**, 441.
[176] R. Schaffer, H. S. Isbell, *J. Amer. Chem. Soc.* **79**, 3864 (1957).
[177] T. D. Inch, *Carbohyd. Res.* **5**, 53 (1967).
[178] T. D. Inch, *Carbohyd. Res.* **5**, 45 (1967).
[179] T. D. Inch, *Advan. Carbohyd. Chem. Biochem.* **27**, 191 (1972).
[180] T. D. Inch, R. V. Lay, P. Rich, *Chem. Commun.* **1967**, 865.

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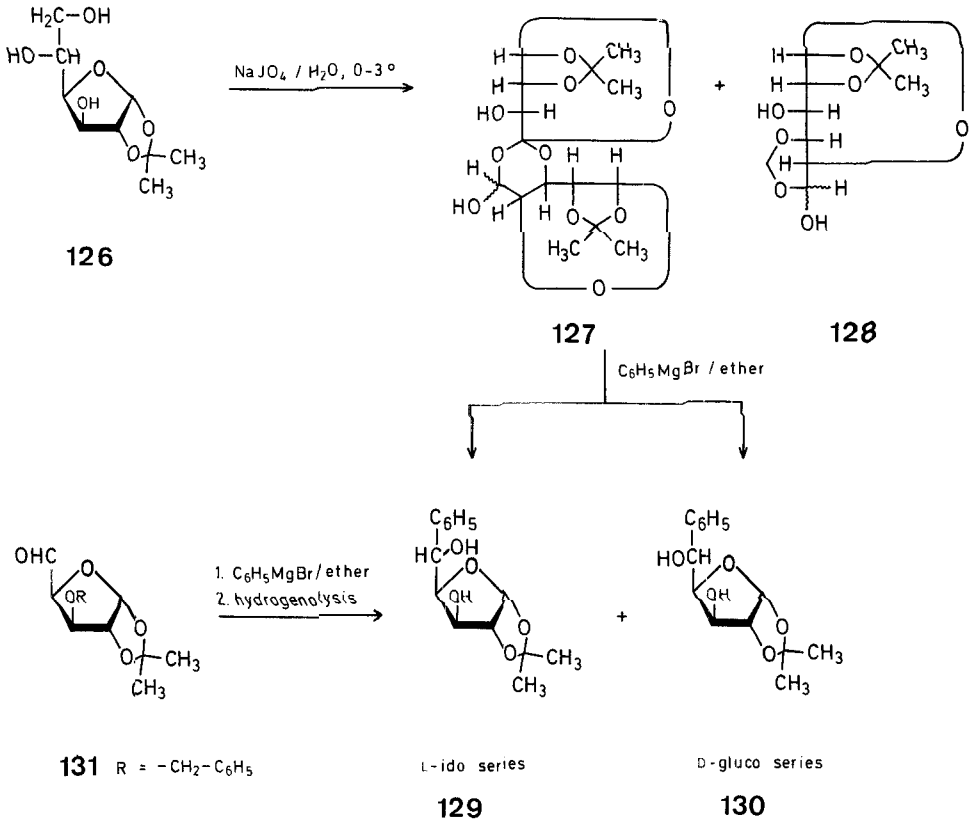
Horton and coworkers[183] have improved the large-scale preparation of D-allose, first by oxidation (ruthenium(VIII) oxide/sodium periodate) of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, followed by the stereoselective reduction (sodium borohydride) of the resulting 3-ulose hydrate (75% yield).

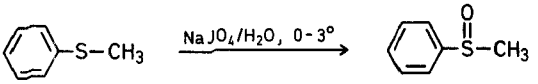


12. Sulfur Compounds

Periodate oxidations were originally applied in structural studies of penicillin (oxidation of a thiazolidine ring)[184], in conversion of penicillin esters[184,185] or penicillin acids[186] to the sulfoxides[187], in conversion of thiols, via disulfides, into sulfonic acids[18], and in degradation of thio derivatives of sugars[188] and amino sugars[189,190,191,192].

12.1. Oxidation of Organic Sulfides and Thioethers to Sulfoxides

The procedure for conversion of organic sulfides into sulfoxides by the use of sodium periodate, originally generalized[74], has been extended and described in detail[193]. The method employs mild reaction conditions and affords high yields of sulfoxides free from contamination by sulfides or sulfones. Thus, the oxidation of thioanisole (**132**) by this procedure[193] produced methyl phenyl sulfoxide (**133**) (91%).



132 **133**

Sodium periodate is easily and safely handled; however, the high cost of this reagent in comparison to that of certain other oxidants, e.g. hydrogen peroxide or ceric ammonium nitrate[194], may restrict its

[181] T. D. Inch, R. V. Lay, P. Rich, *J. Chem. Soc. (C)* **1968**, 1683.

[182] T. D. Inch, G. J. Lewis, G. L. Sainsbury, D. J. Sellers, *Tetrahedron Lett.* **1969**, 3657.
See also M. L. Wolfrom in *The Carbohydrates (Acyclic Derivatives)*, W. Pigman and D. Horton, Eds., Academic Press, New York, 1972, Vol. 1A, p. 380.
See also Ref. 174, pp. 84–117 on similar stereospecific Grignard condensation reactions.
See also C. Schuerch, *Acc. Chem. Res.* **8**, 184 (1973).

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[184] P. Sykes, A. R. Todd in *Chemistry of Penicillin*, H. T. Clarke, J. R. Johnson, R. Robinson, Eds., Princeton University Press, Princeton, N. J., 1949, pp. 156, 927, 946, 1008.
See also K. Heusler in "*Cephalosporins and Penicillins*", E. H. Flynn, Ed., Academic Press, New York, 1972.

[185] A. W. Chaw, N. M. Hall, J. R. E. Hoover, *J. Org. Chem.* **27**, 1381 (1962).

[186] J. M. Essery, K. Dadabo, W. J. Gottstein, A. Hallstrand, L. C. Cheney, J. Org. Chem. **30**, 4388 (1965).

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[188] D. Horton, D. H. Hutson, *Advan. Carbohyd. Chem.* **18**, 123 (1963).

[189] A. B. Foster, M. Stacey, *Adv. Carbohyd. Chem.* **7**, 247 (1952).

[190] L. Hough, M. I. Taha, *J. Chem. Soc.* **1957**, 3994.

[191] B. Coxon, *Ph. D. Dissertation*, University of Bristol, England, 1960.

[192] Z. Fialkiewicz, *Zeszyty. Nauk Mat. Fiz. Chem.* **7**, 179 (1967); *C. A.* **67**, 43031 (1967).

[193] C. R. Johnson, J. E. Keiser, *Org. Syn.* **46**, 78 (1966).

[194] T. L. Ho, C. M. Wong, *Synthesis* **1972**, 561.

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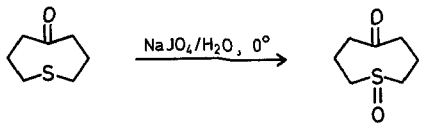
use to laboratory-scale preparation. Sulfide **134** was oxidized with periodate to sulfoxide **135** in 91% yield, although other oxidizing agents failed[74].

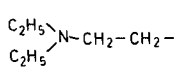
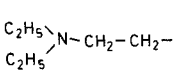
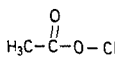


134 **135**

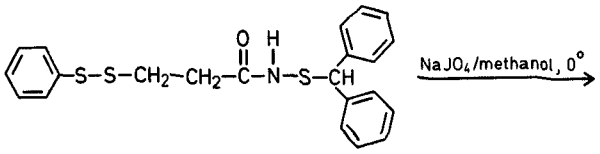
Methyl Phenyl Sulfoxide[193]:

In a 500-ml round-bottomed flask equipped with a magnetic stirrer are placed powdered sodium metaperiodate (22.5 g, 105 mmol) and water (210 ml). The mixture is stirred, cooled in an ice bath, and thioanisole (12.4 g, 100 mmol) is added. The mixture is stirred for 15 hours at ice-bath temperature, and is then filtered though a Büchner funnel. The filter cake of sodium iodate is washed with dichloromethane (3 × 30 ml). The filtrate is transferred to a separatory funnel, the lower layer is removed, and the water layer is extracted with dichloromethane (3 × 100 ml). The extracts are treated with activated carbon, dried (anhydrous sodium sulfate), and evaporated under reduced pressure to yield 13.6–13.9 g of a slightly yellow oil which crystallizes on cooling. The crude sulfoxide is transferred to a 25-ml distillation-flask with the aid of a small amount of dichloromethane. After removal of the solvent, a pinch of activated carbon is added to the distillation flask. Vacuum distillation of the crude product in a shortpath still affords pure methyl phenyl sulfoxide; yield: 12.7–12.8 g (91%); b.p. 78–79°/0.1 torr; m.p. 33–34°.

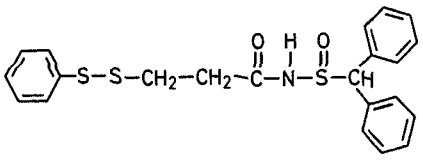
Table 8. Preparation of Sulfoxides[193]

R^1	R^2	Yield (%)
	$-CH_2-COOH$	99
		99
		96
	C_2H_5-	93
	$H_3C-\overset{O}{\overset{\|}{C}}-CH_2-$	89
		85
		83
	CH_3	72
C_2H_5	C_2H_5	65

Sodium periodate may be used successfully for oxidation of thio ethers containing a disulfide linkage, as illustrated by conversion of **136** into **137** in 71% yield[195].



136



137

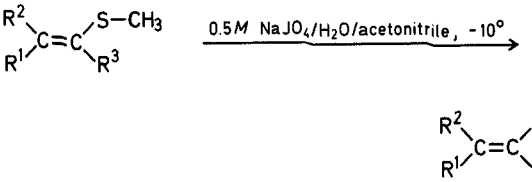
The stability of the disulfide bond was further demonstrated by the failure of sodium periodate or periodic acid to oxidize benzyl disulfide[85]. The method has been used for preparation of 1-azulyl sulfoxide in 93% yield[196].

Sodium periodate was recommended for removal of the dithioacetal protecting group (to release the carbonyl group)[197]. Periodate oxidations of organic sulfides at higher temperatures usually afford sulfones[74].

12.2. Oxidation of Vinyl Sulfides to Vinyl Sulfoxides

The oxidation of vinyl sulfides to vinyl sulfoxides is complicated by epoxidation of the double bond and the possibility of over-oxidation to yield the sulfone. Selective oxidation of a vinyl sulfide to a vinyl sulfoxide can be achieved by using sodium periodate[198], in a modification of the procedure of Leonard and Johnson[74]. High yields of vinyl sulfoxides (68% to 96%) can be obtained by the use of 0.5 *M* sodium periodate in 50% aqueous acetonitrile solution at −10° (see Table 9).

Table 9. Conversion of Vinyl Sulfides into Sulfoxides with Sodium Periodate[198]



R^1	R^2	R^3	Yield (%) of sulfoxide
		H	96
		$-S-CH_3$	96
	H_3C-	$-S-CH_3$	90
	H	H	77
	H	H_3C-	74
	Cl	H	73
	C_2H_5-	$-S-CH_3$	68
			46

[195] R. G. Hiskey, M. H. Harpold, *J. Org. Chem.* **32**, 3191 (1967).
[196] L. L. Replogle, J. R. Maynard, *J. Org. Chem.* **32**, 1909 (1967).

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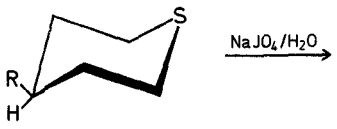
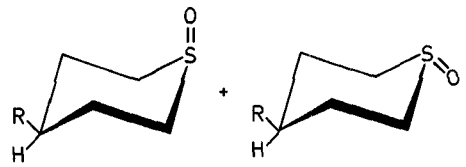
The procedure can also be used for conversion of acetylenic sulfides into acetylenic sulfoxides.

12.3. Stereoselective Oxidation of Sulfides

The method of Leonard and Johnson[74] was employed for the stereoselective oxidation of 4-substituted thianes to the sulfoxides. Periodate oxidation of **138a** gave a mixture of the *cis*-**139a** (70%) and *trans*-**140a** (30%) sulfoxides, and similar oxidation of **138b** gave the *cis*-sulfoxide **139b** in 75% yield, thus showing the favoring of the forms having sulfoxide oxygen axially attached[199].



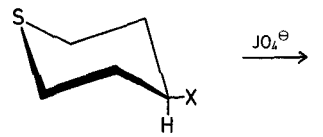
138 a R = Cl-C6H4-
b R = *t*-C4H9-



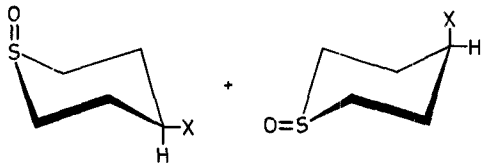
139 **140**

Similar periodate oxidation of **141** gave a mixture of the *cis*-**142** and *trans*-**143** sulfoxides in the ratio of ~8:1; the evidence (N.M.R., I.R., and dipole-moment measurements) suggested a conformational favoring of the forms **142** (having the sulfoxide oxygen atom axially attached) over those having it equatorially attached as in **143**[199].

The periodate oxidation of a chiral acyclic sulfide which was optically active by virtue of deuterium substitution[200] gave a 50:50 mixture of enantiomeric sulfoxides ("racemic" at sulfur), indicating no preferential directing influence by the deuterium-labelled asymmetric carbon; however, periodate oxidation of indane sulfide gave *trans*-sulfoxide exclusively[201].



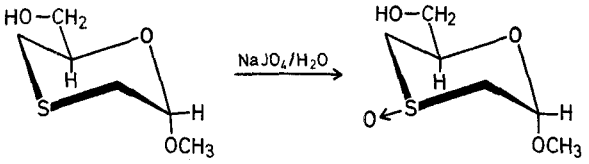
141



142 **143**

X = Cl, OH, OTos.

In contrast to the behavior of 4-substituted thianes, which undergo favored axial *S*-oxygenation with periodate[199], 1,4-oxathianes react under similar conditions to give 90% of the equatorial sulfoxide[202].



144 **145**

Thus, (2*R*,6*S*)-2-(hydroxymethyl)-6-methoxy-1,4-oxathiane (**144**) (derived from methyl α-D-glucopyranoside[203]) was treated with aqueous sodium periodate, and a mixture of sulfoxides in the ratio ~10:1 was obtained[202]; the preponderant isomer (**145**) (90% yield) has the S→O group *cis* to the hydroxymethyl group and in an equatorial orientation. Thus, periodate oxidation of sulfide **144** results in sulfoxide **145**, with predominant equatorial oxygenation of the sulfur atom; this behavior was rationalized by the steric control of the *axial* methoxy group at the anomeric center, assuming that sulfide **144** reacts in a chair conformation[178,203,204,205,206].

This method[202,203,204,205,206] offers a new approach to stereospecific synthesis of asymmetric sulfoxides having known absolute configuration; this is a supplement to the series of the naturally occurring, optically active sulfoxides found, for example, in onion and garlic[207] as D-glucosides[208].

12.4. Degradation of Glycol Side-Chains in Amino Sugar Sulfides (Wolfrom Degradation)

12.4.1. Sugar Sulfides Resistant to Oxidation

In the case of sulfur-containing sugar derivatives, the glycol groups are usually split by periodate with

[197] H. Nieuwenhuyse, R. Louw, *Tetrahedron Lett.* **1971**, 4141.
[198] G. A. Russel, L. A. Ochrymowycz, *J. Org. Chem.* **35**, 2106 (1970).
[199] C. R. Johnson, *J. Amer. Chem. Soc.* **85**, 1020 (1963).
C. R. Johnson, D. McCants, *J. Amer. Chem. Soc.* **86**, 2935 (1964); **87**, 1109 (1965).
See also G. Barbieri, M. Cinguini, S. Colonna, F. Montanari, *J. Chem. Soc. (C)* **1968**, 659.
[200] E. G. Miller, D. R. Rayner, H. T. Thomas, K. Mislow, *J. Amer. Chem. Soc.* **90**, 4861 (1968).
[201] E. Jonsson, *Arkiv Kemi* **26**, 357 (1967).
S. Allenmark, *Arkiv Kemi* **26**, 73 (1967).
[202] K. W. Buck, A. B. Foster, A. R. Perry, J. M. Webber, *Chem. Commun.* **1965**, 433.
[203] K. W. Buck, A. B. Foster, W. D. Pardor, M. H. Qadir, J. M. Webber, *Chem. Commun.* **1966**, 759.
[204] A. B. Foster, J. M. Duxbury, T. D. Inch, J. M. Webber, *Chem. Commun.* **1967**, 881.
[205] A. B. Foster, Q. H. Hasan, D. R. Hawkins, J. M. Webber, *Chem. Commun.* **1968**, 1084.
[206] A. B. Foster, T. D. Inch, M. H. Qadir, J. M. Webber, *Chem. Commun.* **1968**, 1086.
[207] A. I. Virtanen, *Angew. Chem.* **74**, 374 (1962); *Angew. Chem. Intern. Ed.*, **1**, 299 (1962).
[208] A. Kjaer, *Pure Appl. Chem.* **7**, 229 (1963).
K. K. Cheung, A. Kjaer, G. A. Sim, *Chem. Commun.* **1965**, 100.

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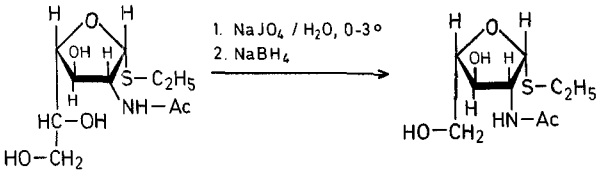
simultaneous oxidation of the functional groups carrying the sulfur atom. For example, thioglycosides yield sulfoxides or even sulfones[190,209,210]. Thioacetals behave in different ways according to their structure[211,212]. In some cases, however, the C—C bond is split without oxidation of the sulfur atom[188,190,213,214]. For instance, ethyl 2-acetamido-2-deoxy-1-thio-α-D-galactofuranoside (**146**) is oxidized by periodate to an aldehyde, isolated as **147** (after reduction with sodium borohydride) in 80% yield[214]; D-galactose dibenzyl dithioacetal yields dibenzyldithioacetaldehyde[190,215]. Conformational and steric factors are apparently responsible for the inhibition of oxidation of the sulfur atom in **146**.



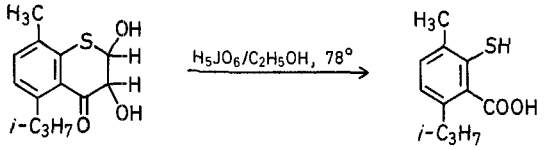
146 **147**

A preferential diol-cleavage by periodate in certain cyclic disulfide-diols has been observed[216]. So oxidation by sodium periodate of *cis*-1,2-dithian-4,5-diol gave 3,4-dithia-adipaldehyde in 45–55% yield; the *trans*-diol, however, yielded the dialdehyde in only 35–45%; both disulfide-diols showed, surprisingly, a high rate of oxidation.

12.5. Oxidative *S*-Ring Opening

An example of the oxidative thio-ring opening by periodic acid is illustrated in a preparation of *o*-mercaptocumenecarboxylic acid.

A solution of 2,3-dihydro-2,3-dihydroxy-5-isopropyl-8-methyl-1-thianaphthalene-4-one (**148**) and periodic acid in 95% ethanol was refuxed for 24 h, and the crude product was warmed for 2 h with aqueous, 10% sodium hydroxide on a warm bath to give 2-mercaptocumene-3-carboxylic acid (**149**, 87%)[217].

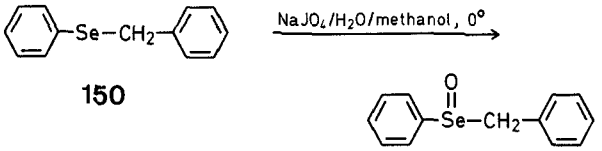


148 **149**

[209] W. A. Bonner, R. W. Drisko, *J. Amer. Chem. Soc.* **73**, 3699 (1951).
[210] S. Okui, *Yakugaku Zasshi*, **75**, 1262 (1955).
[211] H. Zinner, W. Bock, H. P. Klocking, *Chem. Ber.* **92**, 1307 (1959).
[212] S. Akiya, A. Hamada, *Yakugaku Zasshi*, **78**, 119 (1958); *C. A.* **52**, 10892 (1958).
[213] M. L. Wolfrom, K. Anno, *J. Amer. Chem. Soc.* **75**, 1038 (1953).
[214] M. L. Wolfrom, Z. Yosigaqa, *J. Amer. Chem. Soc.* **81**, 3477 (1959).
[215] D. Horton in *The Carbohydrates (Thio Sugars and Derivatives)*, W. Pigman and D. Horton Eds. Academic Press, New York, 1972, Vol. 1B.

12.6. Conversion of Organic Selenides into Selenoxides

The procedure of Leonard and Johnson[74] can be used for oxidation of organic selenides to selenoxides in high yield[218]. Oxidation is achieved by adding dropwise, at 0°, a slight excess of sodium periodate to a solution of the selenide in 7:3 (v/v) methanol/water; the procedure can be applied to diaryl, dialkyl, and aryl alkyl selenides (see Table 10). Oxidation of diaryl selenides by this reagent is slowed down or prevented by the presence of electron-withdrawing groups (e.g. *p*-NO_2). Thus benzyl phenyl selenide (**150**) was oxidized to benzyl phenyl selenoxide (**151**) in 96% yield.



150 **151**

Table 10. Preparation of Selenoxides[218]

R^1	R^2	Yield (%)
H_3CO-	H_3CO-	98
H_3C-	H_3C-	98
-CH_2-	-CH_2-	90
		90
CH_3	CH_3	85
	H_3C-	79
O_2N-	O_2N-	0

13. Periodate as a Co-oxidant

13.1. Periodate/Permanganate Oxidation (Lemieux-von Rudolff Reagent)[219]

A mild, specific reagent for the oxidative cleavage of alkenic double bonds was developed by Lemieux and von Rudolff[219]. It consists of aqueous sodium periodate and potassium permanganate at pH 7 to 8 in the molar ratio of ~60:1. The study

[216] J. E. McCormick, R. S. McElhinney, *J. C. S. Perkin Trans. I* **1972**, 2795.
[217] T. J. Speaker, P. J. Jannke, *J. Pharm. Sci.* **54**, 1073 (1965).
[218] M. Cinquini, S. Colonna, R. Giovini, *Chem. & Ind.* **1969**, 1737.
[219] R. U. Lemieux, E. von Rudolff, *Can. J. Chem.* **33**, 170 (1955).
[220] R. U. Lemieux, E. von Rudolff, *Can. J. Chem.* **33**, 1710 (1955).

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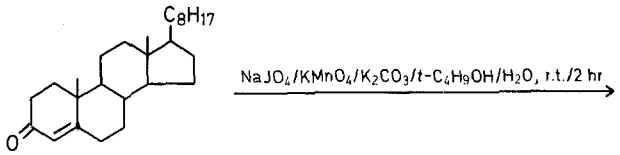
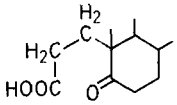
showed[220,221,222,223,224] that oxidation of an alkenic double bond involves hydroxylation of the double bond by permanganate ion via a π-complex and hypomanganate ester[225].

With water-insoluble alkenes, good results were obtained when the reaction was conducted in aqueous *t*-butanol, pyridine[223,224], or *p*-dioxan solution[226]. Ketones and esters were found to be stable towards the reagent (at pH 7 to 8), whereas alcohols reacted slowly[224]. The reagent was found valuable in the analysis and structure-determination of unsaturated fatty acids and their triglyceride derivatives[222,227,228,229,230,231], and in oxidative degradation of terpenes[220,221,224,232,233] and cyclic monoolefins[233,234]. Optimization of oxidative cleavage with permanganate/periodate reagent has been described for monoene[235], diene, and triene fatty acids[235]; the literature cites such advantages as simplicity, and use of the exact amount of the oxidant, thus limiting overoxidation to 1.5–1.7%, and giving a quantitative reaction. However, nonquantitative oxidation of azelaic glycerides by the reagent has been pointed out[237], and unusual behavior of some of the dienes has also been reported[238,239,240,241]. A mechanism of the catalytic action of manganese(II) in the oxidation of *o*-dianisidine by periodate has been proposed[242].

Steroid **152** was oxidized with potassium permanganate/periodate reagent to give the keto acid **153** in 79–88% yield[243].

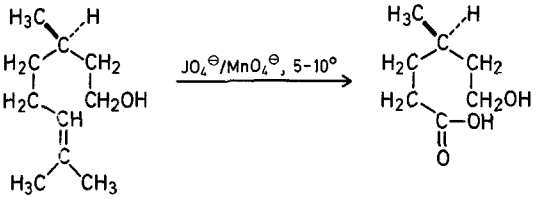


152



153

Acetone/water was used[244] as the medium in the oxidation of (*R*)-(+)-citronellol (**154**) to 6-hydroxy-4-methylhexanoic acid (**155**); the yield of the product was quantitative.



154 **155**

The reagent was used in the oxidation of a tricyclic, α,β-unsaturated ketone to a keto acid in 80% yield[245], and in conversion of bicyclo[2.1.2]hexane to the ketone in 59% yield[246]. The reagent has proved useful in elucidation of the structures of unsaturated natural products; thus 15,16-dihydroxylinoleic acid was oxidized to azelaic acid in good yield[247]. Evidence for the structure of the sex attractant of the gypsy moth was found by similar oxidation of the attractant[248]. The reagent attacked only the double bond, leaving the acetoxy and hydroxy groups unchanged. 3-Acetoxy-1-nonanoic acid was isolated in 92% yield, together with an ω-hydroxy acid, thus supporting the structure suggested for the sex attractant.

The reagent was employed[249] for oxidation of methyl-propyl-propynyl alcohol phosphate to DL-mevalonic acid 5-phosphate; the product was obtained in 80% yield.

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222 E. von Rudolff, *J. Amer. Oil Chem. Soc.* **33**, 126 (1965).
223 E. von Rudolff, *Can. J. Chem.* **34**, 1913 (1956).
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225 K. B. Wiberg, R. D. Geer, *J. Amer. Chem. Soc.* **88**, 5827 (1966).
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See also L. J. Chinn, *Selection of Oxidants in Synthesis: Oxidation at the Carbon Atom*, Marcel Dekker, Inc., New York, 1971, pp. 167–172.
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242 I. F. Dalmanova, N. T. Yastrimskaya, V. M. Pershkova, *Kinet. Katal.* **13**, 678 (1972).
243 T. T. Edward, D. Holder, W. H. Lynn, I. Puskas, *Can. J. Chem.* **39**, 599 (1961).
244 C. G. Overberger, H. Kaye, *J. Amer. Chem. Soc.* **89**, 5640 (1967).
245 H. Ogiso, S. W. Pelletier, *Chem. Commun.* **1967**, 94.
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249 H. Machleidt, E. Cohen, R. Tschesche, *Liebigs Ann. Chem.* **655**, 70 (1962); **672**, 215 (1964).

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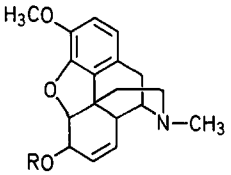
13.2. Periodate/Osmium(VIII) Oxide Oxidation (Lemieux-Johnson Reagent)[250]

Osmium(VIII) oxide adds to a double bond of an unsaturated compound to form an osmic ester, and this is oxidized by periodate, with cleavage to carbonyl compounds and regeneration of the osmium(VIII) oxide. Hydroxylation and cleavage of the double bond have been achieved in one operation in the oxidation of cyclohexene to adipaldehyde by the addition of sodium periodate to a mixture of cyclohexene, osmium(VIII) oxide, and water; the yield of aldehyde was 77%, isolated as the (2,4-dinitrophenyl)hydrazone[250].

Using osmium(VIII) oxide/sodium periodate, certain nitrogen-free, exhaustive-methylation products from codeine (**156**, R = H) were converted[251] through the glycol intermediate into the corresponding aldehyde (**157**→**159**) in good yield.



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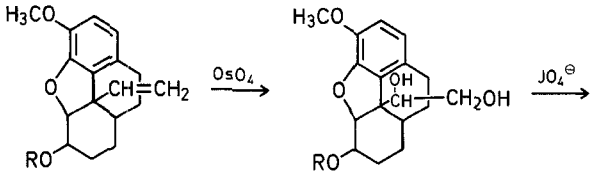
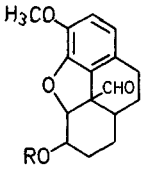
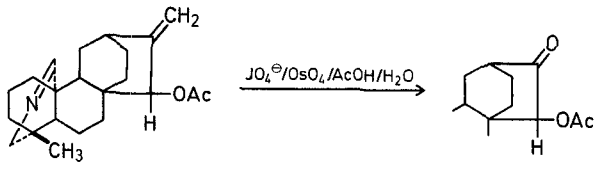


157 **158**



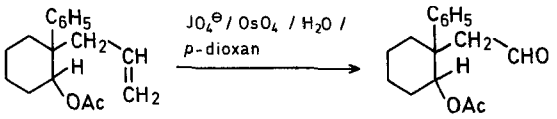
159

The reagent in 80% acetic acid was used[252] successfully for oxidation of the alkaloid derivative **160** to the α-keto acetate **161**, and also for oxidation of F-dihydrogarryfoline diacetate[253] to the α-keto acetate derivative, also in 80% acetic acid at 4°, in good yield. These oxidations proceed without attack on the nitrogen atom.



160 **161**

Oxidation of 4-styryltropolone with the reagent gave 4-formyltropolone in 84% yield[254]. Oxidation[255] of **162** to the aldehyde **163** by the original procedure of Lemieux-Johnson[250] (2 molar equivalents of sodium periodate added over a period of 30–40 min) was found to proceed[231] in high yield when performed on a small scale (less than 5 g). For larger quantities, slow addition[255] of the periodate during up to 10 h is recommended.



162 **163**

An interesting application of the method has been reported by Jeger and coworkers[256]; on oxidation of 8α,20-oxidomannol in aqueous *p*-dioxan, the α-hydroxy aldehyde initially formed suffered reverse aldolization, to give the methyl ketone and formaldehyde. The cleavage of an exocyclic methylene group is effected more cleanly by this reagent than by ozonolysis[257]. The reagent has been used in hydroxylation of pyrene[258] and other condensed aromatic hydrocarbons having an "activated" double bond[259].

Treatment of thiacyclohexane, $S(CH_2)_5$, with osmium(VIII) oxide at −15° for 2 h produced the sulfone $O_2S(CH_2)_5$ in 58% yield, although other sulfides (diphenyl sulfide and dibenzyl sulfide) proved to be inert[260].

13.3. Periodate/Ruthenium(VIII) Oxide Oxidation (Pappo-Becker and Djerassi-Engle Reagent)[261,262]

As compared to osmium(VIII) oxide, the less toxic, but much stronger oxidant, ruthenium(VIII) oxide has found wider synthetic application as a cleavage reagent for alkenes, alkynes, and arenes (to give aldehydes, ketones, or acids) and as an efficient oxidant for alcohols, carbohydrates, sulfur compounds, aromatic steroids, conjugated ketosteroids, and many

[250] R. Pappo, D. S. Allen, Jr., R. U. Lemieux, W. S. Johnson, *J. Org. Chem.* **21**, 478 (1956).
[251] H. Rapoport, A. D. Batcho, J. E. Gordon, *J. Amer. Chem. Soc.* **80**, 5767 (1958).
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[257] K. H. Baggaley, J. R. Dixon, J. M. Evans, S. H. Graham, *Tetrahedron* **23**, 299 (1967).
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[258] F. G. Oberender, J. A. Dixon, *J. Org. Chem.* **24**, 1226 (1959).
[259] R. S. Tipson, *Oxidation of Polycyclic, Aromatic Hydrocarbons*, Nat. Bur. Stand. Monograph **87**, Washington, D. C., 1965, p. 39.
[260] H. B. Henbest, S. A. Khan, *Chem. Commun.* **1968**, 1036.
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[262] C. Djerassi, R. R. Engle, *J. Amer. Chem. Soc.* **75**, 3838 (1953).
[263] D. G. Lee, M. van den Engh in *Oxidation in Organic Chemistry, Part B*, W. S. Trahanovsky, Ed., Academic Press, New York, 1973, pp. 177–227.

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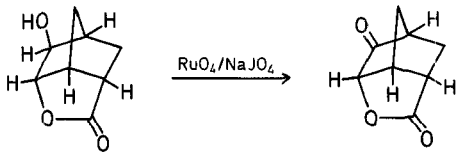
other compounds[263]. Ruthenium(VIII) oxide was used to oxidize a series of sugars[264]; hydroxy groups axially and equatorially attached to pyranoid rings were found to be oxidized with equal ease; also *endo*- and *exo*-hydroxy groups in 1,4:3,6-dianhydrides are equally well oxidized[264].

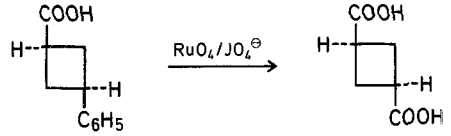
It was found[265] that ruthenium(VIII) oxide/sodium periodate was the only reagent that could convert hydroxy-lactone **163a** into the acid-sensitive ketolactone **163b** (80% yield); other oxidizing procedures failed.



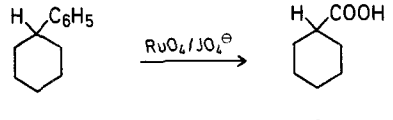
163a **163b**

This reagent was used[266] for the oxidation of isolated secondary groups in carbohydrates to ketone groups; however, similar oxidations are frequently performed with methyl sulfoxide in the presence of an electrophile[266,267].

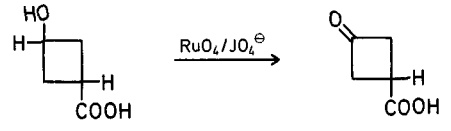
Ruthenium(VIII) oxide/sodium periodate reagent was used[268] in a surprising oxidation of phenyl groups to carboxylic acids in moderate yield (conversion of **164** into **165**, and **166** into **167** in 25% yield) and conversion of cyclobutanols to cyclobutanones (conversion of **168** into **169** in 78% yield).



164 **165**

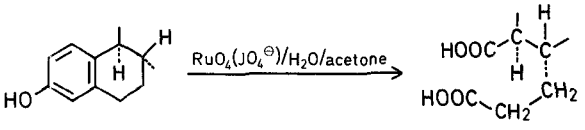


166 **167**



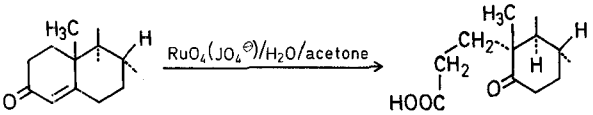
168 **169**

The oxidation of aromatic steroids and conjugated steroids by ruthenium(VIII) oxide was studied[269]; the reagent was generated *in situ* initially from ruthenium dioxide and sodium periodate, and then the tetraoxide was regenerated during the reaction by addition of sodium periodate solution. A mixture of acetone and water was employed as the solvent. Thus, estrone **170** was oxidized to acid **171** in good yield.



170 **171**

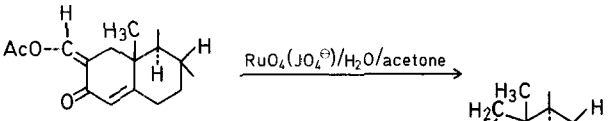
The reagent is useful for cleavage of conjugated, and cross-conjugated, steroidal ketones. Thus, testosterone **172** is cleaved to the keto acid **173** in 80% yield.



172 **173**

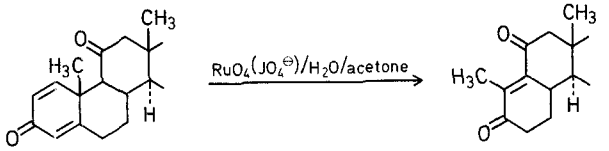
However, when estradiol diacetate was oxidized, an interesting, double-allylic oxidation of ring A phenol was observed; the product isolated was 3,17β-diacetoxy-9α-hydroxy-6-oxoestra-1,3,5(10)triene (40% yield)[270].

Oxidation of **174** gave keto acid **175** by elimination of C-3 and C-4.



174 **175**

Unexpectedly, enediones are formed from 1,4-diene-3,11-diones (**176**→**177**).



176 **177**

[264] P. J. Beynon, P. M. Collins, P. T. Doganges, W. G. Overend, *J. Chem. Soc. (C)* **1966**, 1131.
P. J. Beynon, P. M. Collins, D. Gardiner, W. G. Overend, *Carbohyd. Res.* **6**, 431 (1968).
P. M. Collins, P. T. Doganges, A. Kolarikol, W. G. Overend, *Carbohyd. Res.* **11**, 199 (1969); see also Ref. 267 on ruthenium tetraoxide oxidation of carbohydrates.

[265] R. M. Moriarty, H. Gopal, T. Adams, *Tetrahedron Lett.* **1970**, 4003; *Tetrahedron* **28**, 4259 (1972); see Ref. 7 for additional RuO_4 oxidations.

[266] D. Horton, J. S. Jewell, *Carbohyd. Res.* **2**, 251 (1966).

[267] J. S. Brimacombe, *Angew. Chem.* **81**, 415 (1969); *Angew. Chem. Internat. Edit.* **8**, 401 (1969).
J. G. Moffatt in *Oxidation*, R. L. Augustine, D. J. Trecker, Eds. Vol. 2, Marcel Dekker, New York, 1971, Chapter 1.
F. Butterworth, S. Hanessian, *Synthesis* **1971**, 70.

[268] J. A. Caputo, R. Fuchs, *Tetrahedron Lett.* **1967**, 2729.
See also G. Stork, A. Meisels, J. E. Davies, *J. Amer. Chem. Soc.* **85**, 3419 (1963) for conversion of diphenylalkene to an acid with $RuO_4/NaJO_4$.

[269] D. M. Piatak, H. B. Bhat, E. Caspi, *J. Org. Chem.* **34**, 112 (1969).

[270] D. M. Piatak, G. Herbst, J. Wicha, E. Caspi, *J. Org. Chem.* **34**, 116 (1969), see footnote 7 in this paper for a list of references describing the use of ruthenium tetraoxide in organic chemistry.

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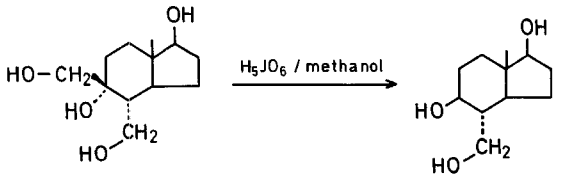
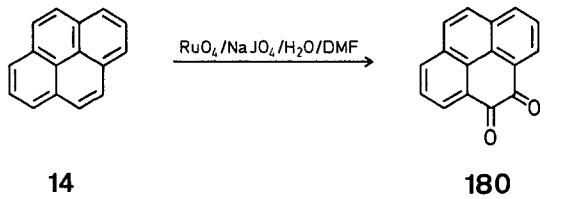
Tetrol **178** was surprisingly converted into **179** when treated with periodic acid[270]; due to the *trans*-diaxial *vic*-glycol configuration of two adjacent hydroxyl groups (that prevents a cyclic transition state, and a carbon-carbon cleavage), the C-10 primary alcohol was apparently oxidized to an aldehyde which underwent a reverse aldol reaction to give **179**.



178 **179**

13.4. Periodate/Osmium or Ruthenium(VIII) Oxide-Catalyzed Oxidation of Pyrene (New $RuO_4/NaIO_4$/DMF System)

Osmium (ruthenium) tetraoxide/sodium periodate was originally used[258] to hydroxylate the 4,5 double bond of pyrene (an ortho-reactive center[259]); the reaction was performed in aqueous acetone, and required eleven days to produce the major product, namely, 4,5-pyrenedione (**180**) in 11 to 23% yield. The results from this laboratory indicate that, when this oxidation is performed in aqueous *N*,*N*-dimethylformamide, the reaction time can be lowered to 48 h, to give the same or a higher yield of dione **180**; the use of the toxic osmium(VIII) oxide can be supplemented by the less toxic ruthenium(VIII) oxide.



14 **180**

Oxidation of Pyrene to 4,5-Pyrenedione (180)[85]:
A solution of pyrene (10 g) in a mixture of *N*,*N*-dimethylformamide (150 ml) and 6 *M* aqueous acetic acid (40 ml) was treated with ruthenium dioxide (0.5 g) and sodium periodate (10 g). The mixture was stirred at 10° for 1 h, and then at room temperature. After 24 h, an additional quantity of sodium periodate (5 g) was added, and stirring was continued for 24 h. The suspension was filtered, and the filtrate was poured into cold water (1.5 l) and stirred for 30 min, to give an orange-yellow solid (10.3 g). The solid was dissolved in ~160 ml of warm 3:1 (v/v) acetic acid/*N*,*N*-dimethylformamide, the solution passed through a column (50 × 4 cm) of silica gel[271], and eluted successively with benzene, 2:1 (v/v) benzene/acetic acid, and 1:1 (v/v) benzene/acetic acid. Elution with benzene gave unreacted pyrene (8.2 g); elution with the 2:1 benzene/acetic acid gave colorless lactol (5-formyl-4-phenanthrenecarboxylic acid; 300 mg, m.p. 273°), and elution with the 1:1 mixture gave yellow needles of 4,5-pyrenedione (1.3 g, ~12%). The product, recrystallized from glacial acetic acid, melted at 303–305°.

13.5. Periodate/Pervanadic Acid Oxidation of Pyrene [$JO_4^{\ominus}/VO_2(OH)_3$ System][85]

In contrast to the oxidations already described, pyrene in warm acetic acid is converted into a mixture of 1,6- and 1,8-pyrenediones on treatment with periodate and pervanadic acid catalyst [prepared by treatment of vanadium(V) oxide with warm, aqueous sodium periodate, followed by filtration of the yellow solution of pervanadic acid, $VO_2(OH)_3$]. The catalyst was even more powerful when prepared with periodic acid (V_2O_5 + aq. H_5JO_6).

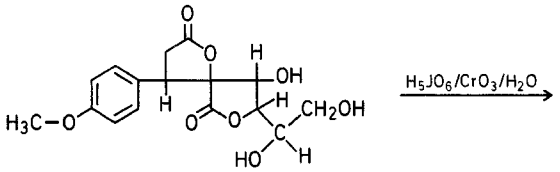
Oxidation of pyrene has also been observed with the following oxidizing systems: JO_4^-/WO_3; JO_4^-/MoO_3; JO_4^-/SeO_2; $JO_4^-/S_2O_8^{2-}$; JO_4^-/MnO_4^-; JO_4^-/Co(III), and JO_3^-/Co(III).

Treatment of an aqueous solution of cobalt acetate with periodic acid yielded a green-yellowish powder [JO_4^-/Co(III)]. The dried material rapidly oxidized phenylhydrazine and converted the bis[phenylhydrazone] of glyoxal into bis[phenylazo]ethylene in 90% yield (after refluxing in chloroform or benzene)[85].

There is an ample evidence in this laboratory that periodate oxidation can be applied to boron, phosphorus, or silicon organic compounds; for example, treatment of triphenylborane or diphenylboric acid in warm acetic acid (or aqueous) solution with periodic acid gives phenol and quinone-type compounds[85]. New applications of periodates to metallo-organic chemistry will be of considerable interest.

13.6. Periodic Acid/Chromic Acid

The combination of periodic acid and chromic acid was used[272] to degrade the primary-secondary glycol grouping of **181** to the carboxy group of **183** in 85% yield. The more powerful oxidant, periodic acid, specifically cleaves the *vic*-glycol bond and also regenerates the chromic acid utilized in oxidation of the intermediate aldehyde **182**.



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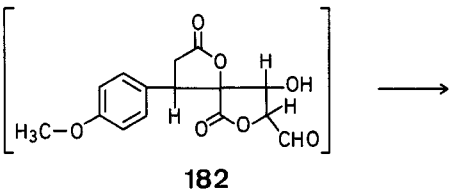

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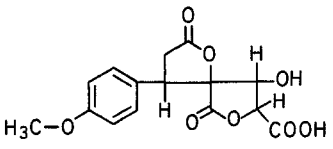

183

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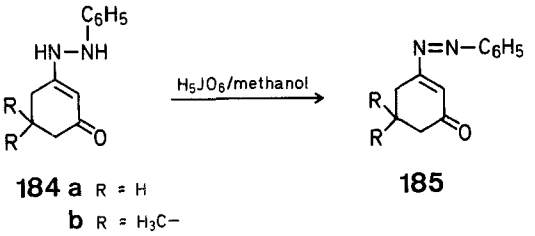
14. Amines and Hydrazine Derivatives

Complexes are apparently formed between potassium periodate and some primary and secondary aliphatic amines[273], and, in the oxidation of diethylamine with sodium periodate, free radicals are involved[66]. Mono- and di-alkylanilines (toluidines) are also oxidized by periodate[274], and aldehydes were obtained from *N*-substituted anilines[275]; free-radical intermediates were observed in the periodate oxidation of aniline[276]. Formation of an *N*-oxide from a tertiary amino group has been observed with erythromycin and erythralosamine[277], and has also been found for *N*-(2-hydroxyethyl)- and *N*-propyl-piperidine[18]. In analogy to other amino alcohols[18,189], tertiary amino alcohols of the type $C_6H_5CHOH(CH_2)_2NR_2$ are also cleaved by periodate. Treatment of $C_6H_5CHOH(CH_2)_2N(C_2H_5)_2$ with sodium periodate gave cleavage products, namely, phenol, 3-hydroxy-3-phenylpropanoic acid, diethyl *N*-oxide, and diethylamine[278]. Similar treatment of 1-phenyl-2-piperidinoethane and 1-phenyl-2-morpholinoethane gave benzene, phenol, phenylacetic acid, piperidine *N*-oxide, or morpholine *N*-oxide, and the corresponding amines[278]. Treatment of *N*,*N*-dimethyl-*p*-anisidine with sodium periodate, with cooling in ice, gave the unstable, cleavage product 4,4-dimethoxyazobenzene (25%) and methanol. This study[278] showed that, in the oxidation of *N*,*N*-dimethyl-*p*-anisidine with periodate, methanol was formed by cleavage of the ether bond of the anisidine, and not by dealkylation. Oxidation of monoalkylhydrazines by sodium periodate gave nitrogen and alkanes in over 85% yield[279] via an alkyldiimine intermediate; treatment of aliphatic and aromatic azines with periodic acid also produced nitrogen and the parent aldehyde or ketone in 95% yield, and, as with benzalazine, the reaction proceeded via a periodate/azine dimer complex[35]. Oxidation of nicotinic hydrazide by periodate at 0° gave nicotinaldehyde in good yield[280].

Treatment of *myo*-inosose-2 phenylhydrazone with aqueous periodic acid at 0–3° gave a crystalline material that detonated violently on heating to 110°[85]. The anticipated, dialdehyde peroxide structure for the unknown was somewhat uncertain, in view of a report on the ability of periodic acid to attack the peroxide linkage in cyclohexane hydroperoxide[281].

14.1. Conversion of a Phenylhydrazine into a Phenylazo Compound

Oxidation of the phenylhydrazino derivative **184a** (or **184b**) with one equivalent of periodic acid in methanol gave the corresponding azo compound **185a** (or **185b**) in 90% yield[282]. The action of periodic acid, a two-electron oxidant, on the phenylhydrazino group can be envisaged as a simultaneous attack of an electrophilic and a nucleophilic species of the reagent on vinyl and phenyl NH groups, respectively. Oxidation of **184a** to **185a** could be regarded as a *cis*-electrocyclic dehydrogenation. However, this would be forbidden (see Ref. 72, particularly MO model 20 mentioned here), so the electrophile/nucleophile route is more likely.



184 a R = H
b R = H_3C–

185

14.2. Conversion of Dehydro-L-Ascorbic Acid Bis[phenylhydrazone] into a Phenylazo-phenylhydrazino Derivative

On treatment of dehydro-L-ascorbic acid bis[phenylhydrazone] **186** with periodic acid, a new phenylazo-phenylhydrazino derivative **187** that still retained the original 1,4-lactone structure was obtained[283].

14.3. Tris[hydrazones] from Mesoxalaldehyde Bis[hydrazones]

On treatment of mesoxalaldehyde bis[hydrazones] (prepared by the periodate oxidation of the corresponding sugar osazones[284]) with phenyl- or acyl-hydrazine, a series of simple, mixed and substituted tris-[hydrazones] have been prepared[285,286] in 60–85% yield. A series of *p*-nitrophenylhydrazones have been prepared from periodate-oxidized nucleosides[287].

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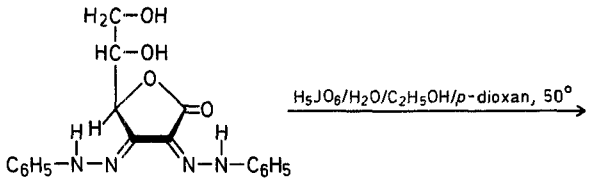

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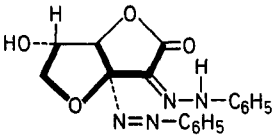
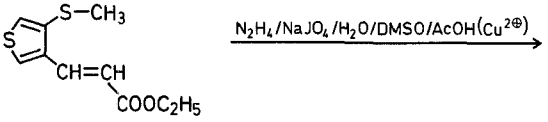


187

14.4. Generation of Diimides from Hydrazine

Diimide (HN=NH), generated by the sodium periodate oxidation of hydrazine, is a particularly useful, reducing system for compounds that contain readily oxidized functional groups[288]. The use of sodium periodate and hydrazine permits quantitative reduction, for example, of the thiophen derivative **188** into **189** at room temperature, without formation either of the sulfone or the sulfoxide. In this way, azobenzene was reduced to hydrazobenzene (95%), acenaphthylene to acenaphthene (91%), cinnamic acid to 3-phenylpropanoic acid (80%), phenylpropiolic acid to 3-phenylpropanoic acid (85%), and maleic acid to succinic anhydride (95%).



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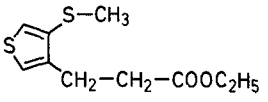
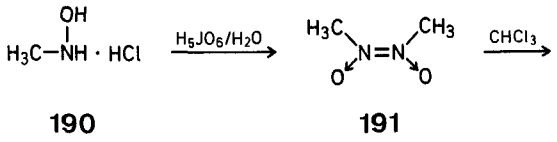


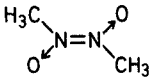
189

15. Hydroxylamine Derivatives

Hydroxylamine is instantly oxidized by sodium periodate or periodic acid, with formation of nitrous oxide and iodine[289]. Similar oxidation of phenylhydroxylamine[290] gave the nitroso compound; oxidation of methylhydroxylamine hydrochloride (**190**) with periodic acid gave *cis*-nitrosomethane dimer **191** (m.p. 93–95°) in 80% yield; on treatment with chloroform, the latter rearranges to the *trans*-isomer **192** (m.p. 120–121°)[291].



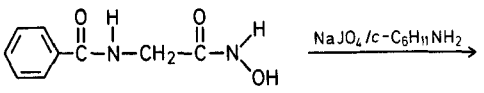
190 191



192

Oxidation of diphenylglyoxime with periodic acid in warm, aqueous acetic acid gives benzonitrile as one of the major cleavage products; dehydration, and rupture of the carbon-carbon bond were observed in similar oxidation of dimethylglyoxime[85]. Hydroxamic acids (R^1—$CONR^2OH$; R^1 = alkyl or aryl, and R^2 = alkyl or H) are rapidly oxidized in aqueous solution by periodic acid to give the corresponding carboxylic acid and nitrous oxide[291,292]. This type of reaction has been used[293] to prepare amides from hydroxamic acids by oxidation in the presence of amines.

The oxidation of hydroxamic acids by sodium periodate in the presence of aliphatic or aromatic amines gives variable yields of amides by the process of oxidative acylation[293]. The first step in the oxidation of hydroxamic acid itself was considered[293] to be a rapid conversion of RCONHOH by periodate into a reactive intermediate (nitrosocarbonyl, RCONO) that later proved to be a radical anion ($RCO—\dot{N}—\bar{O}$)[236,294]. Thus, on treatment with periodate in the presence of cyclohexylamine (at pH 6.5), hippurhydroxamic acid (**193**) gave *N*-cyclohexylhippuramide (**194**) in 45% yield.



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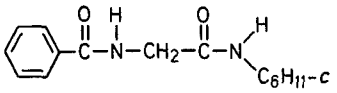
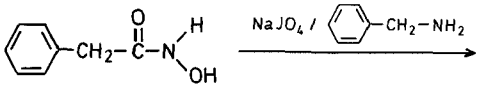


194

Similar treatment of phenylacethydroxamic acid (**195**) in the presence of benzylamine (at pH 7) gave *N*-benzylphenylacetamide (**196**) in 60% yield.



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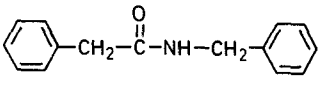

196

The amides obtained in this way can be important intermediates in synthesis of peptides[295] (Table 10).

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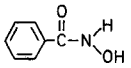
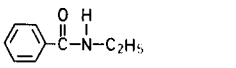
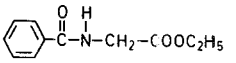
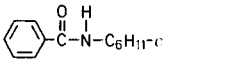
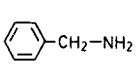
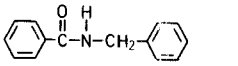
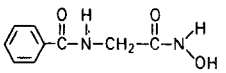
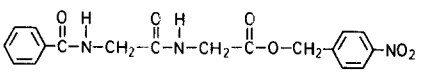
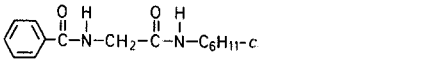
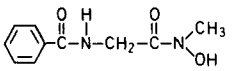
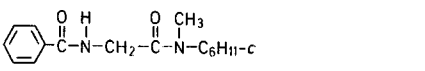
Table 10. Preparation of Amides from Hydroxamic Acids[293]

Hydroxamic Acid	Amine	Amide	Yield (%)
	$C_2H_5NH_2$		37
	$H_2C(NH_2)COOC_2H_5$		25
	$c\text{-}C_6H_{11}\text{-}NH_2$		55
			63
	$H_2C(NH_2)COO\text{-}CH_2\text{-}C_6H_4\text{-}NO_2$		43
	$c\text{-}C_6H_{11}\text{-}NH_2$		45
	$c\text{-}C_6H_{11}\text{-}NH_2$		22

N-Hydroxypyrrolidines having an α-hydrogen atom were oxidized by sodium periodate with formation of a nitrone[118,296].

16. Oxidation of Phenols, Benzenediols, Benzenehexols, and Hydroxy Aromatics

16.1. Oxidation of Benzenediols and their Monoethers (Adler Oxidation)

A comprehensive study by Adler and coworkers[68,297–305,309] called here the Adler oxidation, involves oxidation of benzenediols, their monoethers, and certain methylphenols with sodium periodate in aqueous or 80% acetic acid solution. This work is a useful supplement to an earlier extensive study by Wessely and coworkers[306] that describes oxidation of phenols, benzenediols, benzenetriols, and their ethers with lead tetraacetate (the Wessely oxidation). Other oxidations of phenol ethers have been studied[307,308], and the Adler oxidations of phenols, benzenediols, and their ethers have been thoroughly reviewed[18].

Periodate oxidation of guaiacol[297] gave *o*-benzoquinone and *cis,cis*-muconic acid, derived by further cleavage of the quinone[298]. Oxidation of 2,6-dimethoxyphenol in the cold with sodium periodate gave a complex mixture containing 3-methoxy-*o*-benzoquinone (30 to 60% yield), 2,6-dimethoxy-*p*-benzoquinone (5%), coerulignone (7%), and 3,8-dimethoxy-1,2-naphthoquinone (7%)[301].

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See also: J. B. Bapat, D. St. C. Black, R. F. C. Brown, *Adv. Heterocyclic Chem.* **10**, 199 (1969).
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F. Wessely, J. Koltan, F. Sinwel, *Monatsh. Chem.* **83**, 14 (1952).
F. Wessely, J. Koltan, *Monatsh. Chem.* **84**, 291 (1953).
F. Wessely, E. Schnizel, *Monatsh. Chem.* **84**, 425 (1953).
F. Wessely, E. Schnizel, H. Vilosek, W. Mettesics, *Monatsh. Chem.* **88**, 1069 (1957).
H. Budzikiewicz, G. Schmidt, P. Stockhammer, F. Wessely, *Monatsh. Chem.* **90**, 609 (1959).
See also an excellent article on lead(IV) acetate oxidation of alcohols: M. Lj. Mihailović, Ž. Čeković, *Synthesis* **1970**, 209.
See also: Y. Pocker, B. C. Davis, *J. Amer. Chem. Soc.* **95**, 6216 (1973).
The Wessely oxidation (acetoxylation of phenols with lead tetraacetate) proceeds by very rapid electrophilic attack at both *ortho*- and *para*-positions and is not selective for the *ortho*-position only, see W. A. Bubb, S. Sternhell, *Tetrahedron Lett.* **1970**, 4499; see also Ref. 309, p. 164.

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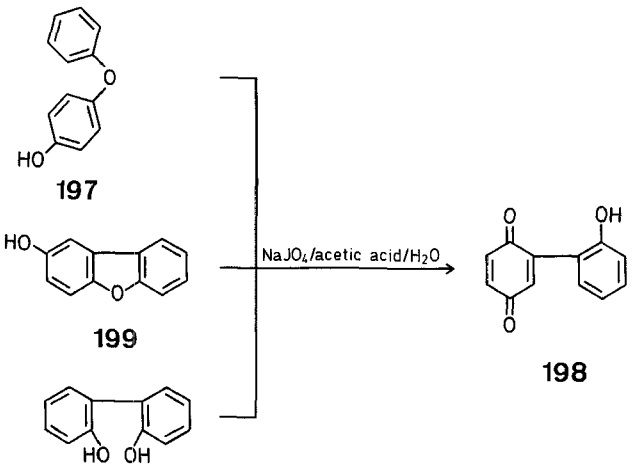
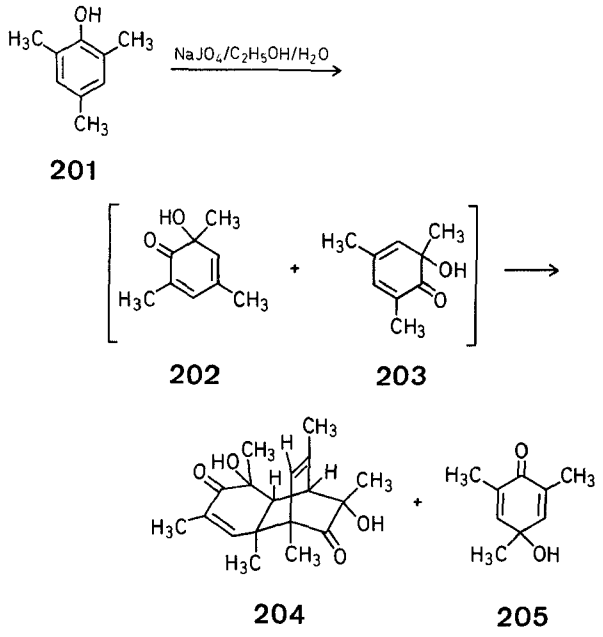
Treatment of monoalkyl, monobenzyl, and monophenyl ethers of 1,2- or 1,4-benzenediols with sodium periodate leads mainly to the oxidative removal of the ether substituents, with the formation of *ortho*- or *para*-quinone and the corresponding alcohol (or phenol). The monophenyl ether of 1,4-benzenediol (**197**) gave the cleavage products (*p*-quinone and phenol) in addition to **198** [(2-hydroxyphenyl)-*p*-benzoquinone] (35%), formed as the result of rearrangement and further oxidation of the intermediate. Compound **198** was also formed by periodate oxidation of 3-hydroxydibenzofuran (**199**) in 49% yield, and on oxidation of 2,2'-dihydroxydiphenyl (**200**) (5%)[298].



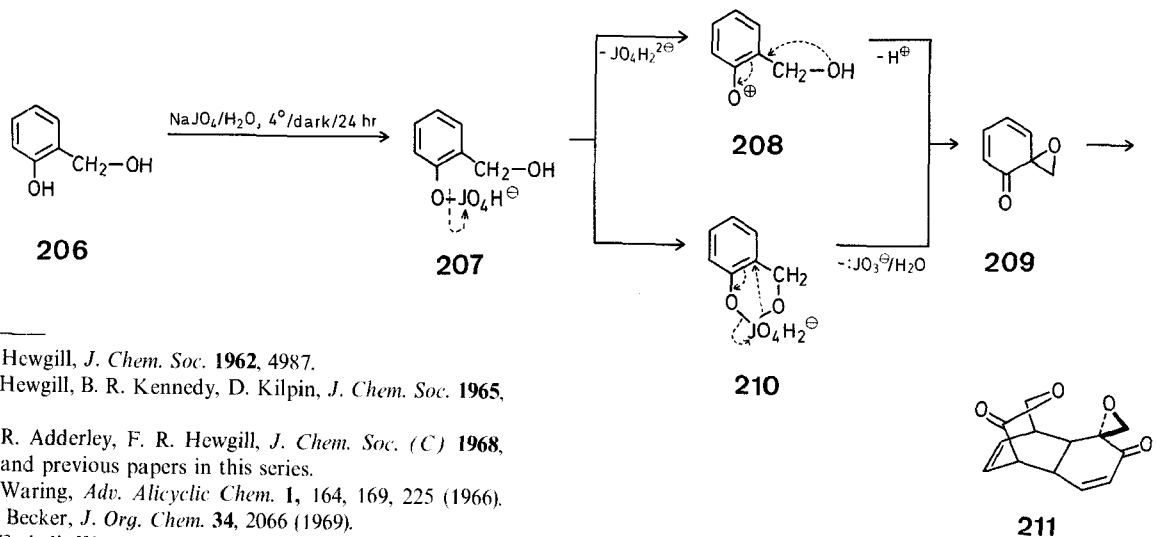
Generally, 1- and 4-hydroxy-dibenzofurans undergo periodate oxidative cleavage at the ring-oxygen atom (*via* a quinol-like hemiacetal intermediate)[298].

Treatment of 2,4,6-trimethylphenol (mesitol) (**201**) in aqueous ethanol with sodium periodate gave, via the dienophilic[309] intermediates **202** and **203**, the Diels-Alder adduct **204** in 53% yield, and compound **205** in 28% yield[304]. Similarly, 2,6-dimethylphenol gave the Diels-Alder dimer in 64% yield[297,300].



In analogy to the behavior of 2-methylphenols unsubstituted on C-3, treatment of salicyl alcohol (**206**) with sodium periodate results in the formation of spiroepoxy-2,4-cyclohexanedienone (**209**), which dimerizes rapidly by the Diels-Alder reaction to give the dimer **211** (1,3,4,4*a*,5,8*a*-hexahydro-1,4-ethenonaphthalene-3,5-bis[spirooxirane]-2,6-dione) in 74% yield[305]. The formation[305] of the monomeric intermediate **209** can proceed by the nucleophilic addition of the phenolic hydroxyl group of **206** to the periodate, to give the periodic ester **207**, followed by two-electron transfer that would lead to the phenoxonium ion **208**, which, by intramolecular, nucleophilic attack of the alcohol oxygen atom on C-2 of the ring would give the epoxide **209**; alternatively, steps from **207** to **209** may proceed directly *via* the cyclic periodic ester **210** (concerted reaction process).

Dimer **211** is the result of the *endo*-addition of two *s*-enantiomers of monomer **209**.



A further example of Adler oxidation is the conversion of 2-methoxyphenanthren-1-ol into 1,2-

[307] F. R. Hewgill, *J. Chem. Soc.* **1962**, 4987.
F. R. Hewgill, B. R. Kennedy, D. Kilpin, *J. Chem. Soc.* **1965**, 2904.
[308] C. J. R. Adderley, F. R. Hewgill, *J. Chem. Soc. (C)* **1968**, 1434, and previous papers in this series.
[309] A. J. Waring, *Adv. Alicyclic Chem.* **1**, 164, 169, 225 (1966).
[310] H. D. Becker, *J. Org. Chem.* **34**, 2066 (1969).
[311] A. J. Fatiadi, W. F. Sager, *Org. Syntheses* **42**, 66, 90 (1962).
A. J. Fatiadi, H. S. Isbell, W. G. Sager, *J. Res. Nat. Bur. Stand.* **67A**, 153 (1963).

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phenanthrenequinone in 79% yield[310] (a reaction process that involves simultaneous oxidation and hydrolysis) and cleavage of the 2,2'-diphenyl ether derivative to give the *p*-benzoquinone derivative in moderate yield[308].

16.2. Oxidation of Benzenehexol and Related Aromatic Derivatives

Oxidation of Benzenehexol:
Treatment of an ice-cold solution of benzenehexol[311] (1 g in 10 ml water) with periodic acid (2 ml, 4.5 *M*) caused a vigorous reaction; the free iodine precipitated was filtered off, and the filtrate was extracted with chlorofom. Cooling of the extract in an ice-bath for 2 h caused deposition of colorless prisms of decahydroxycyclohexane dihydrate, ("triquinoyl octahydrate, $C_6O_6 \cdot 8H_2O$); yield: 0.7 g; m.p. 99°.

No opening of the aromatic ring has been observed[85].

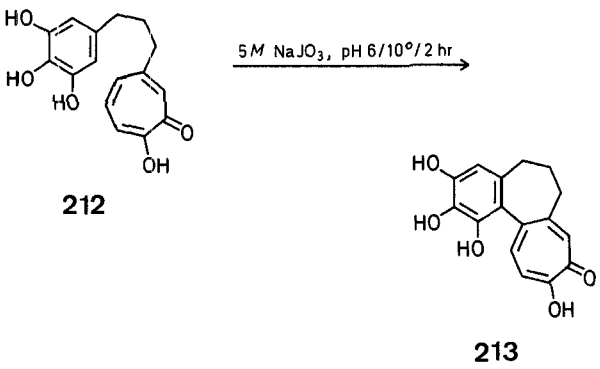
Oxidation of 2,6-di-*t*-pentylhydroquinone in acetic acid with periodic acid (3 min at 75°, dilute with water, and cool) gave golden plates of the corresponding *p*-quinone in 75% yield[85]. Treatment of 1,2,3,5-tetramethoxybenzene or 5-chloro- or bromo- (but not nitro- or other electron-withdrawing group) -1,2,3-trimethoxybenzene in acetic acid with periodic acid (4 min at 75°, with gradual dilution with water) gave 2,6-dimethoxy-*p*-benzoquinone in 25 to 50% yield[85].

Similar oxidation of 2,3-naphthalenediol apparently proceeded with opening of the ring, to give the *o*-carboxyaldehyde derivative of type **102** [isolated as its (2,4-dinitrophenyl)hydrazone], and oxidation of *β*-binaphthol gave a pink complex containing iodine (stable free-radical from E.S.R. measurements). However, 2,3-quinoxalinediol seems to be resistant to periodic acid oxidation, even on warming (in acetic acid/dimethylformamide)[85]. Xanthydrol in acetic acid was oxidized with periodic acid to xanthone, and pentachlorobromo- and -fluorophenols were oxidized to quinones (chloranil, bromanil, and fluoranil) in 70–75% yield[85].

Certain *t*-butylphenols were oxidized with periodic or iodic acid to give either the quinones or the coupling products[69]. Quinol ethers in acetic acid were oxidized with sodium periodate to hydroxyquinones in good yield[312], and sodium iodate has been used occasionally for phenolic coupling, a reaction which was assumed to involve radicals[313,314].

16.3. Cyclization of a Pyrogallol Derivative

In study of the biosynthesis of colchicine alkaloids, Scott and coworkers[313] cyclized the pyrogallol derivative **212** with sodium iodate to a tropolone derivative (**213**) in good yield; the authors[313] proposed a mechanism of cyclization which invoked the participation of the tropolone ring radicals. Other oxidations and hydroxylations of phenols have been reported[315].



212 213

16.4. Sterically Hindered Alcohols

In analogy to chromic acid, periodic acid also failed to oxidize triphenylmethanol. However, in contrast to chromic acid, periodic acid in warm, aqueous acetic acid oxidizes 1-naphthyldiphenylmethanol by attacking the naphthalene portion of the molecule, to give a product probably having a quinone-ether bridge structure[85].

17. Flavanols

The flavanols were oxidized by periodic acid in aqueous *N,N*-dimethylformamide to give a mixture of the tautomers of 2-hydroxyflavan-3,4-diones[316]. In methanol, the methoxy analog was obtained as its methyl hemiacetal in good yield[317].

Sodium periodate was used in structural studies of the 3,4-flavandiols, for example, a naturally occurring leucocyanidin[318] and leucocyanidin methyl ether[319].

Periodate oxidation of the natural dilactone conocarpin methyl ether **213a** (from leaves of *Leucospermum*, South Africa) having 4*S*,5*S*,8*R*,9*R*,10*S* configura-

[312] D. S. Deorha, V. K. Maliesh, S. P. Sareen, *J. Indian Chem. Soc.* **42**, 315 (1965).

[313] A. I. Scott, F. McCapra, J. Nabney, D. W. Young, A. J. Barker, T. A. Davidson, A. C. Day, *J. Amer. Chem. Soc.* **85**, 3040 (1963).

[314] R. Cecil, J. S. Littler, *J. Chem. Soc. (B)* **1968**, 1420.

[315] H. Musso, *Angew. Chem.* **75**, 965 (1963); *Angew. Chem. Intern. Ed.* **2**, 723 (1963).
J. B. Harborne, N. W. Simmons in *Biochemistry of Phenolic Compounds*, J. B. Harborne Ed., Academic Press, New York, 1964, Chapter 3.
A. I. Scott, *Quart. Rev.* **19**, 1 (1965). D. H. R. Barton, *Chem. in Britain* **1967**, 330.
D. I. Meteliza, *Uspekhi Khimii*, **11**, 1211 (1971).
T. Kametani, K. Fukumoto, *Synthesis* **1972**, 657, and references 1–10.
See also P. D. McDonald, G. A. Hamilton in *Oxidation in Organic Chemistry, Part B*, W. S. Trahanovsky, Ed., Academic Press, New York, 1973, pp. 97–134; this is an excellent chapter on oxidative coupling of phenols; it presents novel mechanistic views, and corrects common misconceptions about this very important reaction.

[316] M. A. Smith, *J. Org. Chem.* **28**, 933 (1963).

[317] M. A. Smith, R. A. Webb, L. J. Cline, *J. Org. Chem.* **30**, 995 (1965).
M. A. Smith, W. D. Boswell Jr., K. G. Henzel, D. G. Miller, *J. Org. Chem.* **37**, 2774 (1972).

[318] S. E. Drewes, D. G. Roux, *Chem. & Ind.* **1963**, 532.

[319] V. Krishnamoorthy, T. R. Seshardi, *Current Sci. (India)* **35**, 40 (1966).

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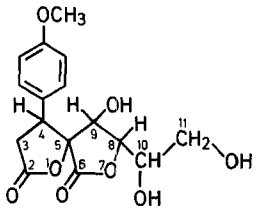
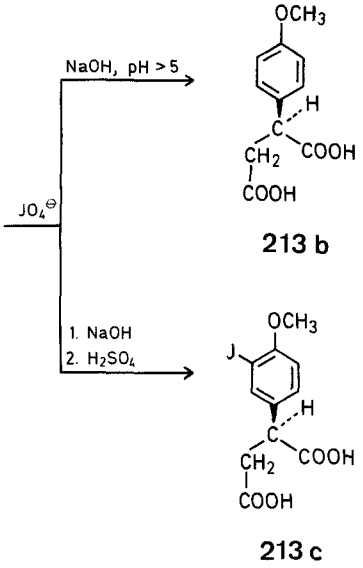
tion[320] (assigned according to the stereochemical rules[321]) destroys four chiral centers and gives either optically active (+)-*p*-methoxyphenylsuccinic acid **213b** (4*S* configuration, under alkaline pH, ~50% yield) or (+)-(3-iodo-4-methoxyphenyl)succinic acid **213c** (~60% yield) under acidic conditions[320].



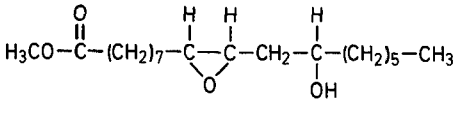
213 a



18. Fatty Acids

18.1. Direct Cleavage of Epoxides to Aldehydes

Reaction of methyl esters of epoxidized fatty acids with periodic acid leads to direct cleavage of the epoxide ring and the production of two aldehydes. A solution of methyl 12-hydroxy-9,10-epoxystearate (**214**) in *p*-dioxan was added to aqueous periodic acid and stirred for 15 min at room temperature, to give methyl azelaaldehyde hydrate (**215**) (83% yield) and pelargonaldehyde[322,323].



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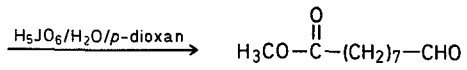

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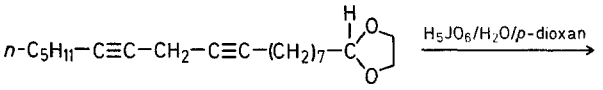
Periodic acid oxidation was used in determination of the epoxidation products resulting from the epoxidation of one of the double bonds of methyl linoleate[324], and in determination of the position of the ethylenic bond in lipids[325]. Pyridine was recommended as the solvent for the periodate oxidation of various vicinally disubstituted lipids. The oxidation occurs in high yield at room temperature. Thus, *cis,cis*-9,12-octadecadiene-1-al has been obtained in 71% yield by oxidation of *cis,cis*-10,13-nonadecadiene-1,2-diol with sodium periodate in dry pyridine[326].

18.2. Hydrolysis of 1,3-Dioxolanes (Ethylene Acetals)

In a total synthesis of linoleic acid[327], quantitative removal of the blocking group (ethylene acetal) was accomplished in aqueous *p*-dioxan solution containing an equivalent amount of periodic acid. This destroyed the ethylene glycol formed, and drove the equilibrium to completion. Thus, the ethylene acetal of octadeca-9,12-diynal (**216**) in *p*-dioxan was mixed with aqueous periodic acid, heated to boiling, cooled, and made neutral with aqueous sodium hydrogen carbonate; extraction with petroleum ether gave aldehyde **217** in quantitative yield. The aldehyde was not isolated, but was oxidized immediately to octadeca-9,12-diynoic acid.



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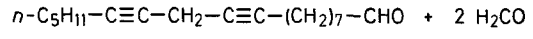
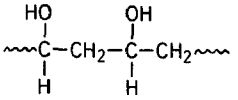


217

19. The Structure of Addition Polymers

The saponification product of a polyvinyl acetate with head-to-tail structure should be a polyvinyl alcohol with 1,3-glycol units (formula **218**), whereas a head-to-head polymer should give a 1,2-glycol product (formula **219**).



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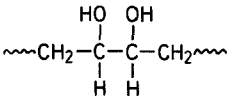

219

[320] G. W. Perold, A. J. Hodgkinson, A. S. Howard, P. E. J. Kruger, *J. C. S. Perkin Trans. I* **1972**, 2457.
P. E. J. Kruger, G. W. Perold, *J. Chem. Soc. (C)* **1970**, 2127.

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Chemical determination of the 1,2-glycol structures should, therefore, enable an estimate to be made of the head-to-head content of the original polymer[328,329,330]. Flory and Leutner[331] have investigated structures in polyvinyl acetate by hydrolyzing the polymer, treating with periodic acid to cleave any 1,2-glycol structures which may be present, reacetylating, and determining the change in molecular weight. Their results indicate 1–2% of head-to-head linkage, the proportion increasing with temperature and comprising 1% of the total links at 25° and 2% at 110°.

In the presence of periodate, graft copolymerization of methyl acrylate on wool has been observed[332], and an atactic polyvinyl alcohol has been cleaved[333]. Ribonucleosides, after treatment with periodate, have been condensed with polyacrylic acid hydrazide to produce polymers containing one base residue per ten acrylic acid hydrazide residues[334].

19.1. Synthesis of Polymers Containing Schiff-Base Rings

New heterocyclic polymeric compounds can be obtained following the reaction of periodate-oxidized starches or other polysaccharides (to give aldehydo derivatives) with *o*- or *p*-phenylenediamine[335,336]. For example, condensation of periodate-oxidized starch with *p*-phenylenediamine[336] gave a 1:1 adduct whose extreme insolubility in various solvents indicated that it was extensively crosslinked. In contrast, *o*-phenylenediamine gives a 1:1 adduct that is soluble in pyridine or hot methanol, and appears to result from condensation of the diamine molecule at individual, oxidized residues to give a non-crosslinked structure. These interesting compounds supplement the known polymers containing *s*-triazine rings[337] or polymers containing other heterocyclic- or metalloorganic rings[338].

20. Bio-Organic Applications of Periodates

Periodate oxidations of ribonucleic acids and their derivatives have been reviewed[15]. This study included periodate oxidation of ribonucleosides and ribomononucleotides, and the influence of periodate oxidation on the stability of the phosphoric ester linkage and of the purine-acid pyrimidine-ribosyl linkages of 5′-nucleotides. The review also covered the periodate oxidation of 5-β-D-ribofuranosyluracil and some of its isomers, oxidation of uridylic acids and of RNase T. A similar review[16] considered the periodate oxidation of polynucleotides and subsequent reduction with sodium borohydride (see the Smith degradation).

20.1. Nucleotide Sequence Analysis

A periodate-oxidation, degradative procedure has been developed to study the sequence of nucleotides in ribonucleic acid (RNA) as a result of contributions from many workers. It involves oxidation of the terminal nucleoside, which contains the vicinal 2′,3′-hydroxyl groups, followed by treatment with an amine. This releases the terminal base (purine or pyrimidine) and also eliminates the phosphate from the oxidized residue, yielding a new terminal 3′-phosphate group. Enzymic removal of this 3′-phosphate monester end-group yields a new terminal nucleoside. As originally proposed[339,340], repetition of the process gives a stepwise degradation procedure for determining nucleotide sequences in RNA. Further contributions[164,341,342,343,344] in the oligoribonucleotide series, in the polyribonucleotide series[345,346,347,349], and other work[80,349,350,351,352,353] permitted practical appli-

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D. M. Brown, M. Fried, A. R. Todd, *J. Chem. Soc.* **1955**, 2206.
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[342] C. T. Yu, P. C. Zamecnik, *Biochim. Biophys. Acta* **45**, (1960).
[343] J. X. Khym, W. E. Cohn, *J. Amer. Chem. Soc.* **82**, 6380 (1960); *J. Biol. Chem.* **236**, PC 9 (1962).
[344] W. E. Cohn, J. X. Khym, *Coll. Inter. Centre Natl. Res. Sci. (Paris)* **106**, 217 (1962).
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[349] H. L. Weith, P. T. Gilham, *J. Amer. Chem. Soc.* **89**, 5473 (1967).
[350] A. Dlugajczyk, F. W. Allen, *Biochim. Biophys. Acta* **51**, 215 (1961).
A. Dlugajczyk, J. J. Eiler, *Nature* **212**, 611 (1966); *J. Biol. Chem.* **244**, 275 (1969).
A. Dlugajczyk, M. T. Malecki, J. J. Eiler, *J. Biol. Chem.* **243**, 2236 (1968).

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cation of the sequence analysis. Nucleosides, or preferably 5'-mononucleotides, serve as good models for studying the sequence analysis. After reaction with periodate in the presence of an amine, nucleosides release the free base, whereas 5'-mononucleotides eliminate inorganic phosphate and release the free base. Although the intermediate dialdehyde, containing the base and the oxidized D-ribose moiety, has been identified, it is an unsuitable derivative for identification purposes. The following reaction conditions were needed to obtain the free base; these conditions were achieved by the quantitative degradative procedure of Neu and Heppel[164], who used a 5 to 10 molar excess of periodate, and conducted the reaction with the amine at 45°. The primary function of the amine (cyclohexylamine, methylamine, lysine, and others) is to precipitate, quantitatively, the parent nucleic acid from its released terminal base and from phosphomonoesterase, for example, in periodate/amine degradation of transfer RNA. By using periodate, it was possible[354] to determine reliably the sequence of nineteen nucleotides in a phenyl-L-alanine transfer RNA. Using periodate degradation, a sequence determination for fourteen dinucleotides from yeast ribonucleic acid was performed[355].

The mechanism of the degradation of nucleic acids by periodate was studied[352,353]. In the degradation of adenosine 5'-phosphate (AMP) with periodate/cyclohexylamine[353], an intermediate was found, in addition to the free base; this confirmed earlier suggestions that, prior to the liberation of the free base, the bond adjacent to the oxygen atom of the oxidized D-ribose is cleaved in such a way that some fragments of the oxidized D-ribose remain temporarily attached both to the phosphate and to the base. An application of DEAE-cellulose chromatography (in addition to paper electrophoresis and paper chromatography) for separation of the elimination products from AMP[353], provides a procedure that can compete with the enzymic, sequence methods[356,357] and other methods[358].

20.2. Related Bio-Organic Applications

In a study of the effect of methylamine on the rate of release of inorganic phosphate by periodate-oxidized adenosine 5'-phosphate, the optimum conditions of dependence upon the pH, solvent, and amine concentration have been found[359]. Although it had lost its acceptor ability, a periodate-oxidized solution of RNA modified by hydroxylamine was still able to interact with the enzyme by inhibition of the transfer of the amino acid (for example, leucine) to tRNA (inhibitor of aminoacyl-RNA-synthetases)[360].

As shown[361], the reactive aldehyde group produced on oxidation of carbohydrate by periodate can couple to a side-chain amino group of proteins by an immunochemical coupling reaction; this was demonstrated when the carbohydrate of an anti-red cell antibody was first oxidized and then allowed to couple to BSA (bovine serum albumin). Treatment of competent cells (cells that are susceptible to genetic transformation by DNA) of *B. subtilis* with sodium periodate markedly decreased the genetic transformation[362]. The primary action of sodium periodate in induction of the lymphocyte transformation appears to be the chemical modification of the lymphocyte membrane[363]. Chromogen formation from *N*-acetylneuraminic acid in aqueous periodate/thiobarbituric acid was investigated[364]. The study showed that the chromogen β-formylpyruvic acid was not a direct product of the periodate oxidation; it was presumed to be formed from the true oxidation product, a hexuronic acid, by aldol splitting during reaction in hot, acidic solution with thiobarbituric acid.

Periodate oxidation of toyocamycin, a pyrimidine ribonucleoside, gave 5-cyano-4-hydroxypyrrolo[2,3-*d*]pyrimidine in good yield[365]. The resistance of collagen and gelatin preparations to attack by periodate is due not to steric hindrance in the protein molecule, but to covalent binding of either the δ-hydroxyl or ε-amino group of the 5-hydroxy-L-lysine[366].

Two anionic phosphonoproteins were isolated on prolonged periodate oxidation of bone collagen[367].

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Atassi[368] studied the periodate oxidation, at pH 5 to 7, of myoglobin and apomyoglobin. In spite of the fact that two methione residues were oxidized by periodate to methionine sulfoxide (in addition to the oxidation of the tryptophyl peptide bonds[369]), the immunochemical efficiency of the protein derivative was equally high (in the antigen/antibody reaction) as that of the original protein. The much lower oxidation rate observed for apomyoglobin, under identical reaction conditions, was ascribed to the catalytic role of the haem iron in myoglobin. Oxidative hydrolysis of pregnanediol D-glucuronide in urine was successfully performed by sodium periodate[370].

Antigenic substances have been formed by the coupling of periodate-oxidized inosine, adenosine, and guanosine to bovine serum albumin; the albumin itself coupled to Sepharose was used as an immunoadsorbent[371]. The formation of sulfenyl iodide and sulfenyl periodide derivatives of bovine serum albumin has been studied[372].

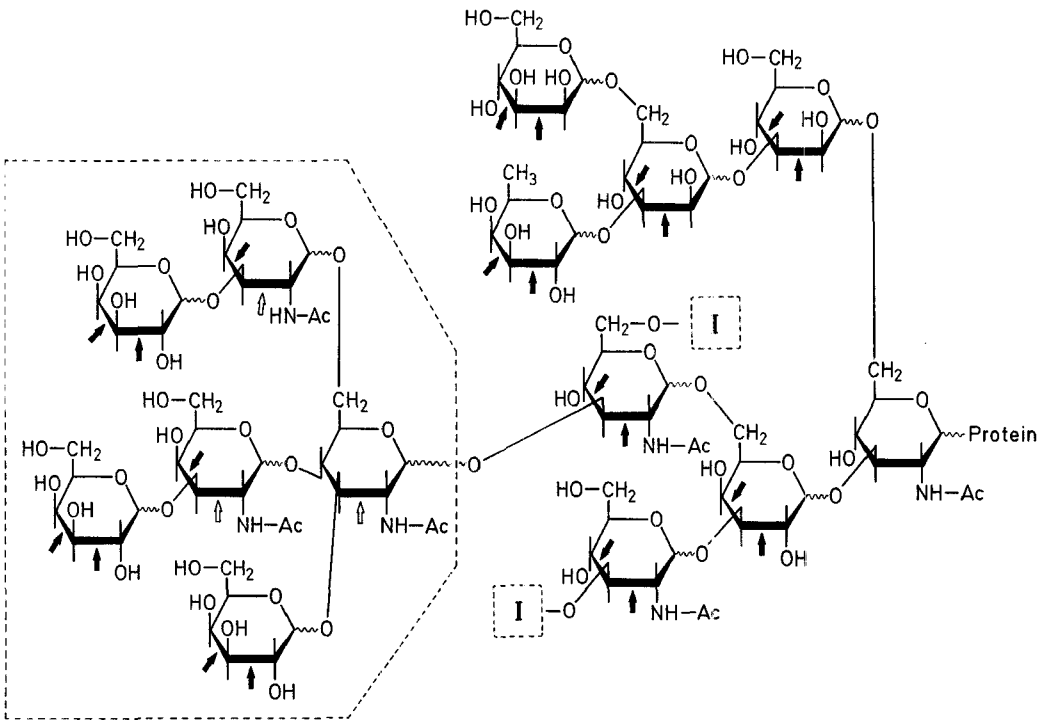
20.3. The Smith Degradation of Glycoproteins

A stepwise degradation of polysaccharide chains that involves a repetitive periodate oxidation, measurement of the reduction of oxidant, and the analysis of the oxidized material, usually after its reduction with sodium borohydride to a polyol and acid hydrolysis, the Smith degradation, is a means of obtaining useful structural information on glycoproteins[6,373,374,375,376].

Application of the procedure to a number of glycoproteins[377,378,379,380,381] has given considerable information about some of the linkages and points of branching of the monosaccharide residues in the carbohydrate prosthetic groups.

Periodate oxidation and the Smith degradation were applied[382] to bovine BSP (bovine bone sialoprotein), a glycoprotein isolated from bovine cortical bone. A tentative structure for the carbohydrate part of the BSP molecule may be suggested as three principal oligosaccharide chains (of possible structure shown in Scheme **H**) in which sialic acids are terminal groups and one chain in which L-fucose may be terminal. These are envisaged as being linked to an inner "core", consisting of three *N*-acetylglucosamine residues, one D-galactose, and one D-mannose, which, in turn, link the prosthetic group to the polypeptide moiety.

The type of bonding proposed for BSP has been suggested for many other glycoproteins, including ovalbumin[383], orosomucoid[384], α-globulins[385], fetin[386], transferrin[387], ovomucoid[388], and others[6,12,388].



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Scheme **H**. Possible structure of carbohydrate prosthetic group, after removal of sialic acid residues, as suggested from the results of Smith degradation. Solid arrows at the bonds indicate sites of rapid oxidation by periodate at the degradation step indicated. Open arrows at the bonds indicate sites of slow oxidation. Ac, acetyl.

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The action of periodate on bovine and ovine interstitial-simulating hormone (a glycoprotein) was studied[389]. The results of this investigation showed that, following treatment with periodate, the biological activity of the hormone is markedly lessened. This was ascribed not only to the observed decomposition of the carbohydrate moieties (L-fucose, D-galactose, and D-mannose, but not the *N*-acetylhexosamine) but also to the destruction of the cystine residues of the hormone. A preparation of a human pituitary hormone was subjected[390] to periodate oxidation, borohydride reduction, and acid hydrolysis (the Smith degradation). Although the preparation lost all of its biological activity, essentially all of the immunological activity of the original hormone was retained. It was concluded that the protein, not the carbohydrate moiety, is associated with the immunological activity.

Similar periodate oxidation studies of human pituitary follicle stimulating hormone (FSH) have been reported[391]. Periodate oxidation followed by borohydride reduction and acid hydrolysis gave propan-1,2-diol but no threitol or erythritol. Determination of the sugar units resistant to oxidation indicated that D-galactose (59%), D-mannose (80%), and 2-acetamido-2-deoxy-glucose (87%) had been oxidized in addition to L-fucose and the *N*-acetylneuraminic acid. Radioimmunological assay of the fragments produced suggested that the carbohydrate was not involved in the immunological activity of the hormone, although essential for manifestation of biological activity.

The Smith degradation has been applied in structural studies of the mucilage of the leaves of "Tabu"[392]. Terminal *N*-acetylneuraminic acid units of ceruloplasmin (a glycoprotein) have been labelled by periodate oxidation, to give a seven-carbon analog of sialic acid, followed by reduction with sodium borotritiide (a general method has been also described for the radiactive labelling of glycoproteins containing terminal sialic acid residues)[393].

An enzymic method for the determination of chain lengths of glycogen and other polysaccharides is based on oxidation with periodate and subsequent determination of the glycerol arising from terminal, non-reducing residues using glycerol kinase[394].

21. Other Periodate Applications

21.1. Organic (General)

Periodate was used in the oxidation of triose reductone[395], citric acid[396], tartaric acid[397], *O*-methylnarciclasine[398], anion-exchange resins[399], mandelic acid[400], leucodrin[401], soluble wood-resin[402], and glyoxal-based resins[403], and also in oxidation of alcohols by diperiodatocuprate(III) ion $[Cu(JO_6)^{7\ominus}]$[404].

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21.2. Carbohydrates (General and Industrial)

The oxidation of methyl glycopyranosides with periodic acid in methyl sulfoxide is unusual, in that only one mole of oxidant is consumed per mole. Most of the stereoselective oxidation observed can be explained on the assumption that *vic-cis*-diols (axial-equatorial) are more reactive than *vic-trans*-diols (di-equatorial or diaxial)[405]. Periodate was used in the oxidation of cellulose[406], lactulose[407], 3-deoxy-D-galactose[408], mukul gum[409], methyl pentofuranosides[410], maltose[411], glucan from endosperm[412], amylose[413], amylopectin[414], D-glucose syrup[415], monosaccharides[416], di- and tri-saccharides[417,418], melibiose[419], and polysaccharides[420], starch and cellulose in aqueous dimethylformamide[421], 6-*O*-tritylcellulose[422], natural gums[423], 1,4-anhydroerythritol[424], galactomannan[425], 3,4,16-triacetylcevine[426], ketohexoses (in the presence of vanadium(V) oxide)[427], cellulose dyed with reactive dyes[428], in the preparation of "dialdehyde starch"[429], and in the oxidation of the sugar moiety in abrin[430]. The oxidant was also applied to study overoxidation ("Non-Malapradian oxidation") of carbohydrates[431,432], cyclohexanepentols[433], and ethers of polyhydroxy compounds[434]; also in the oxidation of methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside[435], perseulose[436], in the preparation of a nitro-D-erythritol derivative from 4,6-*O*-benzylidene-3-deoxy-3-nitro-α-D-glucopyranose[437], and in the oxidation of capsular polysaccharides[438].

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21.3. Bio-Organic

Periodate was applied to deactivate the histamine-sensitizing factor[439], to enhance resistance in a bacterial population[440], to treat bacterial cells[441], to oxidize the protein-5-hydroxy-L-lysine bond[442], to oxidize antibodies[443], to inhibit kinase and DNA polymerase[444], to inhibit anti-tumor activity (from thiopurine)[445], and for induction of an inhibitor of influenza[446].

Periodate was also used to oxidize horseradish peroxidase[447], to oxidize thiopurine[448], polyuronides and mucopolysaccharides[449], glycopeptides (sequential analysis)[450], to oxidize the antibiotic olivin[451], ovotransferrin[452], endotoxin[453], glycopeptide from ovalbumin[454], sensitive antigen[455], allantoic antigen (the Smith degradation[456]), and for demonstration of plasmatogen[457].

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To the action of periodate was also attributed the enhancement of heme agglutination[459], histological fixation of tissue[459], antigenic properties from corticotropic hormone[460], anti-tumor activity from oxidized carbohydrate[461], determination of choline acetyl-transferase[462], a resistance to denaturation of a dialyzable form of antigen[463], and a method for renal tissue (periodic acid-silver methionate treatment)[464].

21.4. Organic (Analytical)

Recent developments in analytical applications of periodates involve many branches of chemistry.

21.4.1. Physical Studies Using Periodates

These include infrared spectra (forbidden transitions)[465], complexes between molybdate ions and periodic acid[466], pulse radiolysis[467], γ-irradiation[468] and action of a solvated electron[469] on a periodate ion, nuclear quadrupole interaction[470], ^{127}J-quadrupole interaction in ammonium trihydrogen periodate[471], stability in acid solution (equilibrium between tetrahedral JO_4^- and octahedral H_5JO_6 species)[472], periodate oxidation of vanadium(IV)[473], removal by ion-exchange resin[474]. Determination has been performed in oxidized mixtures[475] by spot tests[476], by spectrophotometry[477,478], with hexacyanoferrate(II)/ascorbic acid reagent[479], by colorimetric measurement (with benzhydrazide)[480], by ultra-histochemical detection[481], by an automated procedure[482], and by use of periodate as an analytical reagent[483,484].

21.4.2. Periodate as an Analytical and Structural Tool

Determination of glycerides[485], formaldehyde (fluorimetric)[486], formic acid[487], aldehydes[488], aldehydes (potentiometric procedure)[489], dihydroxyacetone (dimer)[490], cortico-steroids in urine[491], periodate-resistant carbohydrate residues[492], tartaric acid (periodate/arsenometric method)[493], polyalcohols[494], sialic acids (periodate/resorcinol method)[495], chondroitin sulfate[497], ephedrine and other pentalkanolamine drugs[497], penicillin (periodimetric)[498], glycerol by the Malaprade method[499,500], invert sugar from sucrose (reductometric)[501], determination of unsaturated linkages in lipids[502], structural analysis[502], and fluorimetric method for the estimation of 1,2-diols (after periodate oxidation)[504].

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21.4.3. Periodates in Microanalysis

Determination of the structure of carbohydrates[505,506,507], periodic acid as a microcolumn (on calcium sulfate) for determination of *vic*-glycols[508] or (on magnesium sulfate) for oxidation of certain double bonds and unsaturated fatty acids[509]. Gas-liquid chromatography of periodate-oxidized polysaccharides[510], glycerol or erythritol glycosides, maltose[511], and glycopeptides[512].

21.4.4. The Periodate/Schiff Reagent

The periodate/Schiff reagent was first applied for histochemical, animal-tissue analysis, and it is known as the McManus-Lillie test[513,514]. The periodate/Schiff spray-reagent was first applied to the detection of carbohydrates and other α-glycols on paper chromatograms[515]; by an improved technique[516], the reagent rapidly became a useful tool in structural analysis.

Recently, the reagent was applied in analysis of oral leukoplakias[517], pig thyroid glands[518], feulgen[519], lipids[520], oligosaccharides (linkage analysis)[521], glycoproteins[522], polysaccharides (aminoglycuronans)[523], chitin[524], blood cells[525], blood in diabetics[526], insect tissues[527], glucose tolerance[528], gastrointestinal tract mucins[529], sulfated polysaccharides of pepsinogenic cells (after treatment with 0.09 *M* periodate up to 24 h)[530], and in fluorescence-optical detection of aldehyde groups[531].

21.4.5. Periodate in Analytical Oxidations

Oxidation of glycogen *in situ*[532], oxidation of phosphite[533], oxidation of polysaccharides of algae[534]. Other applications of periodate: metabolism of calcium periodate[535]; redox photopolymerization of vinyl monomers in the presence of periodates[536]; analytical application of periodates of antipyrine (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one)[537]; 5-aminoisophthalic acid for introduction of carboxyl groups at aldehyde sites[538]; determination of pentosan content (from cotton and pulp cellulose)[539], galactomannan from aspenwood[540], from *Cassia fistula* seed[541], dissolution of cellulose ethers[542], to oxidize alginic acid (tanning properties)[543], to oxidize gums[544], to oxidize wheat-straw xylan[545], to oxidize phenolic glucosides and flavonoids of willow bark[546], to oxidize hydrazine sulfate (reaction mechanism)[547], and for removal of graphite by oxidation with perchloric plus periodic acid[548]. Determination of periodate ions by use of triphenylmethane dye[549], Nile blue[550], manganese(IV) oxide[551] or by ferric oxides or hydroxides as chromatographic sorbents (affinity series)[552].

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22. Miscellaneous Recent Results

Oxidation with periodic acid has been recently surveyed by House[553]; in his comprehensive book the author gives a critical discussion of classical and modern synthetic reactions (e.g. oxidation with chromic acid, potassium permanganate, active manganese dioxide, peracids, sodium periodate, lead(IV) acetate, mercury(II) acetate, selenium dioxide, ruthenium-(VIII) oxide, etc.); the book is an indispensable companion to the Fiesers'[20] classical volumes on synthetic reagents.

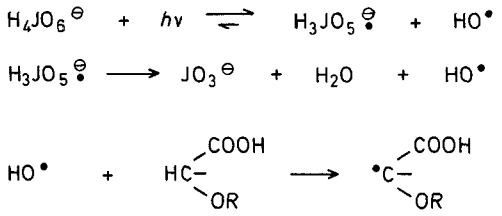
Periodic acid and sodium periodate have been used as specific reagents in preparation of important reaction intermediates needed in total synthesis of cholesterol, cortisone, cephalosporine, and resperine (R. B. Woodward)[554].

Periodate treatment of α-oxo-γ-lactams results in rearrangement, with ring contraction, to give β-lactams in 70% yield[555,556]. Treatment of glycol (2*R*,3*S*)-[4,4,4-$^2H_3$]-3-methyl-1,2-butanediol with sodium periodate gave an isobutyraldehyde intermediate, used in synthesis of a stereospecific β-lactam antibiotic via (2*RS*,3*S*)-[4,4,4-$^2H_3$]valine[557].

In a surprise oxidation of a saturated ketone with periodic acid in 50% aqueous *p*-dioxan, the α,β-unsaturated ketone [1-(2,2-dimethylcyclobutyl)-but-1-en-3-one] was obtained in low yield; this is the first vegetable monocyclic cyclobutane monoterpenoid[558]. A key step in elucidation of the structure of fungal Fusicoccin H (a diterpenoid glycoside) involves sodium periodate oxidation of the allylic α-glycol aglycon to give an α,β-unsaturated dialdehyde[559]. Similar periodate oxidation of a diterpenoid diol (from a tissue culture) yields a structurally important β-diketone[560].

The crystal structure of a new flavin, roseoflavin, a periodate degradation product of a flavin, has been determined[561]. Oxidation of 1-methylpiperidine-2,3-dione with sodium periodate at pH 7 leads to 1-methyl-2-pyrrolidinone-3-carboxylic acid. The reaction is stable to the oxidizing agent at pH 2, which suggests that enolization is required; ^{14}C-labelling experiments are consistent with the cyclopropanone intermediate[562].

Polymer polysaccharides (e.g. polyacetals, polyethylene oxides or polyethers)[563] or proteoglucans[564] rapidly lose viscosity in periodate solution. A mechanism of degradation of these polymers was proposed[563,564] based on a known disproportionation of ether-type free-radicals which is induced by hydroxyl radicals supposedly present in the periodate solution[565,566,567].



Consumption of periodate by carbohydrates has been measured by titrimetric[568] and spectrophotometric[569,570] procedures. Periodate ion absorbs significantly at 222.5 nm[569], 260 nm[570], or 290 nm[571], these wavelengths being chosen to lessen interference from the iodate ion[563,572]. Recent application of periodate oxidation of complex carbohydrates involves the 2-acetamido-2-deoxy-β-D-glucopyranosyl residue[573], carbohydrate in ovalbumin (e.g. the Smith degradation of L-β-aspartamido-carbohydrate fragments[574,575]) and degradation of capsular polysaccharide (of pneumococcal type)[576]. A dinucleotide sulfide has been converted by sodium periodate into the sulfoxide, an intermediate for synthesis of an oligonucleotide[577]; similar oxidation of ethylene episulfide gave the episulfoxide in good yield[578]. A new

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route to α,β-unsaturated carbonyl compounds (aldehydes, ketones, or esters) involves oxidation of α-phenylselenocarbonyl compounds with sodium periodate; elimination of the selenoxide intermediate gave the desired olefin in 46 to 54% yield[579]. Similarly, propiophenone selenide was converted into sensitive acrylophenone in 89% yield[580]. A new method for dehydrogenation of ketones via a selenoxide intermediate involves a periodate oxidation[581]. Quantitative determination of vanillylmandelic acid (DL-4-hydroxy-3-methoxymandelic acid) involves a periodate oxidation[582]. Mercury(II) iodate [$Hg(JO_3)_2$)] reacts with acid anhydrides to give esters [e.g. ethyl propanoate (97% yield) from propanoic anhydride, heptyl octanoate (46% yield) from octanoic anhydride][583].

The lactone structure of the sequiterpene *Carolenin* has been partially deduced from sodium periodate oxidation (to give a keto-aldehyde)[584]. Periodate oxidation of the fungal diterpene antibiotics LL-S491 β and γ revealed the lactol structure[585]. Periodate oxidation of antibiotics *Axenomycin A*, *B*, and *C* confirmed the presence in all of them of a saturated polyhydroxylated chain containing sixteen hydroxyl groups[586]. The structure proof of the antibiotic leucogenol (a metabolic product from *Penicillium gilmanii*) involves periodate degradation of a hydroxycarboxylic acid (1,2-dihydroxy-3-methyl-5-oxocyclohexanecarboxylic acid)[587]. *epi*-Quinide acid series (γ-lactone of 3,4/1,5-tetrahydroxycyclohexanecarboxylic acid) and its isomer *scyllo*-quinide failed to undergo periodate oxidation due to *trans-diaxial* configuration of their two *vic*-hydroxy groups[588] (that prevent a necessary cyclic transition state, a five-member periodate ring from forming)[572]. As expected for the Adler oxidation, treatment of the monomethyl ether of dihydroxynaphthalene derivatives with sodium periodate yields *o*-quinones[589].

Synthetic applications of osmium- or ruthenium-(VIII) oxide oxidation (with sodium periodate as co-oxidant) have been reviewed[590]. Iodate concentration can be determined polarographically[591]. The structure of antibiotic x-5108 has been determined by periodate degradation (the isolated products are goldinono-1,4-lactone 3,7-hemiacetal and goldinamine 4-bromobenzyl ether)[592].

The author is indebted to Dr. R. Stuart Tipson for reading the manuscript.

Received: October 16, 1972

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