Chem. Rev. 1980, 80, 187-213

Osmium Tetraoxide Cis Hydroxylation of Unsaturated Substrates

MARTIN SCHRÖDER

Department of Chemistry, Imperial College of Science and Technology, London, England

Received November 16, 1979

Contents

I. Introduction

Osmium tetraoxide (OsO_4) is the most reliable reagent available for the cis hydroxylation of alkenes to give the corresponding *cis*-diols[1] and is also widely used in electron microscopy as a staining and fixative agent for biological tissues.[2] These two properties are linked since general staining of biological membranes with osmium tetraoxide is thought to proceed via attack of unsaturated entities present in the tissues.[3-5]

The reduction of osmium tetraoxide by unsaturated species has long been known,[6] and it was Hofmann[7,8] who first showed that osmium tetraoxide could be used catalytically in the presence of sodium or potassium chlorate for the hydroxylation of alkenes. This work was later extended by Milas[9,10] who reported the osmium tetraoxide catalyzed oxidation of alkenes by hydrogen peroxide. Other secondary oxidizing agents that have been used in conjunction with osmium tetraoxide for the catalytic oxidation of alkenes include *tert*-butyl hydroperoxide, *N*-methylmorpholine *N*-oxide, oxygen, sodium periodate, and sodium hypochlorite (see section III).

Criegee,[11,12] however, showed that osmium tetraoxide could also be used as an effective cis-hydroxylating agent when used stoichiometrically in the absence of secondary oxidants. He suggested that the reaction occurs via the formation of an intermediate osmium(VI) ester complex which could be hydrolyzed reductively to give insoluble osmium salts or oxidatively to regenerate osmium tetraoxide, in both cases the corresponding vicinal *cis*-diol being formed selectively in good yield. Addition of pyridine to hydroxylation reactions led to a marked increase in the rate of formation of intermediate ester complexes. Although the oxo(amine)osmium(VI) complexes thus formed tend to be more difficult to hydrolyze than the corresponding non-amine products, the stoichiometric use of osmium tetraoxide with pyridine followed by reductive cleavage with bisulfite, alkaline mannitol, hydrogen sulfide, or lithium aluminum hydride remains the most effective method of cis-hydroxylating alkenes. Reactions with imines and nitriles are not generally observed under normal conditions, while the oxidation of alcohols by osmium tetraoxide is appreciably slower than that of alkenes.

Martin Schröder was born in 1954 He carried out his undergraduate studies at Sheffield, England, and obtained his Ph.D. at Imperial College, London. Having completed one-year's postdoctoral research at the E.T.H., Zürich, he is now a research assistant at the University of Cambridge, Cambridge, England.

A few, short review articles concerned with certain aspects of osmium tetraoxide oxidation reactions have been published;[13-17] the present review deals primarily with its use as a catalytic and noncatalytic cis-hydroxylating reagent for unsaturated substrates, namely, alkenes, dienes, and alkynes, with particular reference to the more recent work on the formation, structure, and hydrolysis of the intermediate osmium(VI) ester complexes. The literature coverage extends to mid-1979.

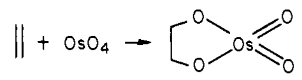
II. Noncatalytic Cis Hydroxylation of Alkenes

A. Oxoosmium(VI) Ester Complexes

1. Formation and Structure

a. In the Absence of Tertiary Amines

The cis hydroxylation of alkenes by osmium tetraoxide is well established to take place via the formation of an osmium(VI) intermediate which on reductive or oxidative hydrolysis yields the corresponding *cis*-diol. The intermediate osmium(VI) complex is usually written as a tetrahedral species (**1**).[1,18,19]



1

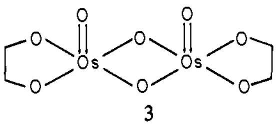
Structure **1**, however, although it may exist as a transient species in solution, would be unlikely to exist in the solid state since this would be an example of a tetrahedral d^2 complex; no examples of tetrahedral d^2 stereochemistry exist for third-row transition metals. In addition, the O(ester)-Os-O(ester) angle for complex **1** would be expected to be highly strained in a tetrahedral configuration. Criegee[11,20-22] has reported the reaction of osmium tetraoxide with alkenes (R) in nonreducing solvents such as diethyl ether or benzene to yield dark green to black products of stoichiometry $OsO_4 \cdot R$ and $OsO_5 \cdot R_2$; structures for these complexes were tentatively proposed on the basis of osmium analyses and hydrolysis of the complexes with sodium sulfite to give the corresponding *cis*-diols and the osmium sulfite complex $Na_4[Os(SO_3)_3] \cdot 6H_2O$ (**2**).[11] The nature of these osmium(VI) intermediates has been recently reinvestigated, and they have been formulated as dimeric monoester complexes *syn*-[23] and *anti*-$[Os_2O_4(O_4R)_2]$[24] (**3** and **4**) and monomeric diester complexes $[OsO(O_2R)_2]$ (**5**),[24] respectively. These diamagnetic products have been shown by X-ray crystallographic studies, in the cases of *anti*-$[Os_2O_4(O_2C_2Me_4)_2]$[25,26] and $[OsO(O_2C_2H_4)_2]$,[27,28] to contain five-coordinate square-based pyramidal osmium(VI) with cyclic ester rings.

The infrared spectra of these complexes show bands near 980 cm^{-1} assigned to the Os=O (terminal) stretching vibration,

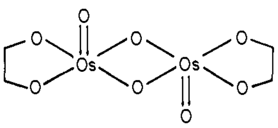
---

* Address correspondence to Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, England.

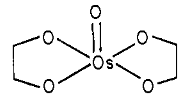
0009-2665/80/0780-0187$05.00/0



3



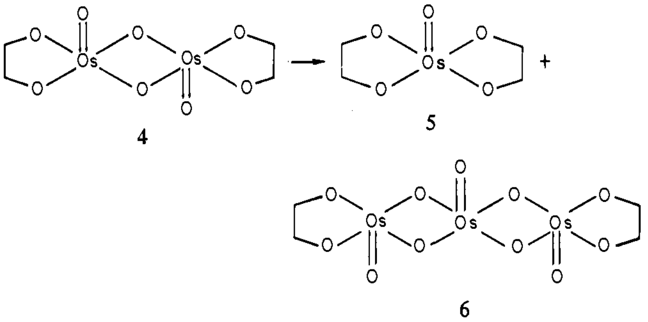
4



5

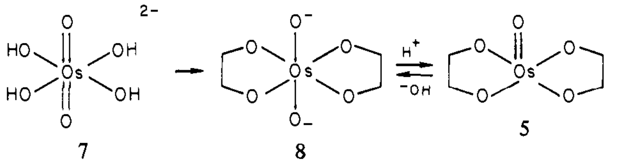
ν(Os=O).[24] Bands assigned to the Os–O (ester) stretching vibration, ν(Os–O), occur near 580 cm^{-1}, while bands near 630 cm^{-1} for the dimeric monoester complexes are assigned to the stretching vibration, $\nu(Os_2O_2)$, of the oxygen bridge system.[24] These latter bridge bands are not observed for the monomeric diester complexes.[24]

The formation of dimeric monoester complexes is generally preferred for reactive alkenes such as cyclohexene, ethylene, and oleic acid, while for less reactive alkenes (i.e., tetrasubstituted alkenes or those incorporating sterically large or electron-withdrawing groups) diester complexes are formed. This may be partially explained by considering the intermediate tetrahedral species **1**. If this species is formed in low concentrations as in the case of less reactive alkenes, the formation of dimeric monoester complexes will be discouraged and the formation of diester complexes preferred. The conversion of monoester to diester products can be achieved by reaction with ethanolic hydrochloric acid or with aqueous alcoholic potassium hydroxide.[11] It seems likely that this reaction occurs via hydrolysis of the monoester to the *cis*-diol followed by subsequent reaction of the diol with another molecule of monoester to yield the corresponding diester species; the reaction of monoesters with *cis*-diols to give diester complexes has been reported.[11,23] It has been noted that the conversion of monoester to diester products occurs also when the former is left to stand in solution, the diester being isolated together with a black, highly insoluble product tentatively formulated as a trimer of stoichiometry $Os_3O_{11}R_2$ (**6**).[29]



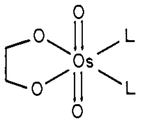
6

An alternative method of preparing osmium(VI) monoester and diester complexes is by reaction of anionic osmium(VI) species such as potassium osmate, *trans*-$K_2[OsO_2(OH)_4]$ (**7**), with *cis*-diols. The resulting osmium(VI) ester salts (**8**) are converted to the neutral complex by acid treatment.[11]



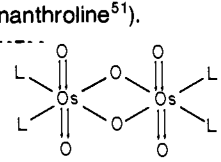
b. In the Presence of Tertiary Amines

It was noted by Criegee[12] that the rate of formation of osmium(VI) ester complexes could be dramatically increased by the addition of an excess of tertiary amine, such as pyridine, to solutions of osmium tetraoxide and alkenes. Brown diamagnetic products were isolated, and these have been recently characterized as diolatodioxobis(amine)osmium(VI) ester complexes, $[OsO_2(O_2R)L_2]$ (**9**) (R = alkene, L = pyridine,[12,21,24,30-38] isoquinoline,[24] quinoline,[12] $^1/_2$bipyridyl,[31-34,37] 3-picoline,[34-36] 4-picoline,[34] (3-pyridyl)mercuric acetate,[35,36] and 3-chloropyridine[34-36]).



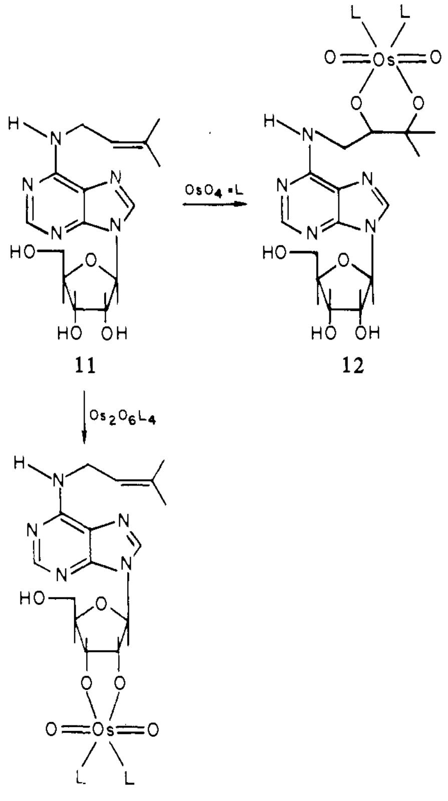
9

The infrared spectra of the complexes **9** show bands near 840 cm^{-1} assigned to the asymmetric stretching vibration, $\nu^{as}(OsO_2)$, of the trans O=Os=O moiety.[24,30] Raman bands near 880 cm^{-1}, polarized in solution, are assigned to the symmetric stretching mode, $\nu^{s}(OsO_2)$.[24,30] X-ray structural analyses have been reported for the bis(pyridine) ester complexes of thymine,[39] 1-methylthymine,[40] 9-methylbenzanthracene,[41] and adenosine,[42] the thymine and adenosine complexes being models for the binding of osmium tetraoxide to nucleic acid components in biological tissues. The reaction of osmium tetraoxide with nucleic acid components such as thymine,[35,36,43] thymidine,[31-33,35,36] ribothymidine,[32,33] disodium thymidine 5-phosphate,[35,36] uridine,[32,33,44] cytidine,[32,33,44] adenosine,[32,33] guanosine,[32,33] and uracil[35,36,44] in the presence of tertiary amines has been observed to give bis(amine)osmium(VI) complexes analogous to **9**. It is of importance to note that exclusive attack of C=C bonds occurred in these reactions, with C=N and C=O functions being unreactive. Similarly, oxidation of RNA by osmium tetraoxide has been shown to occur via attack of C(5) and C(6) of pyrimidinones to give 5,6-dihydro-5,6-diol species,[45] while oxidation of 1-methyluracil yields 5,6-dihydro-4,5,6-trihydroxy-1-methyl-2(1*H*)-pyrimidinone.[44] The preparation of anionic osmium(VI) ester complexes from 3,5-diacetylthymidine, cyclohexene, and 3-butenoic acid has been reported with CN$^-$ and SCN$^-$ ligands.[46] Similar products have been observed for the reaction of osmium tetraoxide with DNA.[46] The osmium(VI) ester complexes **9** can also be prepared by reaction of the monoester or diester complexes **3**, **4**, or **5** with an excess of tertiary amine.[11,12,21] Alternatively, osmium tetraoxide can be reduced with ethanol[47] in the presence of excess of tertiary amine (L) to give the dimeric (amine)osmium(VI) complexes $[Os_2O_6L_4]$ (**10**) (L = pyridine,[30,48] 3-picoline,[48] 3-chloropyridine,[48] $^1/_2$bipyridyl,[49] imidazole,[50] $^1/_2$*N*,*N*,*N'*,*N'*-tetramethylethylenediamine,[51] or $^1/_2$phenanthroline[51]).



10

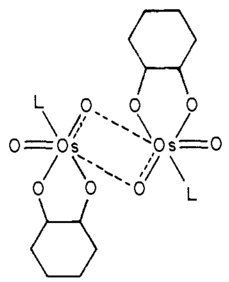
These products contain the trans dioxo "osmyl" moiety and a symmetric Os_2O_2 bridging system similar to that found for the dimeric monoester complexes **3** and **4**[25] and for $K_4[Os_2O_6(NO_2)_4]$.[52,53] The complexes **10**, like potassium osmate (**7**), although unreactive toward alkenes,[54] readily react with *cis*-diols, $R(OH)_2$, to give the corresponding bis(amine) ester complexes $[OsO_2(O_2R)L_2]$ (**9**).[12,48] Whereas osmium tetraoxide reacts readily with alkenes but relatively slowly with *cis*-diols (reaction with an excess of ethane-1,2-diol yields the diester $[OsO(O_2C_2H_4)_2]$ (**5**) after about 10 days[28]), the reverse is true for osmium(VI) complexes **7** and **10** which cannot be used directly as cis-hydroxylating agents, although they may be used as a source of osmium tetraoxide when treated with hydrogen peroxide or potassium chlorate.[54] The relative reactivities of osmium(VIII) vs. osmium(VI) have been illustrated by reactions with isopentenyladenine and -adenosine (**11**).[31] Similar reactivity



comparisons have been made involving uridine analogues.[32,33]

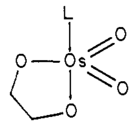
Osmium tetraoxide itself reacts with polydentate and monodentate tertiary amines in nonreducing conditions to give the adducts $OsO_4\cdot L$ (L = pyridine,[12,55] isoquinoline,[56,57] phthalazine,[56,57] quinuclidine,[56,57] pyridazine,[56,57] or ammonia[58,59]) and $(OsO_4)_2\cdot L$ (L = pyrazine,[56,57] hexamethylenetetramine,[56,57,60,61] triethylenediamine,[56,57] and 5-methylpyrimidine[56,57]). These adducts retain the integrity of the Os(VIII)O_4 entity and in the case of the hexamethylenetetramine complex can be used as a stabilized, nonvolatile form of osmium tetraoxide,[61-63] the high volatility and toxicity of osmium tetraoxide being considered a great hazard.[64] X-ray structural analyses have been reported on the adducts derived from quinuclidine and hexamethylenetetramine.[65] Picoline and quinoline have also been used as tertiary amine bases for osmium tetraoxide, but no complexes were fully characterized.[60]

The adducts $OsO_4\cdot L$ (L = pyridine, isoquinoline, or quinuclidine) react with alkenes (R) to give products of stoichiometry $OsO_4\cdot R\cdot L$.[56,57] An X-ray structural analysis[66] on the complex **14**, derived from cyclohexene and quinuclidine, shows it to be a dimeric osmium(VI) ester complex, involving an asymmetric Os_2O_2 bridge system with the O=Os···O (bridge) angle deviating appreciably from linearity. The infrared and Raman spectra of these complexes in the solid state show bands near 890 cm^{-1} assigned to the Os=O stretching vibration, ν(Os=O);[67] these are at higher frequencies than the Os=O stretching vibration found for the bis(amine) complexes **9**. Products analogous to **14** have been isolated from the reaction of osmium tetraoxide with brucine and strychnine.[67] These complexes are thought to be models for the types of compounds formed when osmium tetraoxide interacts with alkaloids containing tertiary amine functions during fixation procedures for electron microscopy studies.[67]



14

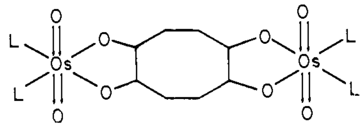
In solution, the complexes **14** dissociate to give monomeric five-coordinate species formulated as dioxo trigonal-bipyramidal complexes **15**, with the oxo ligands occupying equatorial positions.



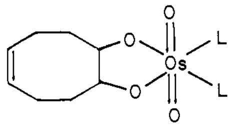
15

The infrared and Raman spectra of the monomeric species **15** in solution each show two bands at 870 and 910 cm^{-1} assigned to the asymmetric and symmetric O=Os=O stretching vibrations $\nu^{as}(OsO_2)$ and $\nu^{s}(OsO_2)$, respectively.[67] Addition of 1 equiv of tertiary amine L′ to the complexes **15** yields the corresponding bis(amine) products $[OsO_2(O_2R)LL']$ (**9**).[67]

The cis hydroxylation of dienes using osmium tetraoxide has been shown to give either unsaturated *cis*-diols[68-70] or tetrols,[10,68,71] depending upon the relative stoichiometries of osmium tetraoxide/diene used. Thus reaction of dienes R with a twofold excess of osmium tetraoxide in diethyl ether in the presence of excess tertiary amine L (L = pyridine or isoquinoline) yields brown diamagnetic osmium(VI) ester complexes $[Os_2O_4(O_4R)L_4]$ **16**, with both double bonds of the starting diene having reacted.[12,72,73] Alternatively, reaction of osmium tetraoxide with a fivefold excess of diene R in the presence of excess tertiary amine L (L = pyridine or isoquinoline) leads to the formation of the complexes $[OsO_2(O_2R)L_2]$ **17**, with only one of the double bonds of the starting diene having reacted.[72,73]



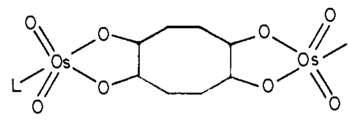
16, R = cycloocta-1,5-diene



17, R = cycloocta-1,5-diene

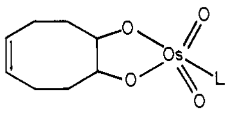
The ^{1}H NMR spectra[72] of the complexes **16** show protons adjacent to the ester oxygen atoms near δ 4.7, while for the complexes **17**,[72] alkene protons are observed near δ 5.6 in addition to protons adjacent to the ester oxygen atoms again near δ 4.7. The infrared and Raman spectra[72] of the complexes **16** and **17** show bands characteristic of the *trans*-dioxo "osmyl" moiety. An X-ray structural analysis confirms the anti configuration of the ester rings for the complex **16** derived from cycloocta-1,5-diene and pyridine.[74]

Reaction of the adduct $OsO_4\cdot L$ (L = quinuclidine) in diethyl ether with dienes R in a 2:1 molar ratio leads to the formation, in solution, of the analogous five-coordinate ester complexes $[Os_2O_4(O_4R)L_2]$ (**18**) with equatorial oxo ligands.[67] Similarly,



18, R = cycloocta-1,5-diene

reaction of the adduct $OsO_4{\cdot}L$ (L = quinuclidine) with an excess of diene R leads to the formation, in solution, of the ester complexes $[OsO_2(O_2R)L]$ (**19**), with only one of the double bonds having reacted.[67]



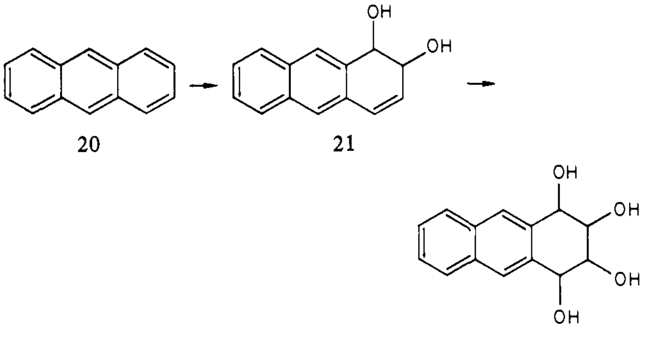
19, R = cycloocta-1,5-diene

The complexes **18** and **19** are thought to be polymeric and dimeric in the solid state, respectively.[67]

2. Hydrolysis of Ester Complexes

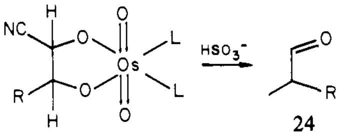
Osmium(VI) ester complexes can be hydrolyzed either reductively or oxidatively. Reductive hydrolysis is generally carried out by using sodium or potassium sulfite or bisulfite,[11,12] lithium aluminum hydride,[75,76] or hydrogen sulfide[77] to yield the corresponding *cis*-diols together with lower forms of osmium which are removed by filtration. Hydrolysis using catechol[23] or alkaline mannitol[11,12] displaces the diol function of the ester complex to yield catechol- or mannitol-based ester products. The reaction of osmium(VI) complexes or osmium tetraoxide with catechols (*o*-hydroxyphenols) has been reported to yield either tris(catechol)osmium(VI) complexes or polymeric osmium(IV) species.[78-80] The reduction and possible hydrolysis of osmium ester complexes by ethylenediaminetetraacetic acid have been recently reported.[81] Tables I and II give data on the noncatalytic cis hydroxylation of alkenes by osmium tetraoxide in the absence and presence of pyridine, respectively.

As well as oxidizing alkenes to the corresponding *cis*-diols,[128-130] osmium tetraoxide also reacts with aromatic hydrocarbons, with attack occurring at the sites of greatest electron density.[95] Thus anthracene (**20**) is oxidized at the 1,2 positions (**21**) and then at the 3,4 positions (**22**), the meso positions remaining unreactive.[95]



20 21 22

The preparation of dioxyporphyrin species has also been reported from the oxidation of porphyrins by osmium tetraoxide.[131] It is of interest to note that oxidations of α,β-unsaturated nitriles by osmium tetraoxide do not yield *cis*-diols, but the corresponding hydroxy aldehydes or ketones[119-121] via elimination of cyanide ion, **23** → **24**.

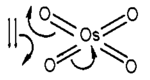


23 24

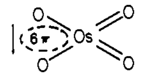
Oxidative hydrolysis of osmium(VI) ester complexes is generally carried out by using metal chlorates, *N*-methylmorpholine *N*-oxide, hydrogen peroxide, or *tert*-butyl hydroperoxide. The *cis*-diol is formed together with osmium tetraoxide which can react further with alkene, thus rendering the process catalytic. The catalytic cis hydroxylation of alkenes is discussed in section III.

B. Mechanism of Cis Hydroxylation

The oxidation of alkenes by osmium tetraoxide and other oxo metal complexes such as chromyl chloride, potassium permanganate, and selenium dioxide has been thought, in general, to proceed via direct oxygen attack at the unsaturated center (**25**). The six-electron transition state (**26**) thus formed will lead

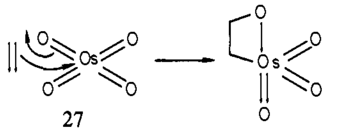


25



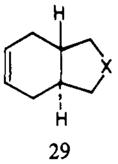
26

to the cis addition of osmium tetraoxide to the alkene, as is observed in practice. Cyclic transition states such as **26** have been proposed as intermediates in the one-step cis addition of osmium tetraoxide to double bonds.[132-134] More recently, however, Sharpless and co-workers[135] have suggested the possibility of indirect attack of alkenes by osmium tetraoxide. Their proposal is based on the observation that nucleophilic attack of the carbonyl (C=O) function occurs exclusively at the carbon center and not at oxygen. Similarly, a C=C bond, although only a weak nucleophile, would be expected to attack not at oxygen but at the more electropositive osmium center of the Os=O bond, thus forming initially an organometallic intermediate (**28**).



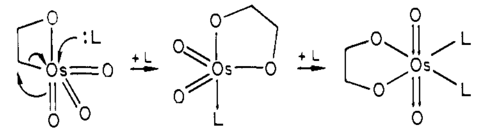
27 28

An intermediate involving Os–C bonding has been previously proposed by Zelikoff and Taylor.[136] Their proposals were based on the differing reactivity of osmium tetraoxide toward alkenes as compared with permanganate ion. The intermediate **28** would be considered to rearrange in a rate-determining step to a five-membered cyclic ester complex, with subsequent hydrolysis occurring relatively quickly.[136] It has been observed that electron-withdrawing groups on the alkene retard its reactivity toward osmium tetraoxide,[91,96,137] presumably due to the lowering of nucleophilicity of the C=C bond. Thus the relative rates of reaction of **29** with osmium tetraoxide decrease from 1 to 0.35 to 0.28 when X = CH_2, O, and $C(OCH_3)_2$, respectively.[91] An opposite effect is noted for permanganate oxidations.[91] Similarly, aromatic hydrocarbons are oxidized by osmium tetraoxide at the sites of greatest electron density.[95] Although no direct experimental evidence is available for the existence of an organometallic intermediate such as **28**, the hypothesis is reasonable on the basis that the Os=O bond would be expected to react with a nucleophile initially at the metal center and not at oxygen. The reaction of osmium tetraoxide with certain primary amines leads to the formation of alkylimidoosmium(VIII) complexes,[139-143] paralleling the reaction of organic carbonyls with primary amines. In addition, the intermediate **28** may be useful in explaining the dramatic increase in the rate of formation of osmium(VI) ester complexes on addition of tertiary amines such as pyridine.[12] Electron donation from the tertiary amine to the osmium atom may induce osmium–carbon bond cleavage



29

with a corresponding rate increase in the rate-determining step leading to the formation of complexes $[OsO_2(OR)L]$ (**15**) and finally $[OsO_2(O_2R)L_2]$ (**9**).[135]



28 15 9

A kinetic study on the oxidation of mandelic acid by osmium tetraoxide has been reported.[144] It was found that the disappearance of osmium tetraoxide is proportional to the concentration of mandelate ion and proportional to the concentration of osmium(VIII). At low and high hydroxyl concentrations the rate showed second-order and zero-order dependence on hydroxyl concentration, respectively. The authors disregarded a radical process for the oxidation of alkenes by osmium tetraoxide on the basis that the oxidation involves a two-electron process, no induction period was noted, and the rate of reaction was unaffected by the addition of acrylonitrile. The relative reactivities of cyclopentene to cyclohexene and norbornene to cyclohexene with osmium tetraoxide have been reported to be 21.9 and 72.3, respectively,[145] and a five-membered transition state was thought to be in agreement with these data. Beer and co-workers[146] have shown that osmium tetraoxide reacts with the thymine base of denatured DNA but not with natural DNA. It was noted that the rate of reaction decreased in the order thymidine > thymine > uracil > adenosine > guanosine. Similar rate effects have been found by Burton and Riley[147] for the reaction of osmium tetraoxide with a series of nucleotides in the presence of ammonia, the relative rates of reaction of thymidine:5-methyldeoxycytidine:uridine:deoxyuridine:cytidine:deoxycytidine being 43:13:4.5:2.8:1.8:1, respectively.

The important observation initially made by Criegee[11,12] that the rate of formation of osmium(VI) ester complexes is greatly increased in the presence of tertiary amines has led to several kinetic studies on the role of amines in this system. The rate of reaction of osmium tetraoxide with thymine in the presence of pyridine has been found[35,36] to be several orders of magnitude greater than the rate observed by Beer[146] with osmium tetraoxide alone. The oxidation of alkenes in the presence of amines (L) has been shown to have a second-order dependence on the amine concentration (L = ammonia,[44] pyridine[35,36,146]). Deviation from this second-order dependence occurs at high pyridine concentrations.[148] Behrman and co-workers[34-36] have reported kinetic studies on the formation of osmium(VI) ester complexes in water and organic solvents; eq 1–5 were proposed for the reaction of osmium tetraoxide with substrate (S) in the presence of pyridine (py).[35,36]

$$OsO_4 + py \rightleftharpoons OsO_4{\cdot}py \qquad (1)$$

$$OsO_4{\cdot}py + py \rightleftharpoons OsO_4{\cdot}py_2 \qquad (2)$$

$$OsO_4{\cdot}py + S \rightleftharpoons OsO_4{\cdot}py{\cdot}S \qquad (3)$$

$$OsO_4{\cdot}py{\cdot}S \rightarrow OsO_4{\cdot}py_2{\cdot}S \qquad (4)$$

$$OsO_4 + py_2 + S \rightarrow OsO_4{\cdot}py_2{\cdot}S \qquad (5)$$

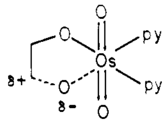
The kinetic data led to the rate law[34-36] shown in eq 6. This

$$\text{rate} = k_0[OsO_4][S] + k_1\beta_1[OsO_4][S][L] + k_2\beta_2[OsO_4][S][L]^2 \qquad (6)$$

rate law, however, considered only the concentrations of the reactants and was therefore later modified to take activity factors into consideration[148] (eq 7). The new rate law (eq 7) replaces

$$\text{rate} = k_0[OsO_4][S] + k_2'[OsO_4][S]a^2(\text{py}) \qquad (7)$$

the second-order dependence on pyridine with a term for an activated complex (**30**) containing two pyridine ligands.



30

possible pathways leading to the formation of the activated species **30** are shown in eq 8–10.[148] However, it has been

$$OsO_4 + S \rightleftharpoons OsO_4{\cdot}S \rightarrow 30 \qquad (8)$$

$$OsO_4{\cdot}py \rightleftharpoons OsO_4{\cdot}S{\cdot}py \rightarrow 30 \qquad (9)$$

$$OsO_4{\cdot}2py + S \rightarrow 30 \qquad (10)$$

noted in these studies and in other cases that osmium tetraoxide generally reacts more readily with tertiary amines than with alkenes, suggesting that the formation of an osmium(VIII) adduct, $OsO_4{\cdot}L$, would be the preferred first product. In addition, no clear experimental evidence has been put forward for adducts of the type $OsO_4{\cdot}py_2$. Raman studies on solutions of osmium tetraoxide in pyridine only show bands for OsO_4, $OsO_4{\cdot}py$, and pyridine,[30] although the tetraoxide has been reported to take up 2 equiv of water[149] or pyridine.[11,12] A pathway involving initial formation of the adduct $OsO_4{\cdot}py$ followed by reaction with alkene and addition of a second pyridine moiety seems therefore the likeliest route to the formation of osmium(VI) ester complexes (**9**). This would be in agreement with Burton's[44] data on osmium tetraoxide oxidations of alkenes in the presence of ammonia. It is important to note that ammonium hydroxide solution deactivates osmium tetraoxide;[150] this is due to the formation of the osmiamate ion, $[OsO_3N]^-$ (**31**),[64] which has been shown to be inactive as a cis-hydroxylating agent.[57,151] Behrman and Clarke have recently reported[152] that sodium phosphate produces moderate rate increases for the cis hydroxylation of alkenes by osmium tetraoxide. This is thought to be an effect due to ionic strength rather than due to the formation of a complex.[152]

The hydrolysis of osmium(VI) ester complexes has been shown to occur with exclusive Os–O(ester) bond cleavage; hydrolysis in $H_2{}^{18}O$ showed no ^{18}O incorporation into the diol.[34] Hydrolysis is also found to be catalyzed by acidic or alkaline media. At high pH (10 M KOH), osmium(VI) ester complexes are hydrolyzed to give potassium osmate, while at lower pH's and in acidic conditions, the disproportionation to osmium(VII) and osmium(V) occurs,[34] with the corresponding formation of osmium(VIII) and osmium(IV) species. The hydrolysis eq 11–14 are shown below.[34,153-155]

$$6Os(VI) \rightarrow 3Os(VII) + 3Os(V) \qquad (11)$$

$$3Os(VII) \rightarrow 2Os(VIII) + Os(V) \qquad (12)$$

$$4Os(V) + 2Os(VIII) + 6H_2O \rightarrow 6Os(IV) + 12H^+ + 3O_2 \qquad (13)$$

$$4Os(V) + 2H_2O \rightarrow 4Os(IV) + 4H^+ + O_2 \qquad (14)$$

The disproportionation of osmium(VI) is analogous to the disproportionation of ruthenium(VI) under acid conditions.[156] At pH 9.5 (carbonate buffer) the hydrolysis of osmium(VI) ester complexes occurs less readily under a nitrogen atmosphere as compared with hydrolyses carried out under air.[34] This suggests that the presence of oxygen may assist the hydrolysis process; the catalytic oxidation of alkenes by osmium tetraoxide in the presence of oxygen is discussed in section III.F.

In general, the hydrolysis of osmium(VI) ester complexes is carried out reductively with lithium aluminum hydride, potassium sulfite, or hydrogen sulfide (see Tables I and II) to give reduced forms of osmium which can be removed by filtration. Ester complexes **3**, **4**, and **5** and amine ester complexes **9** and **14–19** can all be successfully hydrolyzed by using these methods, the

TABLE I. Noncatalytic Cis Hydroxylation of Alkenes in the Absence of Pyridine

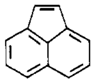
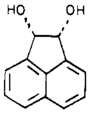
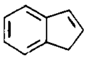
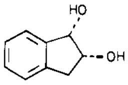
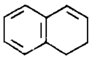
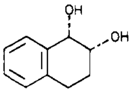
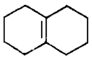
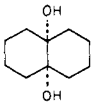
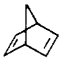
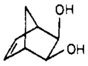
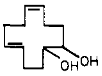
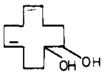
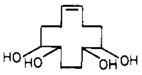
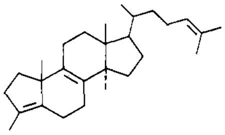
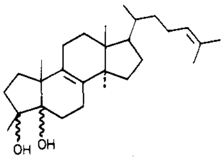
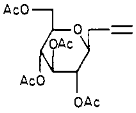
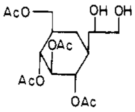
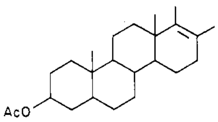
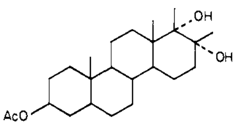
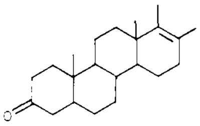
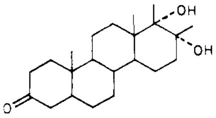
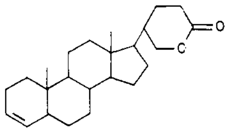
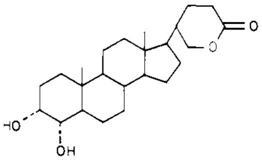
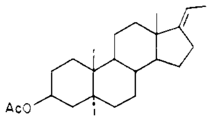
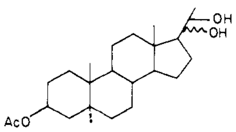
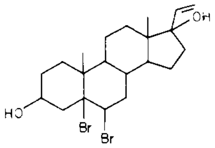
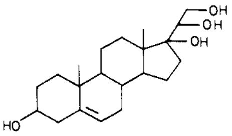
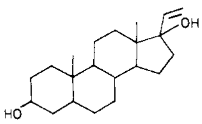
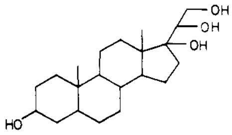
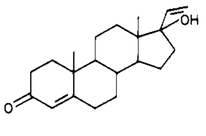
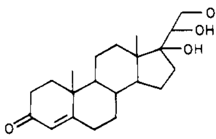
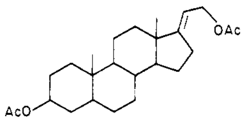
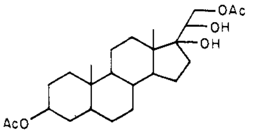
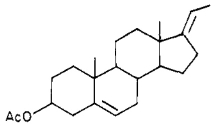
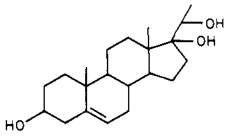
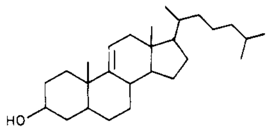
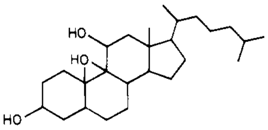
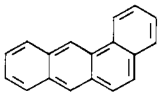
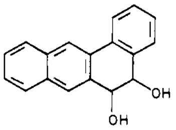
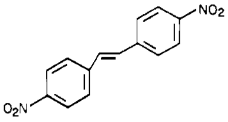
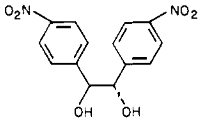
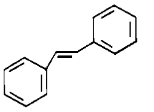
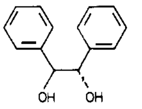
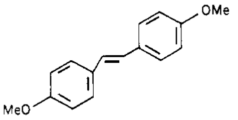
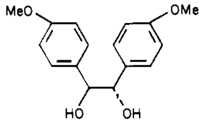
substrate	solvent, time[a]	hydrolysis method	product	yield, %	ref
	diethyl ether, 24 h diethyl ether, 24 h	Na_2SO_3 Na_2SO_3		70^b 84^b $(98)^c$	11 11
	diethyl ether, 24 h	Na_2SO_3		66^b $(99)^c$	
	diethyl ether, 24 h	Na_2SO_3		78^b $(89)^c$	11
	diethyl ether, 24 h	Na_2SO_3		81^b $(96)^c$	11
	diethyl ether	H_2S		21	69
				89	70
				60	70
	diethyl ether, 24 h	$LiAlH_4$			75
isocolumbin	dioxane, 48 h	H_2S	isocolumbindiol	90	77
	tetrahydrofuran, 2 days			73	82
	dioxane, 10 days	H_2S		89	83
	dioxane, 10 days	H_2S		76	83
	diethyl ether, 90 h	$NaHSO_3$			84
	diethyl ether, 3.5 days	KOH			85
	diethyl ether, 90 h	Na_2SO_3		69^d	86
	diethyl ether, 96 h	Na_2SO_3			86

TABLE I (*Continued*)

substrate	solvent, time[a]	hydrolysis method	product	yield, %	ref
	diethyl ether, 96 h	Na_2SO_3		60	86 87
	diethyl ether, 50 h	Na_2SO_3			87
	diethyl ether, 72 h	Na_2SO_3			88
	diethyl ether, 48 h	Na_2SO_3		60 (90)[c]	89
	chloroform				90
	dioxane, 5 days, 20 °C	$NaHSO_3$		32	91
	cyclopentane, 4 days, 20 °C	$NaHSO_3$		48[e]	91
	dioxane, 5 days, 20 °C	$NaHSO_3$		37	91

[a] Solvent and time used for the preparation of osmium(VI) ester complexes. [b] Yield of *cis*-diol from the corresponding osmium(VI) complex. [c] Yield of osmium(VI) ester complex in parentheses. [d] Debromination carried out using zinc metal. [e] 90% yield of *cis*-diol obtained when reaction is carried out in the presence of pyridine.

amine complexes being more resistant to hydrolysis. The oxidative hydrolysis of ester complexes renders the cis-hydroxylation process catalytic and is discussed in the next section.

III. Catalytic Cis Hydroxylation of Alkenes

Although stoichiometric oxidations of alkenes by osmium tetraoxide usually give better yields of diol products and are particularly applicable for the small-scale oxidation of precious materials, it is more usual, for reasons of cost and convenience, to use osmium tetraoxide catalytically. This can be achieved by using osmium tetraoxide in the presence of a secondary oxidant which hydrolyzes the intermediate osmium(VI) ester complex oxidatively to regenerate the tetraoxide which can undergo further reduction by the substrate. The reaction is complete on consumption of the secondary oxidant. A variety of oxidants have been used in conjunction with osmium tetraoxide, the most popular being hydrogen peroxide, metal chlorates, *tert*-butyl hydroperoxide, *N*-methylmorpholine *N*-oxide, oxygen, sodium periodate, and sodium hypochlorite. These catalytic reagents, however, particularly oxygen and sodium periodate, have the disadvantage that appreciable overoxidation can occur, leading to the formation of keto or acid products. This can be minimized by the use of *tert*-butyl hydroperoxide or *N*-methylmorpholine *N*-oxide. It has also been noted that the oxidative hydrolysis of osmium(VI) esters derived from tetra- and trisubstituted alkenes tends to be rather slow,[157,158] particularly in the presence of pyridine; this is thought to be due to internal steric considerations. In these cases, it is more usual to use osmium tetraoxide stoichiometrically and reduce the ester reductively with sulfite or hydrogen sulfide. The catalytic use of osmium tetraoxide, however, is generally highly successful and is applicable to many facets of organic synthesis.

A. With Hydrogen Peroxide

A catalytic amount of osmium tetraoxide in the presence of an excess of hydrogen peroxide (Milas' reagent) readily oxidizes alkenes to give the corresponding *cis*-diols as the major product.[9,10,68] The catalytic reagent is prepared in *tert*-butyl alcohol, to which it is inert, and can be used under anhydrous conditions or with 8% water. Benzene, diethyl ether, and acetone have also been used as solvents; however, benzene is slowly oxidized over prolonged periods of time (a few days) to give initially phenol and then acidic products,[159] thus limiting its use as a solvent.

Although hydrogen peroxide has been shown to act as a hydroxylating agent when irradiated with ultraviolet radiation,[160]

TABLE II. Noncatalytic Cis Hydroxylation of Alkenes in the Presence of Pyridine

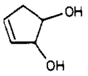
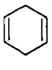
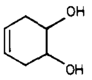
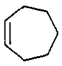
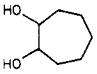
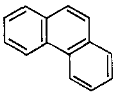
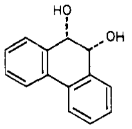
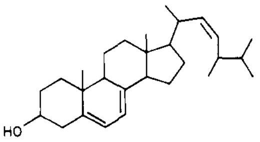
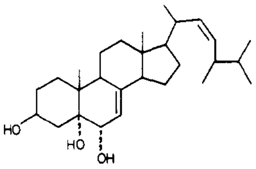
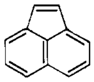
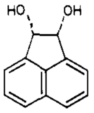
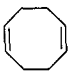
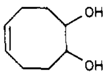
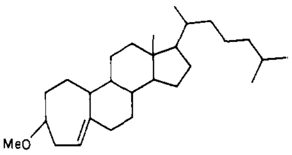
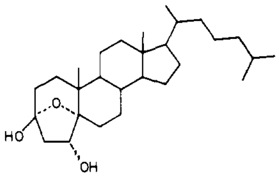
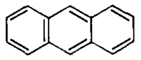
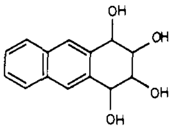
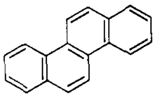
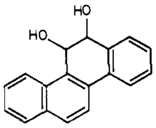
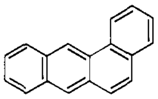
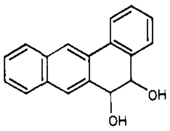
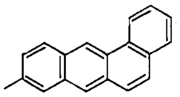
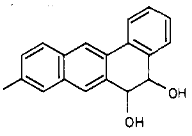
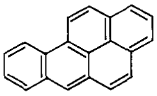
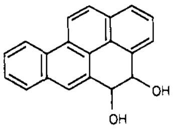
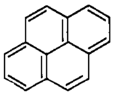
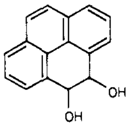
substrate	solvent, time^{a}	hydrolysis method	product	yield, %	ref
	diethyl ether, 20 min	K$_2$CO$_3$/KOH		(99)^{b}	12
	diethyl ether, 30 min	K$_2$CO$_3$/KOH		(100)^{b}	12
	diethyl ether, 30 min, 0 °C	mannitol/KOH		(99)^{b}	12
	benzene, 2 days	mannitol/KOH		64^{c}	12 92 95
	diethyl ether	Na$_2$SO$_3$		40 (90)^{b}	12
	diethyl ether	mannitol/KOH		94^{c}	12
	diethyl ether diethyl ether	H$_2$S Na$_2$SO$_3$		14 76	93 72
	tetrahydrofuran, 48 h	H$_2$S		90	94
	benzene, 1 week	mannitol/KOH			95
	benzene, 2 days	mannitol/KOH			95
	benzene, 2 days	mannitol/KOH			96 95
	benzene, 2 days	mannitol/KOH			95
	benzene, 1 week	mannitol/KOH			95
	benzene, 2 days	mannitol/KOH			95

TABLE II (*Continued*)

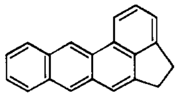
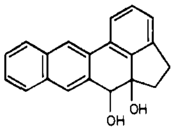
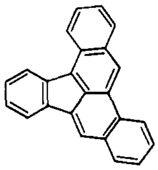
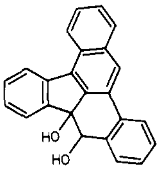
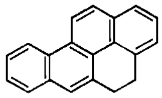
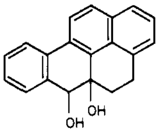
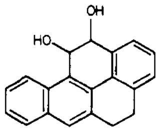
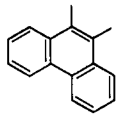
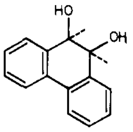
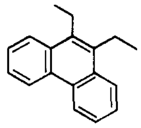
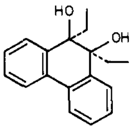
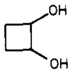
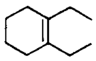
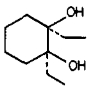
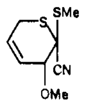
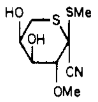
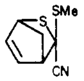
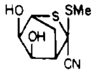
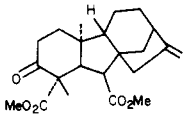
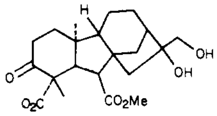
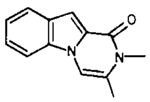
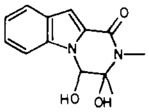
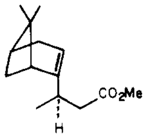
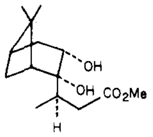
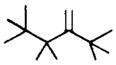
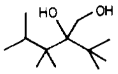
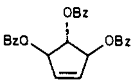
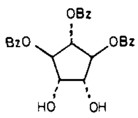
substrate	solvent, time[a]	hydrolysis method	product	yield, %	ref
	benzene, 2 days	mannitol/KOH			96
	benzene, 1 month	mannitol/KOH		*d* 42[d]	97 98
	pyridine pyridine, 8 days	$NaHSO_3$ $NaHSO_3$	 	52	99 100
	benzene, 7 days	Na_2SO_3		79 (100)[b]	101
	benzene, 1 week	Na_2SO_3		94 (100)[b]	101
	diethyl ether, 1.5 h, 0 °C	KOH		41 (100)[b]	101
	diethyl ether	Na_2SO_3			101
	pyridine, 21 h	$NaHSO_3$		65	102
	pyridine, 18 h	$NaHSO_3$		71	102
	pyridine, 71 h	$NaHSO_3$			103
	benzene, 3 days	mannitol/KOH Na_2SO_3		 77[c]	104 104
	diethyl ether, 15 h			62	105
	diethyl ether, 3 weeks	mannitol/KOH		9	106
	benzene, 1 week	H_2S		31	107

TABLE II (*Continued*)

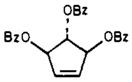
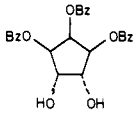
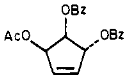
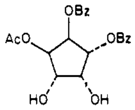
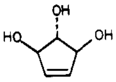
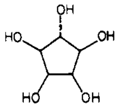
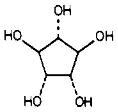
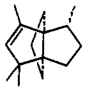
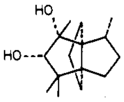
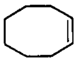
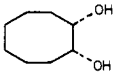
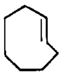
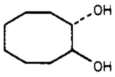
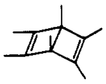
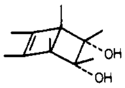
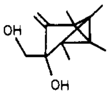
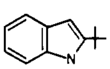
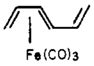
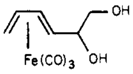
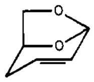
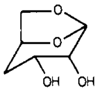
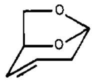
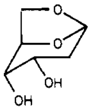
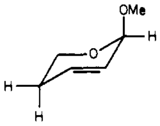
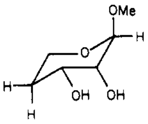
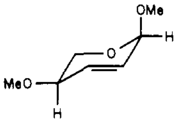
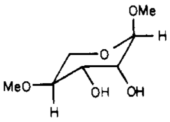
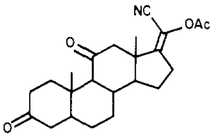
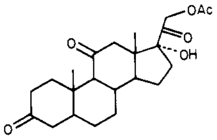
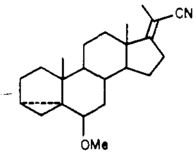
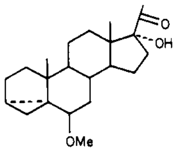
substrate	solvent, time[a]	hydrolysis method	product	yield, %	ref
	benzene, 3 days	H_2S		65	107
	benzene, 24 h	H_2S		49	107
	benzene, 3 days	H_2S		35	107
				17	
	pyridine				108
	diethyl ether, 24 h	Na_2SO_3		38 (93)[b]	109
	diethyl ether, 24 h	Na_2SO_3		36 (93)[b] 64	109 110
	pyridine	$NaHSO_3$			111
	diethyl ether	mannitol/KOH		30	112
	diethyl ether, 5 days, room temp	mannitol/KOH	3-*tert*-butyl-3-hydroxyoxindol		113
	pyridine, 23 h	Na_2SO_3		10	114
	dioxane, 24 h pyridine, 15 h	H_2S $NaHSO_3$		87 96	115 115
	pyridine, 15 h	$NaHSO_3$		92	115
	pyridine, 20 h	$NaHSO_3$		93	116
		$NaHSO_3$		73	116
		Na_2SO_3			117 118
	pyridine	$NaHSO_3$		54	119

TABLE II (*Continued*)

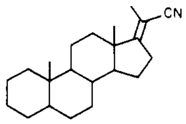
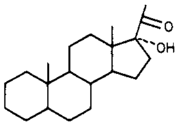
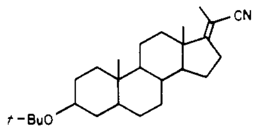
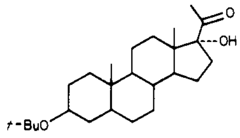
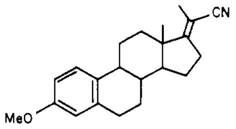
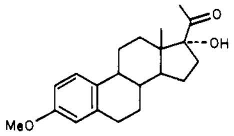
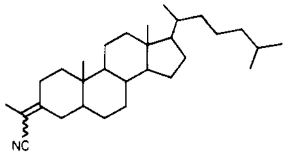
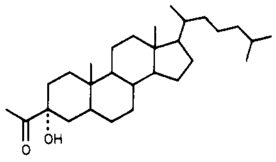
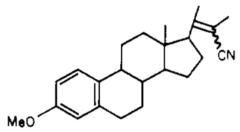
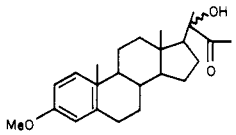
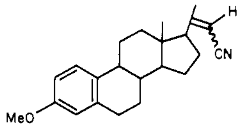
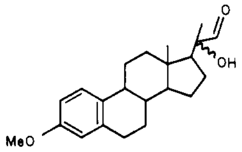
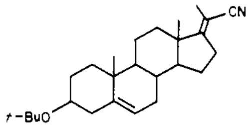
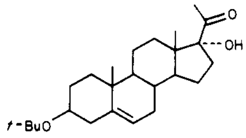
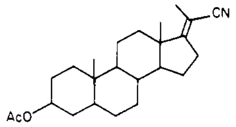
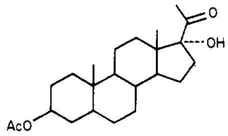
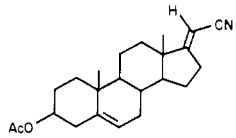
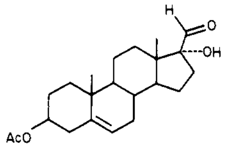
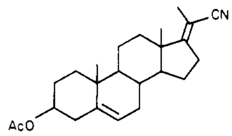
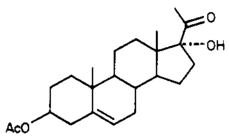
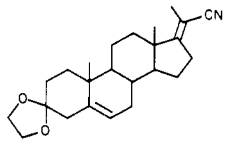
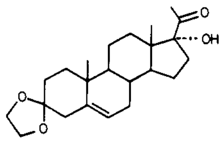
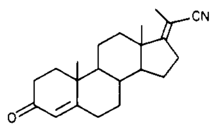
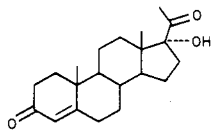
substrate	solvent, time[a]	hydrolysis method	product	yield, %	ref
	pyridine	$NaHSO_3$		43	119
	pyridine	$NaHSO_3$		67	119
	pyridine	$NaHSO_3$		69	119
	pyridine	$NaHSO_3$		34	119
	pyridine	$NaHSO_3$		69	119
	pyridine	$NaHSO_3$		66	119
	pyridine	$NaHSO_3$		10	119
	pyridine	$NaHSO_3$		52	119
	pyridine	$NaHSO_3$		19	119
	pyridine	$NaHSO_3$		19	119
	pyridine	$NaHSO_3$		26	119
	pyridine	$NaHSO_3$		2	119

TABLE II (*Continued*)

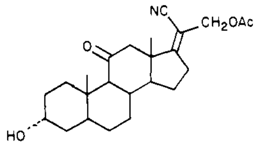
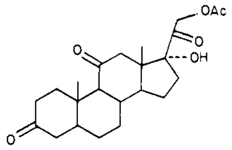
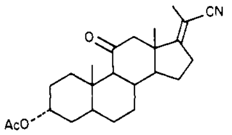
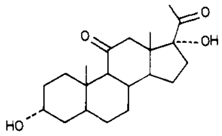
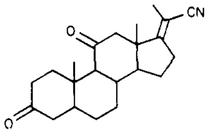
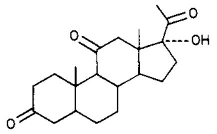
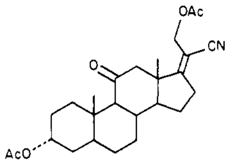
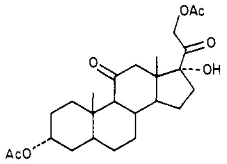
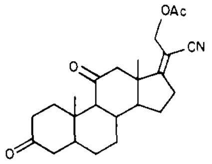
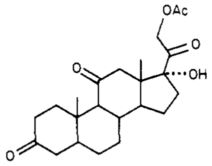
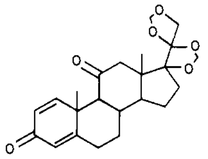
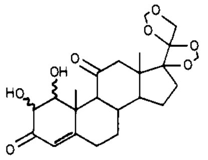
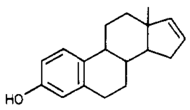
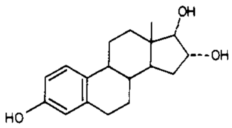
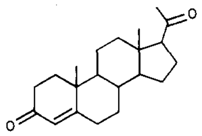
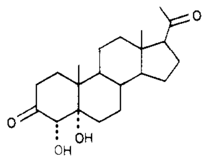
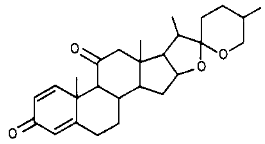
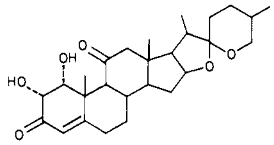
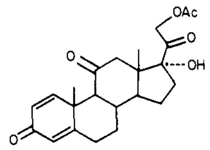
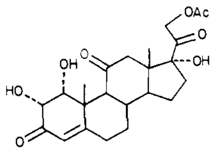
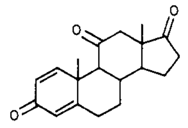
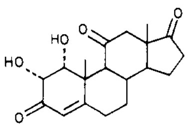
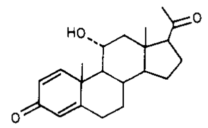
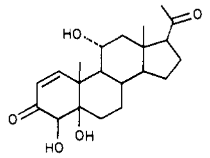
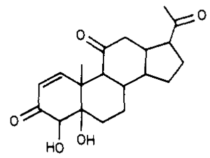
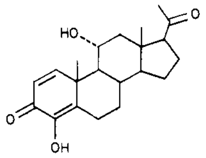
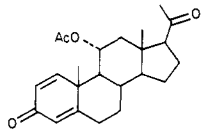
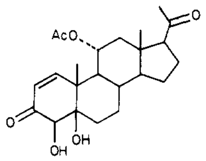
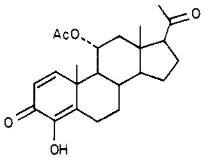
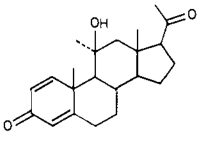
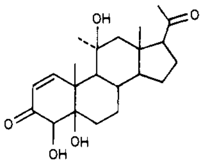
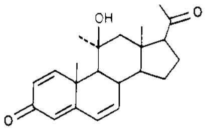
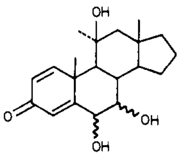
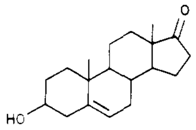
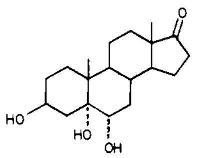
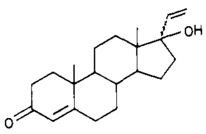
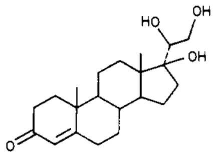
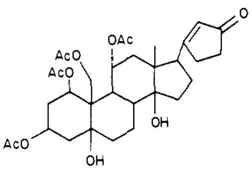
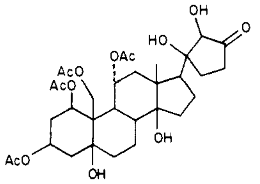
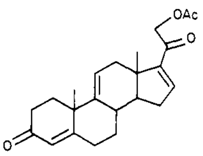
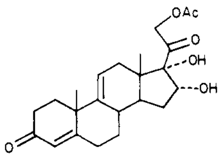
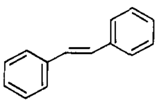
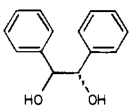
substrate	solvent, time[a]	hydrolysis method	product	yield, %	ref
		Na_2SO_3		46[e]	120
	benzene, 12 h	Na_2SO_3		53	121
	benzene, 12 h	Na_2SO_3		83	121
	benzene, 12 h	Na_2SO_3		45	121
	benzene, 12 h	Na_2SO_3		60	121
	pyridine, 5 days	H_2S		70	122
	diethyl ether, 24 h	mannitol/KOH		59	123
	dioxane, 18 h	$NaHSO_3$		67	124
	pyridine	H_2S		31	125
	pyridine	H_2S		23	125
	pyridine	H_2S		55	125
	pyridine	H_2S		23	125

TABLE II (*Continued*)

substrate	solvent, time[a]	hydrolysis method	product	yield, %	ref
				2	
				1	
	pyridine, 3 days	H_2S		35	125
				5	
	pyridine, 5 days	H_2S		36	125
	pyridine, 3 days	H_2S		25	125
	pyridine, 2 h	$NaHSO_3$		86	126
	pyridine, 20 h	$NaHSO_3$		72	126
	pyridine, 1 day	$NaHSO_3$		81	126
	benzene				127
	cyclopentane	$NaHSO_3$		90	91

[a] Solvent and time used for the preparation of osmium(VI) ester complexes. [b] Yield of osmium(VI) ester complex in parentheses. [c] Yield of *cis*-diol from the corresponding osmium(VI) complex. [d] Originally formulated as *trans*-diol product. [e] Additional oxidation by chromium trioxide.

TABLE III. Catalytic Cis Hydroxylation of Alkenes with Osmium Tetraoxide and Hydrogen Peroxide

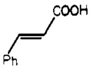
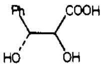
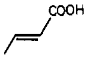
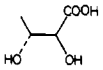
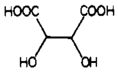
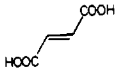
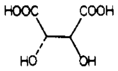
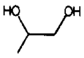
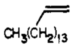
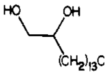
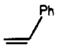
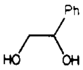
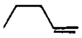
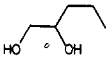
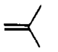
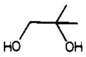
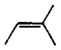
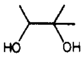
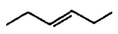
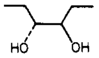
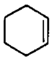
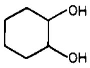
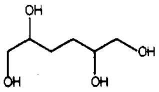
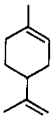
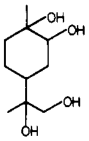
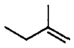
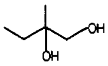
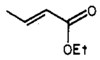
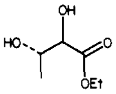
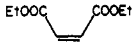
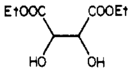
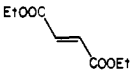
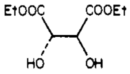
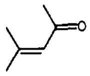
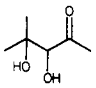
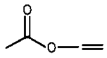
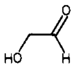
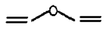
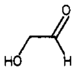
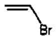
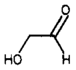
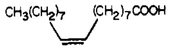
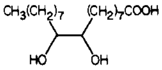
substrate	solvent, time	product	yield, %	ref
	*t*-BuOH, 12 h, 0 °C		56	9
	*t*-BuOH, 12 h, 0 °C		54	9
	*t*-BuOH, 12 h, RT[a]		30	9
	*t*-BuOH, 2 days, 0 °C		48	9
	*t*-BuOH, 2 days, RT		88, 93, 97	10
	*t*-BuOH, 9 h, RT		68	10
	*t*-BuOH, 1 h, RT		77, 82	10
	*t*-BuOH, 2 days, 0 °C		50	10
	*t*-BuOH, 3 days, 0 °C		26, 29, 30	10
	*t*-BuOH, 12 h, 0 °C		38	9, 10
	*t*-BuOH, 24 h, RT		38 40	9 10
	*t*-BuOH, 2 days, 0 °C		36	10
	*t*-BuOH, 12 h, 0 °C		58	10
	*t*-BuOH, 12 h, 0 °C		45	10
	*t*-BuOH, 12 h, 10–15 °C		35	10
	*t*-BuOH, 3 days, 0 °C		45, 51	10
	*t*-BuOH, 3 days, 0 °C		56	68
	*t*-BuOH, 4 days, 0 °C, then 2 days, RT		41	68
	*t*-BuOH, 4 days, 0 °C, then 1 day, RT		58	68
	*t*-BuOH, 2 days, 0 °C		23	68
	*t*-BuOH, 5 days, 0 °C		60	68
	*t*-BuOH		96	68
	*t*-BuOH, 24 days, 5–10 °C		13	68
	*t*-BuOH, 12 h, 0 °C		60	68

TABLE III (*Continued*)

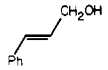
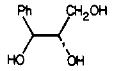
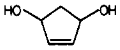
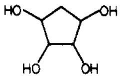
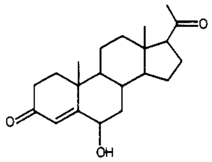
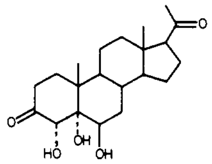
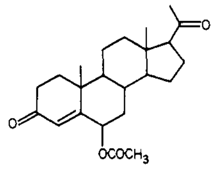
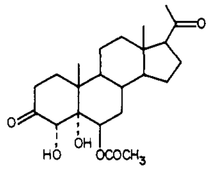
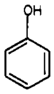
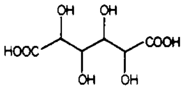
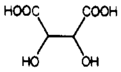
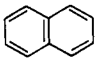
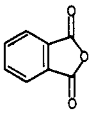
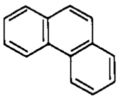
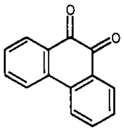
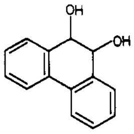
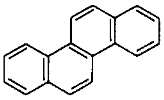
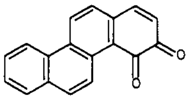
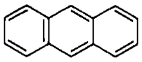
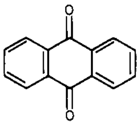
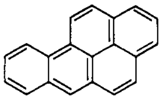
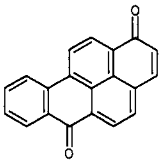
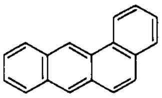
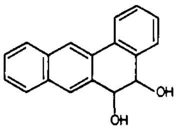
substrate	solvent, time	product	yield, %	ref
	*t*-BuOH, 4 days, 0 °C		13	68
	*t*-BuOH, 3 days, 0 °C		31, 21 26	71 168
	t-BuOH, 3 days, 0 °C		61	71
	*t*-BuOH, 9 days, RT		35	124
	*t*-BuOH, 6 days, RT		44	124
	acetone/*t*-BuOH, several days, RT		 23	159 10
	several days			
	9 months			
	acetone/*t*-BuOH, 18 days			159
	acetone/*t*-BuOH, 26 days		2	159
			1	
	acetone/*t*-BuOH, 3 weeks			159
	acetone/*t*-BuOH, 4 months		58	159
	acetone/*t*-BuOH			159
	acetone/*t*-BuOH, 3–4 days		14	159

TABLE III (*Continued*)

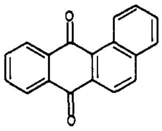
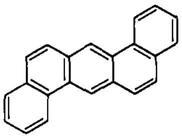
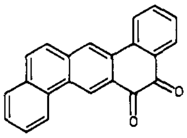
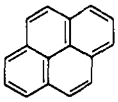
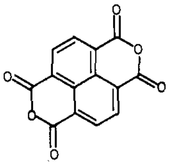
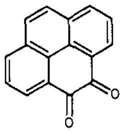
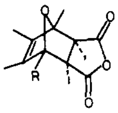
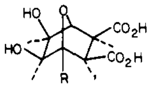
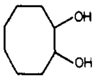
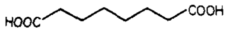
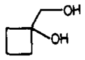
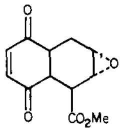
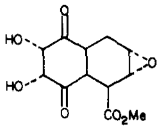
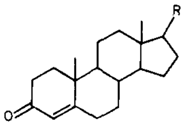
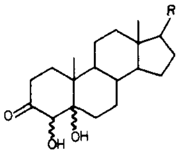
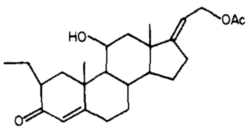
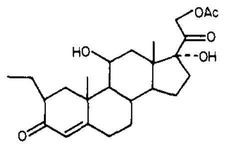
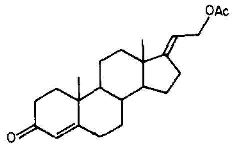
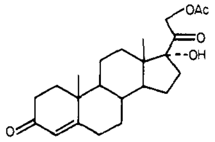
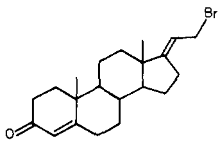
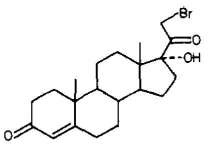
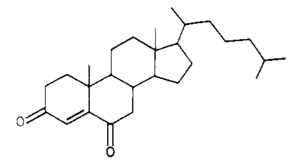
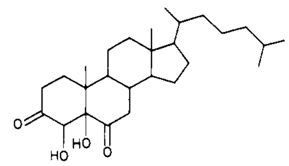
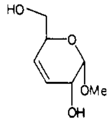
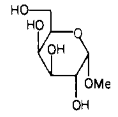
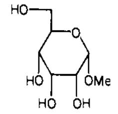
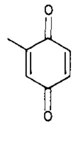
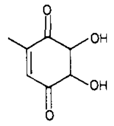
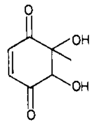
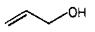
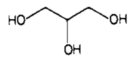
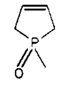
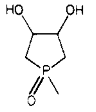
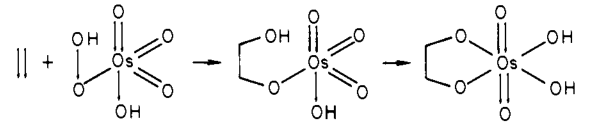
substrate	solvent, time	product	yield, %	ref
			21	
	acetone/*t*-BuOH, 3-4 days, 70 °C		29	159
	acetone/*t*-BuOH, 1 year			159
	acetone/*t*-BuOH, 5 days, RT		7	169
	*t*-BuOH/water/acetone			170
R = H	24 h, 30 °C, then 4 h, 0 °C		50	
R = CH_3	24 h, 30 °C		31	
R = Br	24 h, 30 °C, then 48 h, RT		67	
R = CH_3CO	24 h, 30 °C		54	
	*t*-BuOH, 42 h, 0-5 °C		11	171
			4	
	*t*-BuOH, 2 days, 0 °C		39	172
	diethyl ether/benzene, 37 h, RT		48	173
				
R = C_8H_{17}	*t*-BuOH, 24 h, RT		64	124
	diethyl ether, 15 h, 20 °C		60	174
	diethyl ether, 24 h, RT		51	175
R = CH_3CO	diethyl ether, 24 h, RT		30	174
	t-BuOH, 24 h, RT		70	124
R = $OCOCH_3$	diethyl ether, 24 h, RT		77	174
				176
	*t*-BuOH, 72 h, RT		48	177
	*t*-BuOH, 146 h, RT			177

TABLE III (*Continued*)

substrate	solvent, time	product	yield, %	ref
	diethyl ether, 12 h, RT			174
	*t*-BuOH	 		178
	water/dioxane, 4 h, 25 °C	 	66	179
	water, 1.5 h		67	54
	t-BuOH, 3 h		60	9
	t-BuOH, 2 days, RT; 1 h, RT; 2 h, 70 °C		68, 100, 56	180
	water, 50 °C		100	181

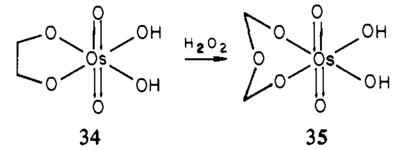
[a] RT = room temperature.

under normal conditions negligible oxidation of alkenes occurs. On the addition of osmium tetraoxide, however, vigorous reaction takes place with reduction and subsequent reoxidation of osmium until all the peroxide is consumed. Milas and others have studied the mechanism of the catalytic process. On addition of osmium tetraoxide to hydrogen peroxide, the formation of a complex,[161,162] formulated as peroxyosmic acid, H_2OsO_6 (**32**),[163-166] takes place; this rapidly reacts with alkenes to form ester species. Hydrolysis is thought to occur via cleavage of the osmium(VIII) ester complex **34** to give osmium tetraoxide and the corresponding *cis*-diol.[166]



32 33 34

The main disadvantage of this catalytic method is that overoxidation to give carbonyl products often occurs, thus lowering the final yield of *cis*-diol. Although *cis*-diols are slowly cleaved by hydrogen peroxide, the formation of carbonyl compounds occurs at too fast a rate for diols to be considered as intermediates in the formation of aldehydes and ketones. Milas and co-workers[166] have proposed that hydrogen peroxide attack of the osmium(VIII) ester complex **34** occurs, leading to carbon–carbon cleavage of the ester species **35**.



34 35

The incorporation of two alkene moieties per osmium atom has also been noted during the catalytic process, and this can be directly explained by the formation of analogous diester complexes **5** as discussed in section II. Potassium osmate (**7**)[54] and osmium trichloride[167] have been also used with hydrogen peroxide as cis-hydroxylating agents. These reagents behave as nonvolatile sources of osmium tetraoxide, the tetraoxide being generated in situ by hydrogen peroxide oxidation. Table III gives data on substrates oxidized catalytically by osmium tetraoxide and hydrogen peroxide.

B. With Metal Chlorates

Hofmann[7] showed in 1912 that osmium dioxide could be readily oxidized to osmium tetraoxide by treatment with aqueous sodium or potassium chlorate. It was later observed that potassium chlorate in the presence of a catalytic amount of tetraoxide could oxidize a series of alkenes, ethylene, propylene, amylene, indene, pinene, and dichloroethylene, to give the corresponding *cis*-diols.[7,8,182] These oxidations presumably occurred via the formation of an osmium(VI) ester complex which could be hydrolyzed by chlorate ion to regenerate osmium tetraoxide, analogous to that found for Milas' reagent. It has been noted, however, that the oxidation potential of potassium chlorate is raised by the addition of a trace of osmium tetraoxide, and the formation of an addition product has been proposed.[7] Alternatively, the formation of free hypochlorous acid which could act as a source of hydroxyl radicals has also been thought to occur.[183] This would explain the appreciable amounts of chloro hydroxy products formed when osmium tetraoxide is used in conjunction with sodium or potassium chlorate. Thus crotonic acid can be oxidized to chlorohydroxycrotonic acid by using osmium tetraoxide catalytically in the presence of barium

TABLE IV. Catalytic Cis Hydroxylation of Alkenes with Osmium Tetraoxide and Metal Chlorates

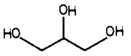
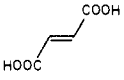
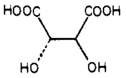
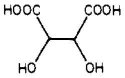
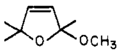
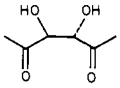
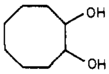
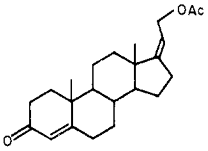
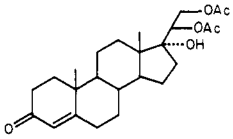
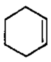
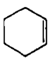
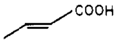
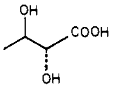
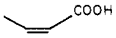
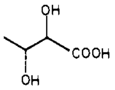
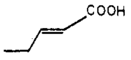
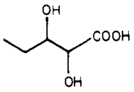
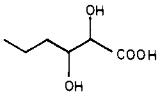
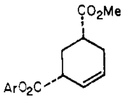
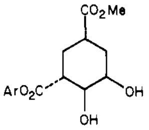
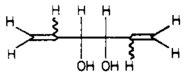
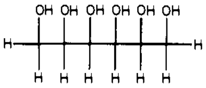
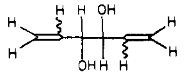
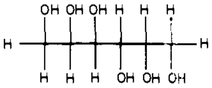
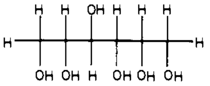
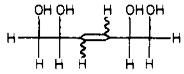
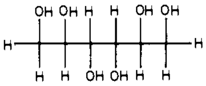
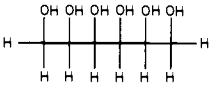
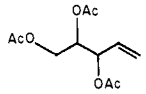
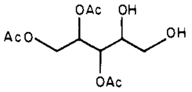
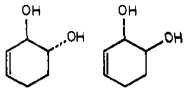
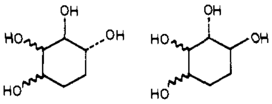
substrate	conditions	product	yield, %	ref
	$NaClO_3$, water, 50 °C		74	8
	$NaClO_3$, water, 6-10 h, 40 °C $NaClO_3/KClO_3$, water, 10-14 h, 40-50 °C		41 90-100	8 196
	$NaClO_3$, water $NaClO_3$, water, 7-10 h, 40-50 °C		 98	8 196 136
	$KClO_3$, THF/water, 18 h, 45-50 °C		100	210
	$NaClO_3$, acetic acid, water, *t*-BuOH, dioxane, 72 h, 80 °C		30	171
	$KClO_3$, diethyl ether, 7 days		14[a]	177
	$NaClO_3$, water, 11 h, 50-55 °C $KClO_3$, water, 9 h, 50 °C $NaClO_3$, water, 9 h, 50 °C		76 46	54 182 197
	$AgClO_3$, water, 2 weeks, 0 °C-RT[e] $AgClO_3$, water, 3 weeks, RT $KClO_3$, water, 8 h, 50 °C		38,[b] 83 66, 70 17	184 198 198, 199, 211
	$AgClO_3$, water, 4 weeks, 0 °C		83	184
	$AgClO_3$, water, 0 °C		80	185
	$AgClO_3$, water, 0 °C		86	185
	$NaClO_3$, water, RT		84-88	186
	$AgClO_3$, several days, water		14	190[c]
	$AgClO_3$, water	 	 8	190 191
	$AgClO_3$, water	 	 11	190
	$AgClO_3$, water			190
	$AgClO_3$, water, 2-3 days		70	200

TABLE IV (*Continued*)

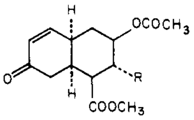
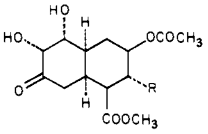
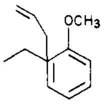
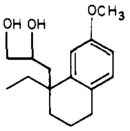
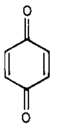
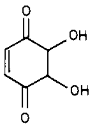
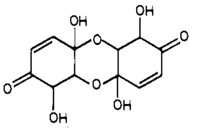
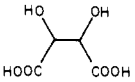
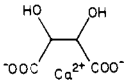
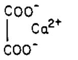
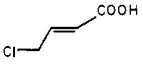
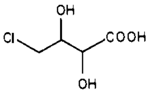
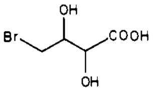
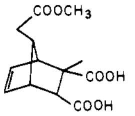
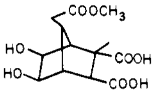
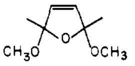
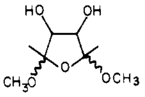
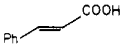
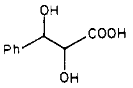
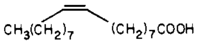
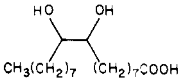
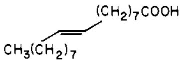
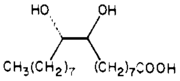
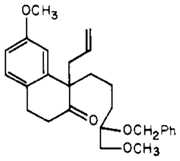
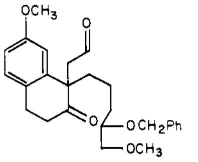
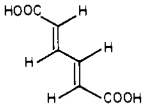
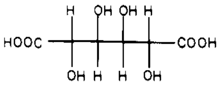
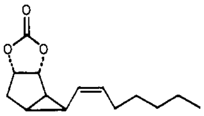
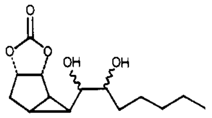
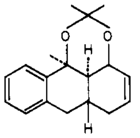
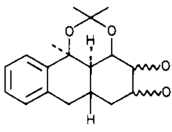
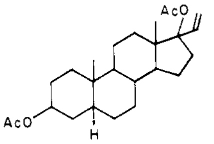
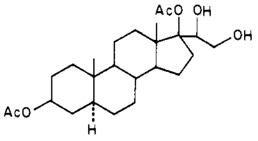
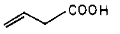
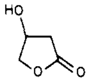
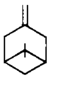
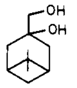
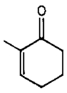
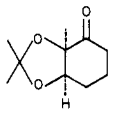
substrate	conditions	product	yield, %	ref
	$Ba(ClO_3)_2$, water, 5h			
R = CH_3			93	201
R = CH_2CH_3			93	201
R = OCH_3			65	202
	$NaClO_4$, 22 h, tetrahydrofuran, water		88	195
	$NaClO_3$, 54 h, RT, aqueous 1 N HCl		50	203
	$NaClO_3$, 60 h, RT, aqueous 2 N HCl		10	204
	$NaClO_3$, 110 h, 50 °C, aqueous 1 N HCl		49	205
pyromucic acid	$NaClO_3$, water, 60 h, 50 °C			205
				205
	$Ba(ClO_3)_2$, water, 32 h $Ba(ClO_3)_2$, water		78 75	206 207
	$Ba(ClO_3)_2$, water, 24 h		70	208a
	$KClO_3$, water		35	209
	$KClO_3$, 63 h, 30 °C, tetrahydrofuran, water		10	210
	$NaClO_3$, water, 10 h, 80 °C		50	211
	$NaClO_3$, water, 66 h, 100 °C		31	211
	$NaClO_3$, water, 100 h, 100 °C			211
	$NaClO_3$, water, tetrahydrofuran		97^d	212
	$NaClO_3$, water, 20 h		38	213

TABLE IV (*Continued*)

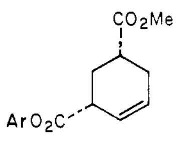
substrate	conditions	product	yield, %	ref
	$NaClO_3$, tetrahydrofuran, water		75	214
	$KClO_3$, tetrahydrofuran, water, 5 h, 50 °C		69	215
	$KClO_3$, diethyl ether, 3 days		*a*	216
	$Ba(ClO_3)_2$, water, 3 days, <35 °C		35	207
	$NaClO_3$, 4 h, diethyl ether/dioxane/water		50	208b
	$Ba(ClO_3)_2$, tetrahydrofuran/water 10 °C		65	187

[a] Intermediate osmium(VI) ester complex oxidatively hydrolyzed with potassium chlorate. [b] Catalytically oxidized with barium chlorate. [c] See ref 191–193. [d] *cis*-Diol product oxidized with sodium periodate. [e] RT = room temperature.

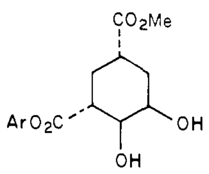
chlorate.[184] As a result, Braun[184,185] suggested the use of silver chlorate as an alternative source of chlorate ion. In this case, any hypochlorous acid formed is removed from solution in the form of the insoluble silver salt. In general, silver (and barium) chlorate gives better yields of *cis*-diol products and are more easily removed from solution than the corresponding sodium or potassium salts.

Some mechanistic studies have been carried out on the oxidation of fumaric and maleic acids.[136] The reactions were found to be first order with respect to acid concentration and zero order with respect to water and chlorate ion concentrations, the chlorate being reduced to chloride.[136] The rate-determining step was thought to be that of ester formation, in agreement with Behrman's studies[34–36] on noncatalytic cis hydroxylation of alkenes. The rates of oxidation of fumaric and maleic acids were also found to be pH dependent. Thus, the free carboxylic acids were more efficiently oxidized than the corresponding carboxylates, suggesting some form of acid catalysis.[136]

The osmium tetraoxide/sodium chlorate catalytic reagent (Hofmann's reagent) is widely used as a cis-hydroxylating agent in spite of the disadvantage of formation of chloro hydroxy products. Trost and co-workers[186] have used the reagent in an enantioconvergent synthesis of prostanoids. This involves oxidation of **36** from the less hindered side to give **37** in 84–88% yield.

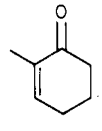


36

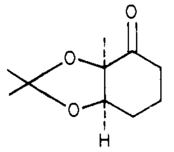


37

More recently Grieco and co-workers[187] in their total synthesis of the Prelog–Djerassi lactone used osmium tetraoxide in conjunction with barium chlorate to oxidize **38** to the corresponding *cis*-diol, isolated as its protected cyclic diether **39** in 65% yield.

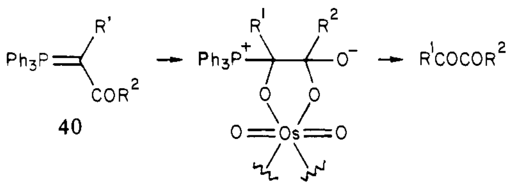


38



39

The epoxidation of propylene to propylene oxide using Hofmann's reagent has been reported; the epoxide oxygen has been shown to originate from the chlorate.[188] The oxidation of (β-oxoalkylene)phosphoranes (**40**) with osmium tetraoxide and



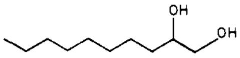
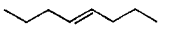
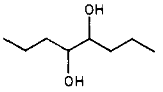
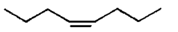
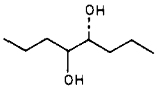
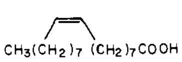
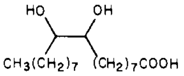
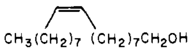
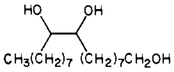
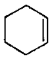
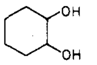
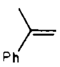
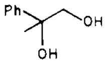
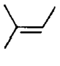
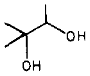
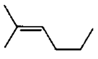
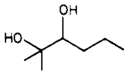
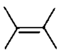
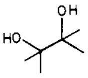
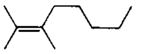
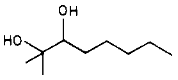
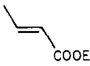
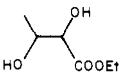
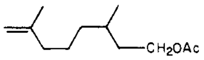
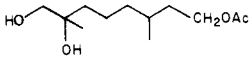
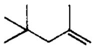
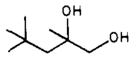
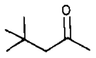
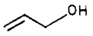
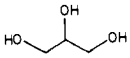
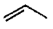
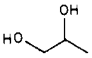
40

41

barium chlorate yields the corresponding α-diketones.[189] This reaction is thought to proceed via formation of an osmium(VI) ester complex (**41**) which on hydrolysis yields the corresponding dione together with triphenylphosphine which is oxidized to the oxide by osmium tetraoxide.[189]

The use of Hofmann's reagent in the synthesis of polyalcohols, particularly in carbohydrate chemistry, has been of great success.[190–194] Sodium perchlorate has also been used as a secondary oxidant with osmium tetraoxide.[195] The catalytic oxidation of alkenes by osmium tetraoxide with hypochlorite is

TABLE V. Catalytic Cis Hydroxylation of Alkenes with Osmium Tetraoxide and *tert*-Butyl Hydroperoxide

substrate	conditions	product	yield, %	ref
	*t*-BuOH/Et$_4$NOH		73	157
	*t*-BuOH/Et$_4$NOH acetone/Et$_4$NOAc		73 81, 78, 74	157 158
	*t*-BuOH/Et$_4$NOH		61	157
	*t*-BuOH/Et$_4$NOH		70	157
	*t*-BuOH/Et$_4$NOH		51	157
	*t*-BuOH/Et$_4$NOH acetone/Et$_4$NOH		62 52, 45, 51	157 158
	*t*-BuOH/Et$_4$NOH		71	157
	*t*-BuOH/Et$_4$NOH		63	157
	*t*-BuOH/Et$_4$NOH		67	157
	*t*-BuOH/Et$_4$NOH		72	157
	*t*-BuOH/Et$_4$NOH acetone/Et$_4$NOAc		69 0	157 158
	acetone/Et$_4$NOAc		71, 72, 58	158
	acetone/Et$_4$NOAc		83	158
		 formaldehyde 		217
				219
				219

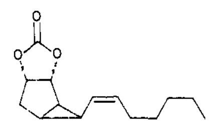
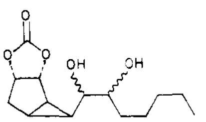
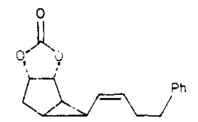
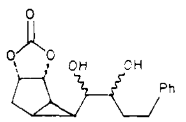
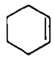
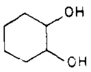
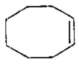
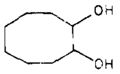
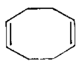
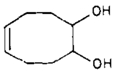
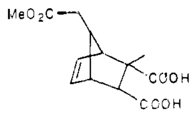
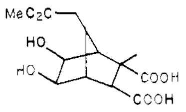
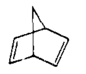
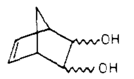
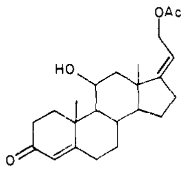
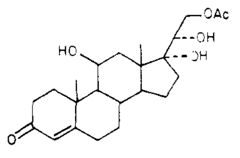
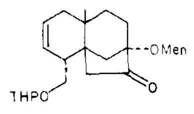
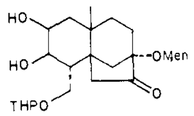
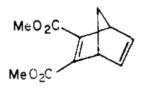
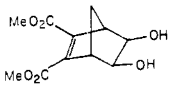
discussed in section III.G. Table IV gives data on oxidations using metal chlorates and osmium tetraoxide.

C. With *tert*-Butyl Hydroperoxide

Although the catalytic use of osmium tetraoxide with metal chlorates or hydrogen peroxide is generally successful, these methods have the disadvantages that overoxidation may occur, leading to high yields of ketols and other aldehydic products. In addition, tri- and tetrasubstituted alkenes are often difficult to oxidize since their corresponding osmium(VI) ester complexes are inert toward oxidative hydrolysis.[157,158] This has led to the search for more efficient catalytic cis-hydroxylating methods; the development of *tert*-butyl hydroperoxide and *N*-methylmorpholine *N*-oxide (see section III.D) as secondary oxidants for osmium tetraoxide oxidation have been the most successful in this respect.

Byers and Hickinbottom[217] were the first to use osmium tetraoxide catalytically in the presence of *tert*-butyl hydroperoxide; oxidation of 2,4,4-trimethylpent-1-ene yielded 2,4,4-trimethylpentane-1,2-diol together with formaldehyde and 2,2-dimethylpentan-4-one. No yields were reported. Later, McCasland and co-workers[218] reported the cis hydroxylation of alkenes using *tert*-butyl hydroperoxide and osmium tetraoxide; however, these latter workers actually used hydrogen peroxide in *tert*-butyl alcohol (i.e., Milas' reagent) for their oxidations. Sharpless and co-workers have developed a catalytic reagent involving osmium tetraoxide and *tert*-butyl hydroperoxide in the presence of tetraethylammonium hydroxide[157] or tetraethylammonium acetate[158] in *tert*-butyl alcohol or acetone, re-

TABLE VI. Catalytic Cis Hydroxylation of Alkenes with Osmium Tetraoxide and *N*-Methylmorpholine *N*-Oxide

substrate	conditions	product	yield, %	ref
	aqueous acetone/*t*-BuOH		95	214
	aqueous acetone/*t*-BuOH		95	214
	aqueous acetone/*t*-BuOH		91	214
	aqueous acetone/*t*-BuOH		79	214
	aqueous acetone/*t*-BuOH		31	214
	aqueous acetone/*t*-BuOH		55	214
	aqueous acetone/*t*-BuOH		25	214
	10:3:1 *t*-BuOH/ tetrahydrofuran/water		78	214
	1:2.5 water/ acetone, 80 h, 23 °C		89	222
				223

spectively. The reactions were suppressed by the addition of excess sodium bisulfite to precipitate lower forms of osmium. A recent patent also reports the use of osmium tetraoxide with *tert*-butyl hydroperoxide.[219] The results obtained with this catalytic reagent are listed in Table V.

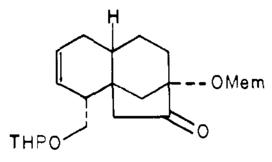
In general, the use of tetraethylammonium acetate in acetone was found to give better results than tetraethylammonium hydroxide in *tert*-butyl alcohol, particularly for the oxidation of base-sensitive alkenes.[158] In both cases, however, better yields of *cis*-diol products were obtained than with Milas' or Hofmann's reagent, the yield of aldehydic products being much reduced. However, the problem of hydroxylation of tri- and particularly tetrasubstituted alkenes still remains. Addition of hindered alkenes such as cholesterol to hydroxylation reaction mixtures inhibited further oxidation, presumably by trapping the osmium as a nonhydrolyzable osmium(VI) ester. The catalytic cis hydroxylation of 2,3-dimethyl-2-octene with *tert*-butyl hydroperoxide gave no *cis*-diol product.[158] The problem of hindered and tetrasubstituted alkenes notwithstanding, the use of *tert*-butyl hydroperoxide is probably the most efficient catalytic procedure available.

D. With *N*-Methylmorpholine *N*-Oxide

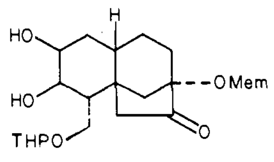
The use of amine *N*-oxides such as *N*-methylmorpholine *N*-oxide as secondary oxidants for the catalytic cis hydroxylation of alkenes has, like *tert*-butyl hydroperoxide catalyst, the advantage that yields of *cis*-diols are substantially higher than those obtained with hydrogen peroxide or metal chlorate reagents.[214]

Triethylamine *N*-oxide has been used in conjunction with osmium tetraoxide for the oxidation of pregnadiene steroids.[220] More recently, the use of *N*-methylmorpholine *N*-oxide has been reported[214,221] as an efficient secondary oxidant for cis-hydroxylation reactions. The catalytic reagent is prepared in a water–acetone–*tert*-butyl alcohol solvent system, the *N*-oxide being readily prepared by treatment of *N*-methylmorpholine with hydrogen peroxide.[214] Workup involves reduction by sodium bisulfite and extraction with ethyl acetate.[214] Good yields of the corresponding *cis*-diols are obtained. Table VI gives data on the oxidation of substrates by osmium tetraoxide and *N*-methylmorpholine *N*-oxide.

Corey and co-workers[222] have used osmium tetraoxide catalytically with *N*-methylmorpholine *N*-oxide in their synthesis of gibberillic acid, **42** being successfully oxidized to **43** in 89% yield. Likewise, Danishefsky and co-workers[223] in their synthesis of *dl*-pentalenolacetone oxidized **44** to **45**. Attack in both cases

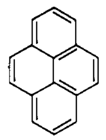
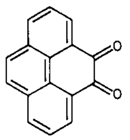
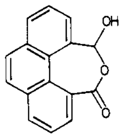
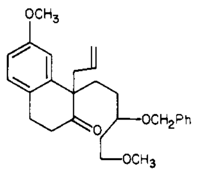
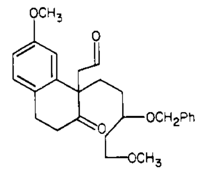
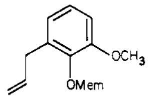
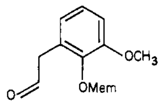
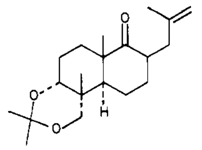
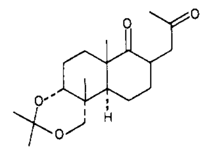
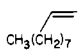
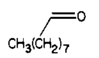
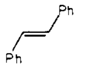
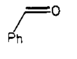
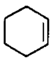
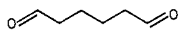
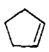
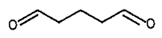
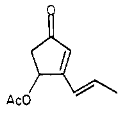
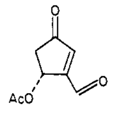
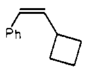
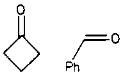


42



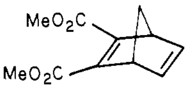
43

TABLE VII. Catalytic Oxidation of Alkenes with Osmium Tetraoxide and Sodium Periodate

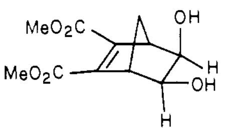
substrate	conditions	product	yield, %	ref
			10, 23	169
			13, 24	
	tetrahydrofuran/water		97[a]	212
	3:1 tetrahydrofuran/water, 2 h, 0–23 °C		74	222
	dioxane/water		86	224
	dioxane/water, 25 °C		68	227
	dioxane/water		85	227
	diethyl ether/water		77	227
	diethyl ether/water		76	227
	acetone/water		86	228
	dioxane/water, 25 °C			229

[a] Initial oxidation with osmium tetraoxide/potassium chlorate.

occurred predominantly from the less-hindered side of the substrate.



44

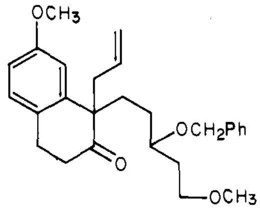


45

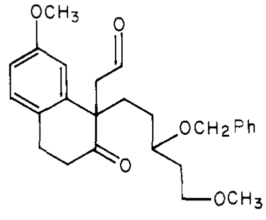
The catalytic reagent, however, like *tert*-butyl hydroperoxide, is not very efficient for the cis hydroxylation of tetrasubstituted alkenes. Sharpless[158] has reported that the *N*-methylmorpholine *N*-oxide reagent failed to oxidize 2,3-dimethyl-2-octene. In addition, the greater cost of *N*-methylmorpholine *N*-oxide as compared with *tert*-butyl hydroperoxide makes the latter more economical, particularly with respect to large-scale oxidations. The most efficient method of cis hydroxylating a hindered or tetrasubstituted alkene is therefore Criegee's using osmium tetraoxide quantitatively with pyridine followed by reductive hydrolysis.

E. With Sodium Periodate

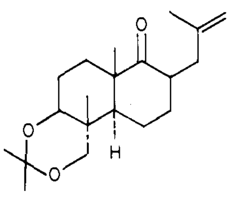
The oxidation of vicinal *cis*-diols by sodium periodate is well-known to give dialdehydic products.[1] As a result, the catalytic oxidation of alkenes by osmium tetraoxide in the presence of sodium periodate gives exclusively aldehydes or ketones as the major products in direct contrast to the reagents discussed previously. The oxidations can be carried out in a variety of solvent systems although water is required to obtain solubility of sodium periodate. The *cis*-diol products formed initially by osmium tetraoxide oxidation are effectively cleaved to higher oxidation products. Thus oxidation of **46** gives **47** in 97% yield.[212] The osmium tetraoxide/periodate reagent has also recently been used in McMurry's synthesis of aphidicolin,[224] synthetically replacing an alkene moiety in **48** with a ketone in **49** in a reported 86% yield.



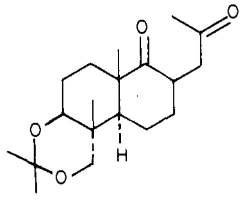
46



47



48



49

An important side reaction that can occur with this catalytic reagent is the oxidation of alcohols. Thus aromatic alcohols such as phenol can be oxidized to aldehydic and acidic products.[225,226] This means that oxidations of alkenes using this method have to be carried out with protected alcohol functions. Table VII gives data on oxidations of alkenes by osmium tetraoxide and sodium periodate.

F. With Oxygen

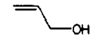
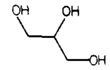
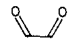
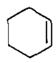
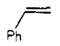
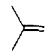
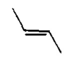
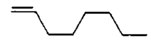
Willstätter and Sonnenfeld[230] have shown that metallic osmium can act as an oxidizing agent for alkenes in the presence of oxygen. The facile oxidation of osmium (0) to osmium(VIII) is well-known,[84] and it is reasonable to assume that the formation of osmium tetraoxide from osmium metal and oxygen occurred in the above experiments. Pērichon and co-workers[231] have reported that air oxidation of osmium(VI) to osmium(VIII) in aqueous solution is possible. They found that the oxidation was highly pH dependent, being rapid at pH 11 but appreciably lower at pH's above 12.5 and below 8, disproportionation occurring below pH 8.

These observations led Cairns and Roberts[151] to investigate the oxidation of alkenes in buffered (trisodium phosphate and disodium hydrogen phosphate) alkaline solution at 80 °C with osmium tetraoxide and oxygen. Their results are listed in Table VIII. The rate of oxidation was slow at 25 °C but increased to a maximum at 80 °C. Under these conditions, however, oxidation of *cis*-diols also occurred; thus oxalic acid was obtained as the major product in many of the oxidations, together with carbon dioxide. At pH 8.5–9.5 at 50 °C, ethylene can be oxidized to ethylene glycol; however, under the same conditions oct-1-ene yields formic and heptanoic acids.[232] If the pH is increased above 9.5, the yield of diol decreases.[232] The catalytic use of osmium tetraoxide in the presence of oxygen, therefore, is highly pH and temperature dependent, yields of *cis*-diols often being low or nonexistent.

G. With Sodium Hypochlorite

The use of sodium hypochlorite as a secondary oxidant for osmium tetraoxide cis hydroxylations is a more recent development and is presumably linked to the observation that hypochlorous acid is formed in the reaction between osmium tetraoxide and metal chlorates. In the latter reactions the formation of hypochlorous acid from chlorate ion led to the formation of appreciable amounts of chlorinated products. A recent patent, however, describes the successful cis hydroxylation of allyl alcohol to glycerol in 98% yield, using osmium tetraoxide in the presence of sodium hypochlorite.[233] Propene, 1-octene, cyclohexene, cyclooctene, 1-decene, 3-chloroprene, acrylamide, acrylic acid, and methyl acrylate were also successfully oxidized.[233] The oxidations of potassium oleate and sodium 10-undecenoate to give *erythro*-9,10-dihydroxystearic acid and 10,11-dihydroxyundecanoic acid in 95% and 50–60% yields, respectively,[234] have been described. Terminal alkenes, however, were found to be overoxidized by the catalytic reagent, leading to C–C bond cleavage.[234]

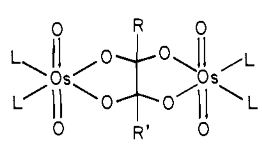
TABLE VIII. Catalytic Oxidation of Substrates with Osmium Tetraoxide and Oxygen

substrate	pH	temp, °C	product	ref
	12.3	80	oxalic acid	151
	12.3	80	oxalic acid	151
	12.3	80	oxalic acid + CO_2	151
	12.3	80	oxalic acid + CO_2	151
	12.3	80	oxalic acid + CO_2	151
	12.3	80	oxalic acid + CO_2	151
	12.3	80	benzoic acid	151
	12.3	80	oxalic acid + CO_2	151
	12.3	80	oxalic acid + CO_2	151
	12.3	80	oxalic acid	151
formic acid	12.3	80	CO_2	151
acetic acid	12.3	80	no reaction	151
sucrose	12.3	80	oxalic acid	151
glucose	12.3	80	oxalic acid + CO_2	151

Osmium tetraoxide can be used catalytically with aqueous nitric acid,[235] alkenes being oxidized to the corresponding acid derivatives; thus cyclohexene yields adipic acid in 88% yield. In addition, the oxidations of *cis*-diols,[236–238] phosphites,[239] and amino acids[240,241] by osmium tetraoxide and alkaline hexacyanoferrate(III) have been reported. Dimethyl sulfoxide[242] and benzaldehyde[243] can be oxidized by osmium tetraoxide in the presence of chloramine-T; the formation of an osmium tetraoxide/chloramine-T complex was proposed in the latter work.

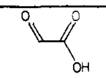
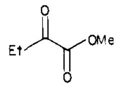
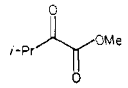
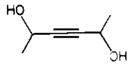
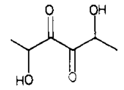
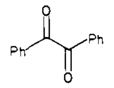
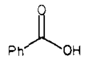
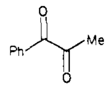
IV. Hydroxylation of Alkynes

Although the cis hydroxylation of alkenes by osmium tetraoxide is well-established, relatively little work has been carried out on the interaction of osmium tetraoxide with alkynes. The reduction of osmium tetraoxide by acetylene gas has been used for the quantitative determination of osmium metal;[6] Criegee reported the oxidation of acetylene to give glyoxalic acid.[11] More recent studies[72] have reported the isolation of osmium(VI) ester complexes $[Os_2O_4(O_4C_2RR')L_4]$ derived from alkyne $R'C_2R$ and tertiary amine L (L = isoquinoline or pyridine). These products were prepared in diethyl ether by reaction of the alkyne with osmium tetraoxide in the presence of excess tertiary amine or by reaction with the osmium(VIII) adducts $OsO_4{\cdot}L$.[72] The infrared spectra of the complexes show bands near 840 cm^{-1} which were assigned to the asymmetric stretching vibration of the *trans*-dioxo moiety, $\nu^{as}(OsO_2)$; bands in the Raman spectrum near 880 cm^{-1} were assigned to the symmetric stretching vibration, $\nu^{s}(OsO_2)$. On this basis, the complexes were formulated as tetrolatoosmyl ester complexes **50**.[72]



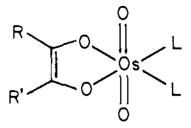
50

TABLE IX. Oxidation of Alkynes with Osmium Tetraoxide

substrate	hydrolysis method	solvent[a]	product	yield, %	ref
H—≡—H	$KClO_3$[b]	water/diethyl ether		48	244
Et—≡—OMe	$KClO_3$[b]	water/diethyl ether		69	244
i-Pr—≡—OMe	$KClO_3$[b]	water/diethyl ether		80	244
	$KClO_3$[b]	water/diethyl ether		85	244
Ph—≡—Ph	Na_2SO_3[c]	water/diethyl ether		65	72
	$KClO_3$[b]	water/acetone/*t*-BuOH		79	245, 72
	NMO[b,d]	water/acetone/*t*-BuOH		74	245
	TBHP[b,e]	water/acetone/*t*-BuOH		78	245
Ph—≡—H	Na_2SO_3[c]	water/diethyl ether		57	72
	$KClO_3$[b]	water/acetone/*t*-BuOH		72	245
	NMO[b,d]	water/acetone/*t*-BuOH		82	245
	TBHP[b,e]	water/acetone/*t*-BuOH		71	245
Ph—≡—Me	Na_2SO_3[c]	water/diethyl ether		54	72
	$KClO_3$[b]	water/acetone/*t*-BuOH		59	245
	TBHP[b,e]	water/acetone/*t*-BuOH		62	245

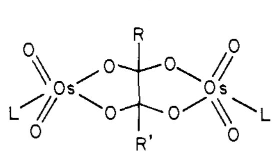
[a] Solvent in which hydrolysis is carried out. [b] Catalytic oxidation. [c] Stoichiometric oxidation. [d] *N*-Methylmorpholine *N*-oxide. [e] *tert*-Butyl hydroperoxide.

The corresponding ester complexes, $[OsO_2(O_2C_2RR')L_2]$ (**51**), involving one osmium per alkyne moiety have not been isolated in the solid state, although such species have been proposed to exist in solution.[244]



51

The adduct $OsO_4{\cdot}L$ (L = quinuclidine) reacts with alkynes to give, in solution, the corresponding five-coordinate osmium(VI) complexes, $[Os_2O_4(O_4C_2RR')L_2]$ **52**.[67] These complexes are



52

polymeric in the solid state, involving asymmetric oxo bridges as described for the complexes **14**.[67] The vibrational spectra of these complexes are also analogous.[67] Hydrolysis of the complexes **50** with sodium sulfite yields the corresponding α,β-diketones from nonterminal alkynes and the corresponding carboxylic acids from terminal alkynes.[72] Similar products are obtained from the catalytic oxidation of alkynes by osmium tetraoxide in the presence of potassium chlorate,[244,245] *tert*-butyl hydroperoxide,[245] *N*-methylmorpholine *N*-oxide,[245] or hydrogen peroxide[246] (see Table IX). These oxidations were carried out by using methods analogous to those described for the cis hydroxylation of alkenes.

Acknowledgments. I particularly thank Dr. W. P. Griffith for his invaluable advice and for checking the manuscript. Thanks are also due to Dr. Mitsunori Ono and Dr. Paul R. Jenkins for their encouragement and help.

V. References

(1) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1–6, Wiley, New York.
(2) J. C. Riemersma, *Biochim. Biophys. Acta*, **152**, 718 (1968).
(3) E. D. Korn, *J. Cell. Biol.*, **34**, 627 (1967).
(4) H. B. Wigglesworth, *Proc. R. Soc. London, Ser. B*, **147**, 185 (1957).
(5) J. R. Baker, *J. Histochem. Cytochem.*, **6**, 303 (1958).
(6) O. Makowka, *Chem. Ber.*, **41**, 943 (1908).
(7) K. A. Hofmann, *Chem. Ber.*, **45**, 3329 (1912).
(8) K. A. Hofmann, O. Ehrhart, and O. Schneider, *Chem. Ber.*, **46**, 1657 (1913).
(9) N. A. Milas and S. Sussman, *J. Am. Chem. Soc.*, **58**, 1302 (1936).
(10) N. A. Milas and S. Sussman, *J. Am. Chem. Soc.*, **59**, 2345 (1937).
(11) R. Criegee, *Justus Liebigs Ann. Chem.*, **522**, 75 (1936).
(12) R. Criegee, B. Marchand, and H. Wannowius, *Justus Liebigs Ann. Chem.*, **550**, 99 (1942).
(13) F. D. Gunstone, *Adv. Org. Chem.*, 1, 110 (1960).
(14) P. N. Rylander, *Engelhard Ind., Tech. Bull.*, **9**, 90 (1968).
(15) W. P. Griffith, *Platinum Met. Rev.*, **18**, 94 (1974).
(16) L. G. Marzilli, *Prog. Inorg. Chem.*, **23**, 255 (1977).
(17) A. Mailhe, *J. Usines Gaz*, **43**, 177, 193, 217 (1919); *Chem. Abstr.*, **13**, 2795 (1919); S. Adolfo, *Rev. Centro. Estud. Farm. Bioquim.*, **27**, 19 (1937); *Chem. Abstr.*, **31**, 5315^9 (1937).
(18) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", 3rd ed., Interscience, New York, p 1003.
(19) H. O. House, "Modern Synthetic Reactions", 2nd ed., Benjamin, San Francisco, CA, 1972, p 277.
(20) R. Criegee, *Angew. Chem.*, **50**, 153 (1937).
(21) R. Criegee, *Angew. Chem.*, **51**, 519 (1938).
(22) R. Criegee, *Congr. Int. Chim. Roma*, **3**, S95 (1938).
(23) L. G. Marzilli, B. E. Hanson, T. J. Kistenmacher, L. A. Epps, and R. C. Stewart, *Inorg. Chem.*, **15**, 1661 (1976).

(24) R. J. Collin, J. Jones, and W. P. Griffith, *J. Chem. Soc., Dalton Trans.*, 1094 (1974).
(25) F. L. Phillips and A. C. Skapski, *J. Chem. Soc., Dalton Trans.*, 2586 (1975).
(26) R. J. Collin, W. P. Griffith, F. L. Phillips, and A. C. Skapski, *Biochim. Biophys. Acta*, **320**, 745 (1973).
(27) F. L. Phillips and A. C. Skapski, *Acta Crystallogr., Sect. B*, **31**, 1814 (1975).
(28) R. J. Collin, W. P. Griffith, F. L. Phillips, and A. C. Skapski, *Biochim. Biophys. Acta*, **354**, 152 (1974).
(29) W. P. Griffith and A. Vintner, unpublished results.
(30) W. P. Griffith and R. Rossetti, *J. Chem. Soc., Dalton Trans.*, 1449 (1972).
(31) J. A. Ragazzo and E. J. Behrman, *Bioinorg. Chem.*, **5**, 343 (1976).
(32) F. B. Daniel and E. J. Behrman, *J. Am. Chem. Soc.*, **97**, 7352 (1975).
(33) F. B. Daniel and E. J. Behrman, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **33**, 1538 (1974); Abstracts, 166th National Meeting of the American Chemical Society, Chicago, Aug. 3, 1973, BIOL-026.
(34) L. R. Subbaraman, J. Subbaraman, and E. J. Behrman, *Inorg. Chem.*, 11, 2621 (1972).
(35) L. R. Subbaraman, J. Subbaraman, and E. J. Behrman, *Bioinorg. Chem.*, 1, 35 (1971).
(36) E. J. Behrman, L. R. Subbaraman, and J. Subbaraman, Symposium on Oxidation, 2nd Northeast Regional Meeting, American Chemical Society, Providence, RI, Oct., 1970.
(37) C-H. Chang, M. Beer, and L. G. Marzilli, *Biochemistry*, **16**, 33 (1977).
(38) J. J. Rosa and P. B. Sigler, *Biochemistry*, **13**, 5102 (1974).
(39) S. Neidle and D. I. Stuart, *Biochim. Biophys. Acta*, **416**, 226 (1976).
(40) T. J. Kistenmacher, L. G. Marzilli, and M. Rossi, *Bioinorg. Chem.*, **6**, 347 (1976).
(41) T. Prangé and C. Pascard, *Acta Crystallogr., Sect. B*, **33**, 621 (1977).
(42) J. F. Conn, J. J. Kim, F. L. Suddath, P. Blattman, and A. Rich, *J. Am. Chem. Soc.*, **96**, 7152 (1974).
(43) G. F. Bahr, *Exp. Cell. Res.*, **7**, 457 (1953).
(44) K. Burton, *Biochem. J.*, **104**, 686 (1967).
(45) K. Burton, N. F. Varney, and P. C. Zamecnik, *Biochem. J.*, **99**, 29C (1966).
(46) P. J. Highton, B. L. Murr, F. Shafa, and M. Beer, *Biochemistry*, **7**, 825 (1968).
(47) C. Paal and C. Amberger, *Chem. Ber.*, **40**, 1378 (1907).
(48) L. R. Subbaraman, J. Subbaraman, and E. J. Behrman, *J. Org. Chem.*, **38**, 1499 (1973).
(49) A. B. Nikol'skii, Yu. I. D'yachenko, and L. Myund, *Russ. J. Inorg. Chem.*, **19**, 1368 (1974).
(50) A. J. Nielson and W. P. Griffith, *J. Chem. Soc., Dalton Trans.*, 1084 (1979).
(51) C-H. Chang, W. R. Midden, J. S. Deetz, and E. J. Behrman, *Inorg. Chem.*, **16**, 1364 (1979).
(52) L. Atovmyan and O. A. L'yachenko, *J. Struct. Chem. (Engl. Transl.)*, **15**, 733 (1975).
(53) L. Atovmyan and O. A. L'yachenko, *J. Struct. Chem. (Engl. Transl.)*, **8**, 143 (1967).
(54) W. D. Lloyd, B. J. Navarette, and M. F. Shaw, *Synthesis*, 610 (1972).
(55) Yu. I. D'yachenko, *Sovrem. Probl. Khim.*, 17, (1973); *Chem. Abstr.*, **81**, 130291d (1974).
(56) M. J. Cleare, P. C. Hydes, W. P. Griffith, and M. J. Wright, *J. Chem. Soc., Dalton Trans.*, 941 (1977).
(57) M. J. Wright, Ph. D. Thesis, University of London, 1977.
(58) M. L. Hair and P. L. Robinson, *J. Chem. Soc.*, 106 (1958).
(59) M. L. Hair and P. L. Robinson, *J. Chem. Soc.*, 2775 (1960).
(60) L. Tschugajeff and J. Tschernjajeff, *Z. Anorg. Chem.*, **172**, 216 (1928).
(61) J. S. Hanker, D. K. Romanovicz, and H. A. Padykula, *Histochemistry*, **49**, 263 (1976).
(62) J. S. Hanker, D. K. Romanovicz, and H. G. Moore III, *J. Cell. Biol. Abstr.*, **63**, 262 (1974).
(63) P. C. Hydes and M. J. Cleare, German Offen. 2 630 823, 1977; *Chem. Abstr.*, **86**, P102806 (1977).
(64) W. P. Griffith, "The Chemistry of the Rarer Platinum Metals", Interscience, New York, 1967.
(65) W. P. Griffith, A. C. Skapski, K. A. Woode, and M. J. Wright, *Inorg. Chim. Acta*, L413 (1978).
(66) B. A. Cartwright, W. P. Griffith, M. Schröder, and A. C. Skapski, *J. Chem. Soc., Chem. Commun.*, 853 (1978).
(67) M. Schröder, A. J. Nielson, and W. P. Griffith, *J. Chem. Soc., Dalton Trans.*, 1607 (1979).
(68) N. A. Milas, S. Sussman, and H. S. Mason, *J. Am. Chem. Soc.*, **61**, 1844 (1939).
(69) Y. F. Shealy and J. D. Clayton, *J. Am. Chem. Soc.*, **91**, 3075 (1969).
(70) M. Ohno and S. Torimitsu, *Tetrahedron Lett.*, 2259 (1964).
(71) N. A. Milas and L. S. Maloney, *J. Am. Chem. Soc.*, **62**, 1841 (1940).
(72) M. Schröder and W. P. Griffith, *J. Chem. Soc., Dalton Trans.*, 1599 (1978).
(73) R. Criegee, W. Hörauf, and W. Schellenberg, *Chem. Ber.*, **86**, 126 (1953).
(74) B. A. Cartwright, W. P. Griffith, M. Schröder, and A. C. Skapski, unpublished work.
(75) D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 903 (1954).
(76) J. Castell, G. D. Meakins, and R. Swindells, *J. Chem. Soc.*, 2917 (1962).
(77) D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 2085 (1956).
(78) A. J. Nielson and W. P. Griffith, *J. Histochem. Cytochem.*, **26**, 138 (1978).
(79) A. J. Nielson and W. P. Griffith, *J. Chem. Soc., Dalton Trans.*, 1501 (1978).
(80) M. B. Hursthouse, T. Fram, L. New, W. P. Griffith, and A. J. Nielson, *Transition Met. Chem.*, **3**, 255 (1978).
(81) R. V. Casciani and E. J. Behrman, *Inorg. Chim. Acta*, **28**, 69 (1978).
(82) Y. A. Zhdanov, L. A. Urzlova, and Z. I. Glebova, *Zh. Obshch. Khim.*, **44**, 2049 (1974); *Chem. Abstr.*, **82**, 17017 (1975).
(83) M. Uskoković, M. Gut, E. Trachtenberg, W. Klyne, and R. I. Dorfman, *J. Am. Chem. Soc.*, **82**, 4965 (1960).
(84) H. Wieland and H. Behringer, *Justus Liebigs Ann. Chem.*, **549**, 209 (1941).
(85) H. Reich, M. Sutter, and T. Reichstein, *Helv. Chim. Acta*, **23**, 170 (1940).
(86) A. Serini and W. Logemann, *Chem. Ber.*, **71**, 1362 (1938).
(87) A. Serini, W. Logemann, and H. Hildebrand, *Chem. Ber.*, **72**, 391 (1939).
(88) A. Butenandt, J. Schmidt-Thomé, and H. Paul, *Chem. Ber.*, **72**, 1112 (1939).
(89) H. Wieland and W. Benend, *Chem. Ber.*, **75**, 1708 (1942).
(90) G. M. Badger and K. R. Lynn, *J. Chem. Soc.*, 1726 (1950).
(91) H. B. Henbest, W. R. Jackson, and B. C. G. Robb, *J. Chem. Soc. B*, 803 (1966).
(92) J. Booth, E. Boyland, and E. E. Turner, *J. Chem. Soc.*, 1188 (1950).
(93) K. Tanaka, *J. Biol. Chem.*, **247**, 7465 (1972).
(94) W. S. Johnson, M. Neeman, S. P. Birkeland, and N. A. Fedonik, *J. Am. Chem. Soc.*, **84**, 989 (1962).
(95) J. W. Cook and R. Schoental, *J. Chem. Soc.*, 170 (1948). J. W. Cook and R. Schoental, *Nature (London)*, **161**, 237 (1948).
(96) G. M. Badger, *J. Chem. Soc.*, 456 (1949).
(97) O. Perrin-Roussel, F. Périn, and P. Jacquignon, *Tetrahedron Lett.*, 1227 (1974).
(98) P. Jacquignon, O. Perrin-Roussel, F. Perrin, O. Chalvet, J. M. Lhoste, A. Mathieu, B. Saperas, P. Viallet, and F. Zajdela, *Can, J. Chem.*, **53**, 1670 (1975).
(99) H. Yagi, G. M. Holder, P. M. Dansette, O. Hernandez, H. J. C. Yeh, R. A. Le Mahieu, and D. M. Jerina, *J. Org. Chem.*, **41**, 977 (1976).
(100) J. V. Silverton, P. M. Dansette, and D. M. Jerina, *Tetrahedron Lett.*, 1557 (1976).
(101) R. Criegee, E. Höger, G. Huber, P. Kruck, F. Marktscheffel, and H. Schellenberger, *Justus Liebigs Ann. Chem.*, **599**, 81 (1956).
(102) D. M. Vyas and G. W. Hay, *Can. J. Chem.*, **53**, 1362 (1975).
(103) B. E. Cross, *J. Chem. Soc. C*, 501 (1966).
(104) J. A. Elvidge and F. S. Spring, *J. Chem. Soc.*, 2935 (1949).
(105) B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton, and T. J. Dietsche, *J. Am. Chem. Soc.*, **100**, 3416 (1978).
(106) P. D. Bartlett and M. Stiles, *J. Am. Chem. Soc.*, **77**, 2806 (1955).
(107) G. Wolczunowicz, L. Bors, F. Cocu, and T. Pasternak, *Helv. Chim. Acta*, **53**, 2288 (1970).
(108) L. H. Zalkow, R. N. Harris III, and D. Van Derveer, *J. Chem. Soc., Chem. Commun.*, 420 (1978).
(109) A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Am. Chem. Soc.*, **75**, 3212 (1953).
(110) A. C. Cope and A. S. Mehta, *J. Am. Chem. Soc.*, **86**, 5626 (1964).
(111) G. R. Krow and J. Reilly, *Tetrahedron Lett.*, 3129 (1972).
(112) R. F. Heldeweg, H. Hogeveen, and E. P. Schuddle, *J. Org. Chem.*, **43**, 1912 (1978).
(113) F. Piozzi and M. Cecere, *Atti. Accad. Nazl. Lincei, Rend. Cl. Sci. Fis., Mat. Nat.*, **28**, 639 (1960); *Chem. Abstr.*, **55**, 9372c (1961).
(114) B. F. G. Johnson, J. Lewis, D. G. Parker, and R. S. Postle, *J. Chem. Soc., Dalton Trans.*, 794 (1977).
(115) T. P. Murray, U. P. Singh, and R. K. Brown, *Can. J. Chem.*, **49**, 2132 (1971).
(116) R. M. Srivastava and R. K. Brown, *Can. J. Chem.*, **49**, 1339 (1971).
(117) R. B. Woodward, F. Sondheimer, D. Taub, K. Hemsler, and W. M. McLamone, *J. Am. Chem. Soc.*, **74**, 4223 (1952).
(118) R. B. Woodward, F. Sondheimer, and D. Taub, *J. Am. Chem. Soc.*, **73**, 4057 (1951).
(119) R. W. Freerksen, M. L. Raggio, C. A. Thomas, and D. S. Watt, *J. Org. Chem.*, **44**, 702 (1979).
(120) L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 2443 (1949).
(121) L. H. Sarett, *J. Am. Chem. Soc.*, **70**, 1454 (1948).
(122) R. Hirschmann, G. A. Bailey, R. Walker, and J. M. Chermerda, *J. Am. Chem. Soc.*, **81**, 2822 (1959).
(123) V. Prelog, L. Ruzicka, and P. Wieland, *Helv. Chim. Acta*, **28**, 250 (1945).
(124) A. D. Tait, *Steroids*, **20**, 531 (1972).
(125) T. Kubota and F. Hayashi, *Tetrahedron*, **23**, 995 (1967).
(126) J. Baran, *J. Org. Chem.*, **25**, 257 (1960).
(127) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littel, S. M. Stolar, L. I. Feldman, and R. H. Blank, *J. Am. Chem. Soc.*, **78**, 5693 (1956).
(128) S. H. Goh and S. G. Harvey, *J. Am. Chem. Soc.*, **95**, 242 (1973).
(129) P. Dansette and D. M. Jerina, *J. Am. Chem. Soc.*, **96**, 1224 (1974).
(130) D. I. Railton, *Z. Pflanzenphysiol.*, **81**, 323 (1977); *Chem. Abstr.*, **86**, 86204e (1977).
(131) H. Fischer and H. Eckoldt, *Justus Liebigs Ann. Chem.*, **544**, 138 (1940).
(132) M. J. S. Dewar, *Ind. Chim. Belge*, **15**, 181 (1950); *Chem. Zentralbl.*, **1**, 1716 (1951).
(133) M. J. S. Dewar and H. C. Longuet-Higgins, *Proc. R. Soc. London, Ser. A*, **214**, 482 (1952).
(134) M. J. S. Dewar, *J. Am. Chem. Soc.*, **74**, 3341 (1952).
(135) K. B. Sharpless, A. Y. Teranishi, and J. E. Bäckvall, *J. Am. Chem. Soc.*, **99**, 3120 (1977).
(136) M. Zelikoff and H. A. Taylor, *J. Am. Chem. Soc.*, **72**, 5039 (1950).
(137) K. B. Sharpless and D. R. Williams, *Tetrahedron Lett.*, 3045 (1975).
(138) N. A. Milas and M. I. Iliopulos, *J. Am. Chem. Soc.*, **81**, 6089 (1959).
(139) A. F. Clifford and C. S. Kobayashi, *Inorg. Synth.*, **6**, 204 (1960).

(140) A. F. Clifford and C. S. Kobayashi, Abstracts of the 130th National Meeting of the American Chemical Society, Atlantic City, NJ, Sept. 1956, No. 50R.
(141) K. B. Sharpless, D. W. Patrick, L. K. Truesdale, and S. A. Biller, *J. Am. Chem. Soc.*, **97**, 2305 (1975).
(142) A. O. Chong, K. Oshima, and K. B. Sharpless, *J. Am. Chem. Soc.*, **99**, 3420 (1977).
(143) D. W. Patrick, L. K. Truesdale, S. A. Biller, and K. B. Sharpless, *J. Org. Chem.*, **43**, 2628 (1978).
(144) B. L. Chandwani and D. G. Menghani, *Z. Naturforsch. B*, **33**, 291 (1978).
(145) R. E. Erickson and R. L. Clarke, *Tetrahedron Lett.*, 3997 (1969).
(146) M. Beer, S. Stern, D. Carmalt, and K. H. Mohlhenrich, *Biochemistry*, **5**, 2283 (1966).
(147) K. Burton and W. T. Riley, *Biochem. J.*, **98**, 70 (1966).
(148) R. L. Clarke and E. J. Behrman, *Inorg. Chem.*, **14**, 1425 (1975).
(149) J. C. Bavay, G. Nowogrocki, and G. Tridot, *Bull. Soc. Chim. Fr.*, 2026 (1967).
(150) F. Solymosi and J. Csik, *Chemist-Analyst*, **49**, 12 (1960).
(151) J. F. Cairns and H. L. Roberts, *J. Chem. Soc. C*, 640 (1968).
(152) R. L. Clarke and E. J. Behrman, *Bioinorg. Chem.*, **5**, 359 (1976).
(153) J. C. Bavay, J. Nicole, G. Nowogrocki, and G. Tridot, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **266**, 1293 (1968).
(154) J. C. Bavay, G. Nowogrocki, and G. Tridot, *Bull. Soc. Chim. Fr.*, 2030 (1967).
(155) J. P. Beaufils, M. Hellin, and F. Coussemant, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **266**, 496 (1968).
(156) G. Nowogrocki and G. Tridot, *Bull. Soc. Chim. Fr.*, 688 (1965).
(157) K. B. Sharpless and K. Akashi, *J. Am. Chem. Soc.*, **98**, 1986 (1976).
(158) K. Akashi, R. E. Palermo, and K. B. Sharpless, *J. Org. Chem.*, **43**, 2063 (1978).
(159) J. W. Cook and R. Schoental, *J. Chem. Soc.*, 47 (1950).
(160) N. A. Milas, P. F. Kurz, and W. P. Anslow, *J. Am. Chem. Soc.*, **59**, 543 (1937).
(161) L. Tschugajeff and I. Bikerman, *Z. Anorg. Chem.*, **172**, 229 (1928).
(162) G. B. Payne, *World Pet. Congr., Proc., 5th*, **4**, 185 (1959).
(163) L. J. Csányi, *Acta Chim. Acad. Sci. Hung.*, **21**, 35 (1959); *Chem. Abstr.*, **54**, 11672c (1960).
(164) N. A. Milas, in "The Chemistry of Petroleum Hydrocarbons", Vol. II, B. T. Brookes, Ed., Reinhold, New York, 1955, Chapter 37.
(165) C. J. Norton and R. E. White, *Adv. Chem. Ser.*, **No. 51**, 1 (1965).
(166) N. A. Milas, J. H. Trepagnier, J. T. Nolan, and M. I. Illiopulos, *J. Am. Chem. Soc.*, **81**, 4730 (1959).
(167) C. J. Norton, U.S. Patent 3 335 174, 1967; *Chem. Abstr.*, **67**, 108240a (1967).
(168) L. N. Owen and P. N. Smith, *J. Chem. Soc.*, 4035 (1952).
(169) F. G. Oberender and J. A. Dixon, *J. Org. Chem.*, **24**, 1226 (1959).
(170) R. Daniels and J. L. Fischer, *J. Org. Chem.*, **28**, 320 (1963).
(171) A. Cope, S. W. Fenton, and C. F. Spencer, *J. Am. Chem. Soc.*, **74**, 5884 (1952).
(172) J. D. Roberts and C. W. Sauer, *J. Am. Chem. Soc.*, **71**, 3925 (1949).
(173) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).
(174) A. Butenandt and H. Wolz, *Chem. Ber.*, **71B**, 1483 (1938).
(175) J. F. Eastham, G. B. Miles, and C. A. Krauth, *J. Am. Chem. Soc.*, **81**, 3114 (1959).
(176) J. A. Hogg, F. H. Lincoln, R. W. Jackson, and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955).
(177) K. Miescher and J. Schmidlin, *Helv. Chim. Acta*, **33**, 1840 (1950).
(178) A. Banaszek and A. Zamojski, *Carbohydr. Res.*, **25**, 453 (1972).
(179) J. Y. Savoie and P. Brassard, *Can. J. Chem.*, **49**, 3515 (1971).
(180) M. Mugdan and D. P. Young, *J. Chem. Soc.*, 2988 (1949).
(181) R. Schliebs and H. D. Black, German Offen. 2602646, 1977; *Chem. Abstr.*, **87**, P168 198 (1977).
(182) J. Boerseken, *Recl. Trav. Chim. Pays-Bas*, **41**, 199 (1922).
(183) W. A. Waters, *Annu. Rep. Progr. Chem.*, **42**, 152 (1945).
(184) G. Braun, *J. Am. Chem. Soc.*, **51**, 228 (1929).
(185) G. Braun, *J. Am. Chem. Soc.*, **52**, 3188 (1930).
(186) B. M. Trost, T. M. Tinko, and J. L. Stanton, *J. Chem. Soc., Chem. Commun.*, 436 (1978).
(187) P. A. Grieco, Y. Ohfune, Y. Yokoyama, and W. Owens, *J. Am. Chem. Soc.*, **101**, 4749 (1979).
(188) W. Kruse, *J. Chem. Soc., Chem. Commun.*, 1610 (1968).
(189) E. Zbiral and M. Rasberger, *Tetrahedron*, **24**, 2419 (1968).
(190) R. Lespieau, *Adv. Carbohydr. Chem.*, **2**, 107 (1946).
(191) R. Lespieau and J. Wiemann, *Bull. Soc. Chim.*, **53**, 1107 (1933).
(192) R. Lespieau, *C. R. Hebd. Seances Acad. Sci., Ser. B*, **203**, 92 (1936).
(193) R. Lespieau and J. Wiemann, *C. R. Hebd. Seances Acad. Sci., Ser. B*, **194**, 1946 (1932).
(194) J. Wiemann, *Ann. Chim. (Paris)*, **5**, 267 (1936).
(195) K. Wiesner, K. K. Chan, and C. Dermeson, *Tetrahedron Lett.*, **33**, 2893 (1965).
(196) N. A. Milas and E. M. Terry, *J. Am. Chem. Soc.*, **47**, 1412 (1925).
(197) M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, 315 (1949).
(198) J. W. E. Glattfield and J. W. Chittum, *J. Am. Chem. Soc.*, **55**, 3663 (1933).
(199) J. W. E. Glattfield and S. Woodruff, *J. Am. Chem. Soc.*, **49**, 2309 (1927).
(200) Th. Posternak and H. Friedl, *Helv. Chim. Acta*, **36**, 251 (1953).
(201) I. Ernest, *Collect. Czech. Chem. Commun.*, **29**, 266 (1964).
(202) L. Bláha, J. Weichet, J. Žváček, S. Šmolík, and B. Kakáč, *Collect. Czech. Chem. Commun.*, **25**, 237 (1960).
(203) E. M. Terry and N. A. Milas, *J. Am. Chem. Soc.*, **48**, 2647 (1926).
(204) H. A. Anderson and R. H. Thomson, *J. Chem. Soc. C*, 2152 (1967).
(205) N. A. Milas, *J. Am. Chem. Soc.*, **49**, 2005 (1927).
(206) G. Braun, *J. Am. Chem. Soc.*, **52**, 3176 (1930).
(207) J. W. E. Glattfield and E. Rietz, *J. Am. Chem. Soc.*, **56**, 974 (1940).
(208) (a) G. Braun, *J. Am. Chem. Soc.*, **54**, 1133 (1932); (b) W. Tubiana and B. Waegell, *Angew. Chem., Int. Ed. Engl.*, **11**, 640 (1972).
(209) R. C. Kelly and I. Schletter, *J. Am. Chem. Soc.*, **95**, 7156 (1973).
(210) G. Büchi, E. Demole, and A. F. Thomas, *J. Org. Chem.*, **38**, 123 (1973).
(211) S. S. Medvedev and E. N. Alekseeva, *Papers Karpov. Chem. Inst. Bach., Mem. Vol.*, 128 (1927); *Chem. Abstr.*, **22**, 3133^1 (1928).
(212) K. Wiesner and J. Santroch, *Tetrahedron Lett.*, **47**, 5939 (1966).
(213) R. Behrend and G. Heyer, *Justus Liebigs Ann. Chem.*, **418**, 294 (1919).
(214) V. Van Rheenan, R. C. Kelly, and D. Y. Cha, *Tetrahedron Lett.*, 1973 (1976).
(215) H. Muxfeldt and G. Hardtmann, *Justus Liebigs Ann. Chem.*, **669**, 113 (1963).
(216) D. A. Prins and T. Reichstein, *Helv. Chim. Acta*, **25**, 300 (1942).
(217) A. Byers and W. J. Hickinbottom, *J. Chem. Soc.*, 1328 (1948).
(218) G. E. McCasland, S. Turuta, and L. J. Durham, *J. Org. Chem.*, **33**, 2835 (1968).
(219) M. N. Sheng and W. A. Mameniskis, U.S Patent 4 049 724, 1977; *Chem. Abstr.* **88**, P22130 (1978).
(220) R. Bucourt, U.S. Patent 3 383 385, 1968.
(221) W. P. Schneider and A. V. McIntosh, U.S. Patent 2 769 824.
(222) E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J. L. Gras, *J. Am. Chem. Soc.*, **100**, 8031 (1978).
(223) S. Danishefsky, M. Hirama, K. Gombatz, T. Harayana, E. Berman, and P. Schuda, *J. Am. Chem. Soc.*, **100**, 6536 (1978).
(224) J. E. McMurry, A. Andrus, G. M. Ksander, J. H. Musser, and M. A. Johnson, *J. Am. Chem. Soc.*, **101**, 1330 (1979).
(225) S. C. Patai and Y. Sriramulu, *Indian J. Chem., Sect. A*, **16A**, 74 (1978).
(226) G. P. Panigrahi and P. K. Misro, *Indian J. Chem.*, **16A**, 201 (1978).
(227) R. Pappo, D. S. Allen, P. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).
(228) L. A. Mitscher, G. W. Clarke III, and P. B. Hudson, *Tetrahedron Lett.*, 2553 (1978).
(229) S. H. Graham and A. J. S. Williams, *J. Chem. Soc. C*, 655 (1966).
(230) R. Willstätter and E. Sonnenfeld, *Chem. Ber.*, **46**, 2952 (1913).
(231) J. Périchon, S. Palous, and R. Buvet, *Bull. Soc. Chim. Fr.*, 982 (1963).
(232) Celanese Corporation, British Patent 1 028 940, 1966.
(233) F. M. C. Corporation, Netherlands Appl. 74, 11, 150, 1976; *Chem. Abstr.*, **86**, P4925 (1976).
(234) T. A. Foglia, P. A. Barr, A. J. Malloy, and M. J. Costanzo, *J. Am. Oil Chem. Soc.*, **54**, 870 A (1977).
(235) E. I. du Pont de Nemours and Co., British Patent 1 138 131, 1968.
(236) H. S. Singh, V. P. Singh, J. M. Singh, and P. N. Srivastava, *J. Catal.*, **49**, 135 (1977); *Chem. Abstr.*, **87**, 151426 (1977).
(237) S. S. Srivastava and P. C. Mathur, *J. Indian Chem. Soc.*, **53**, 576 (1976).
(238) H. S. Singh, V. P. Singh, J. M. Singh, and P. N. Srivastava, *Indian J. Chem., Sect. A*, **15A**, 520 (1977).
(239) D. Mohan and Y. K. Gupta, *J. Chem. Soc., Dalton Trans.*, 1085 (1977).
(240) S. K. Upadhyay and M. C. Agrawal, *Indian J. Chem., Sect. A*, **15A**, 416 (1977).
(241) S. K. Upadhyay and M. C. Agrawal, *Indian J. Chem., Sect. A*, **15A**, 709 (1977).
(242) P. S. Radhakrishnamurti and S. C. Padhi, *Curr. Sci.*, **46**, 517 (1977); *Chem. Abstr.*, **87**, 183 721 (1977).
(243) P. S. Radhakrishnamurti and B. Sahu, *Indian J. Chem., Sect. A*, **15A**, 700 (1977).
(244) L. Bassignani, A. Brandt, V. Caciagli, and L. Re, *J. Org. Chem.*, **43**, 4245 (1978).
(245) W. P. Griffith and M. Schröder, unpublished results.
(246) N. A. Milas, U.S. Patent 2 347 358, 1944; *Chem. Abstr.*, **39**, $P84^3$ (1945).