Organic Syntheses by Oxidation with Metal Compounds

Edited by

W. J. Mijs

and

C. R. H. I. de Jonge

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Akzo Research
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PREFACE

This book is concerned with the synthetic aspects of oxidation reactions involving metal compounds, which are readily available or easy to prepare. The sequence followed in the chapters is as follows: a general introduction, a limited treatment of reaction mechanisms to serve as a basis for synthesis, and scope and limitations of the oxidant system, mostly in terms of substrate and product classes. Finally, at the end of each chapter, representative synthetic procedures are given together with relevant experimental considerations.

A general table is included as an appendix. This contains substrate classes and resulting product classes, referring to the oxidative procedures in the chapters. The table provides the synthetic organic chemist with a quick overview of oxidation possibilities with metal-containing oxidants, enabling him to select the right method for his purpose.

The editors hope that not only organic research chemists in industry and at universities, but also advanced undergraduate and graduate students in organic chemistry, will find this book a useful guide in the design, understanding, and practical performance of oxidative organic syntheses.

The editors are grateful to the authors not only for their contributions, containing interesting new developments in oxidation chemistry, but also for the way they fitted the text into the general framework given for the book. Their suggestions and comments are gratefully acknowledged. Thanks are also due to Mrs. A. I. Rohnström-Ouwejan, secretary to the editors, for her administrative support.

W. J. Mijs and C. R. H. I. de Jonge

Arnhem, The Netherlands

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Organic Syntheses by Oxidation with Metal Compounds

1

Oxidation by Vanadium Compounds

Fillmore Freeman

1. INTRODUCTION

According to IUPAC recommendations the abbreviation Va(V) is used to indicate pentavalent vanadium.

The redox potential of the vanadium(V)–vanadium(IV) couple increases with acidity in the region from pH 1.5 to 2 *M* acid.[1–9] The vanadium(IV)–vanadium(III) couple (E_0) is 0.36 V[8]. The potential for the vanadium(V)–vanadium(III) couple is 0.68 V and is not likely to be involved in many organic oxidations.

$$VO_2^+ + 2H^+ + e \rightleftarrows VO^{2+} + H_2O \tag{1}$$

Compounds of pentavalent vanadium are generally considered as one-electron oxidants. The reactive species in aqueous solution is the VO_2^+ cation, which is stable in acid media and unstable in neutral media.[1–9] In acidic solution, vanadium can exist in four oxidation states, i.e., violet $V(H_2O)_6^{2+}$, dark blue $V(H_2O)_6^{3+}$, bright blue VO^{2+}, and yellow Va(V).

$$VO_2^+{}_{aq} + H_3O^+ \rightleftarrows V(OH)_3^{2+}{}_{aq} \tag{2}$$

$$VO(OH)_3^{2+}{}_{aq} + H^+ \rightleftarrows V(OH)_4^+{}_{aq} \tag{3}$$

Vanadium-51 NMR chemical shifts, linewidths, and area ratios have been obtained for various metavanadate ions in aqueous solutions as a function of counterion, pH, and vanadium concentration.[10] Eight vanadium(V) species were identified. In the pH range 7.0–8.5, ^{51}V NMR resonances were observed at 574 ppm ($V_3O_9^{3-}$ and $V_4O_{12}^{4-}$) and 582 ppm ($V_6O_{17}^{4-}$). It was also shown that tetraalkylammonium cations stabilize $V_4O_{12}^{4-}$ species in solution.

The catalysis of organic reactions under homogeneous (soluble metal complexes) and heterogeneous conditions has become a major synthetic tool in the laboratory and in industrial chemistry processes.[11–65] Although fundamental research has become fairly

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sophisticated in some areas of transition metal oxidations, it is still developing in certain areas of vanadium oxidations.

It is of interest to note that a major new application of homogeneous catalysis began in 1967 when Halcal Corporation announced a new synthesis of 1, 2-epoxypropane from the molybdenum catalyzed epoxidation of propene with alkyl hydroperoxides.[56] The epoxidation can be done with a wide variety of olefins and transition metal catalysts (Cr, Mo, Ti, V, Zr). Although the most active catalysts are molybdenum salts and complexes, vanadium compounds are also effective.

It is the purpose of this chapter to provide a description of homogeneous and heterogeneous vanadium oxidations which are synthetically useful or have potential for synthetic use in the laboratory. A variety of selective vanadium catalyzed oxidations which may be developed for laboratory scale synthesis are also included.

2. MECHANISMS

2.1. Alkanes, Alkylaromatics, and Aromatic Compounds

There appears to be very little evidence for direct attack by vanadium compounds on alkanes.[31] Indeed, alkane activation remains one of the most worthwhile challenges to the ingenuity and imagination of the chemist.[41–44]

The vanadium catalyzed oxidation of alkylbenzenes to benzoic acids[45] or to phthalic anhydride[46] proceeds via free radical mechanisms. The rate of oxidation of fluorene and its $1-CH_3$, $2-C_2H_5$, $2-NO_2$, and 2-halo derivatives by vanadium(V) decreases with the increasing dipole moment of the substrate, which is contrary to the theory of Moelwyn–Hughes.[47]

2.2. Carbon–Carbon Double Bonds: Synthesis of Epoxides and Glycols

The oxidation of carbon–carbon double bonds by vanadium compounds has received considerable study.[66–130]

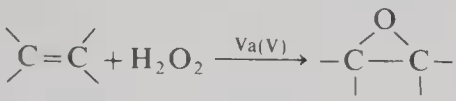
Vanadium(V) oxide,[82] RuO_4, MoO_3, OsO_4, and CrO_3 have been used as catalysts* for the conversion of olefins to epoxides, which can be hydrolyzed to 1,2-glycols under the acidic reaction conditions [Eqs. (5) and (6)].[81–83] Vanadium(V) oxide and other acidic metal oxides (Cr, Mo, Nb, Ta, Th, Ti, U, W, Zr) catalyze the reactions of hydrogen peroxide via the formation of inorganic peroxy acids (**1**; see Chapter 16).[79,80] These peracids (**1**) are hydroxy hydroperoxides which result from the addition of hydrogen peroxide to an M=O

$$MO_3 + H_2O_2 \rightleftharpoons \underset{\mathbf{1}}{\overset{HO}{\underset{O}{}}\!\!\overset{O}{\underset{\|}{}}\!\!M\!-\!O\!-\!OH} \qquad (4)$$

group. Thus, the conjugate base of the peracid (**1**) is an excellent leaving group for nucleophilic displacement. Although inorganic peracids (**1**) closely resemble organic peroxy acids, their peroxidic oxygen atoms are more electrophilic owing to the presence of the oxometal group (M=0).

Although the kinetics of the V_2O_5 catalyzed hydrogen peroxide oxidation of simple olefins have not been investigated, from the studies with SeO_2, MoO_3, and WO_3, and by

* It was shown that the OsO_4 and RuO_4 catalyzed reactions proceeded via a different mechanism than that catalyzed by MoO_3 and WO_3.[115]



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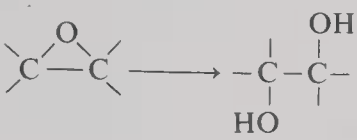
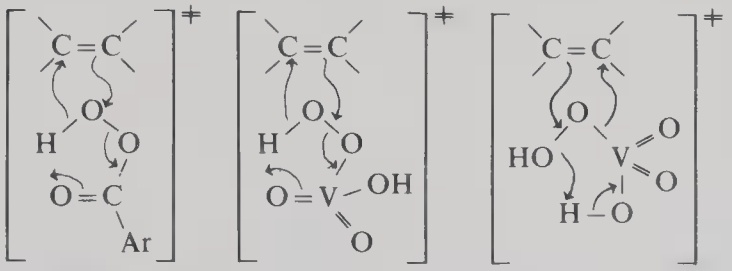


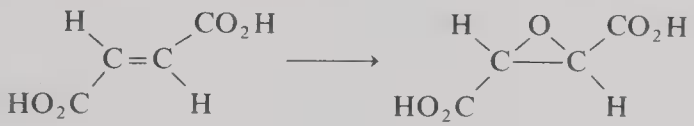
(6)

analogy with the peroxy acid oxidation of alkenes (**2**)[84] and thiosulfinates,[85] one can envisage an activated complex resembling **3**[88–93] or **4**[94] for the inorganic peracid oxidation of double bonds.



2 **3** **4**

The kinetics and mechanisms of epoxidation of fumaric acid (**5**) and maleic acid (**6**) by hydrogen peroxide in the presence of sodium orthovanadate (Na_3VO_4) have been studied.[66]



5 **7**

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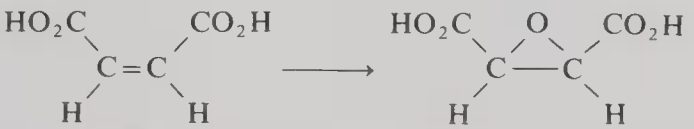
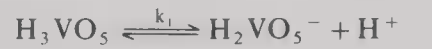


6 **8**

(8)

The epoxidation rate of **5** to (E)-epoxysuccinic acid (**7**) is faster than the epoxidation of **6** to (Z)-epoxysuccinic acid (**8**). The reaction is first order with respect to unsaturated acid and Na_3VO_4, and zero order with respect to H_2O_2. A polar concerted electrophilic rate-determining step is proposed for the epoxidation. Contrary to expectation, the pH dependence of the epoxidation by aqueous H_2O_2 is still different from the molybdate- or tungstate-catalyzed process.[66]

In the above system, H_2O_2 does not bring about epoxidation of **5** or **6** without the catalyst and the catalyst alone fails to bring about epoxidation. Thus, in acidic medium,[67] orthovanadate changes into V_2O_5, which dissolves in aqueous H_2O_2 to give peroxyvanadic acid.[69] Therefore, in the above system,[66] it is presumed that peroxyvanadic acid reacts with **5** or **6** to give epoxides (**7** and **8**) and vanadic acid, which is reconverted to peroxyvanadic acid by H_2O_2. Equations (9)–(11) represent a reasonable mechanistic scheme.[66]



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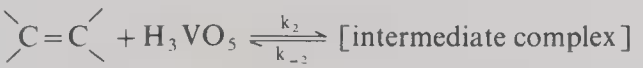

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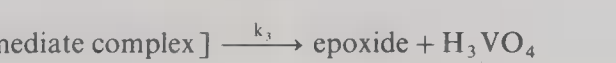
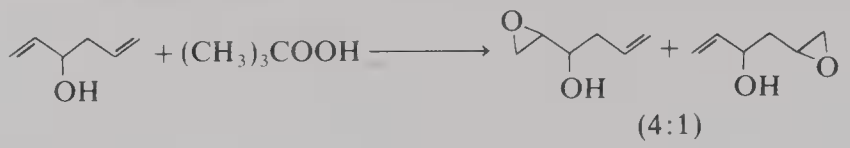


(11)

Vanadium(V) and other metal [Mo(VI), Ti(IV), and W(VI)] complexes facilitate the heterolysis of alkyl hydroperoxides by forming complexes similar to inorganic peroxy acids (**1**). These complexes are effective for the regioselective and stereoselective epoxidation of allylic and homoallylic alcohols.[56,86,87,97,98,115]



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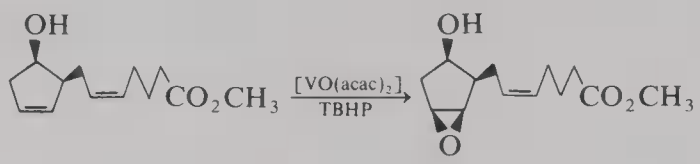

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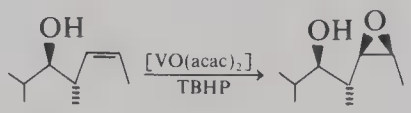
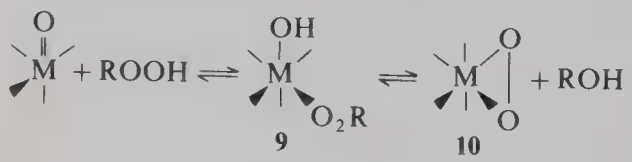


(14)

Although mechanistic details are yet to be established, several reasonable mechanisms have been proposed for oxometal epoxidations. One proposed mechanism involves a peroxometal intermediate [Eqs. (15) and (16)]. Other mechanisms [Eqs. (17)–(21)][100–103] involve the alkyl hydroperoxide directly in the oxygen transfer step. Another mechanism



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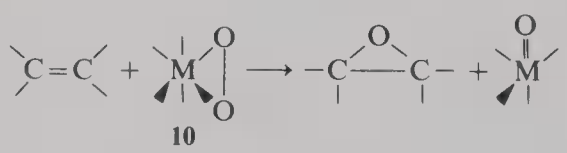
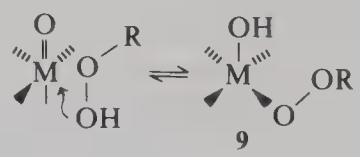


(16)

involving a quasiperoxymetallocyclic intermediate (**15**) has also been proposed [Eqs. (22) and (23)].[104] Oxygen-**18** labeling studies are consistent with activated complexes **11** and



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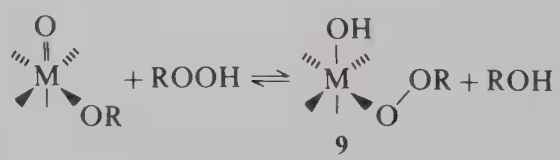

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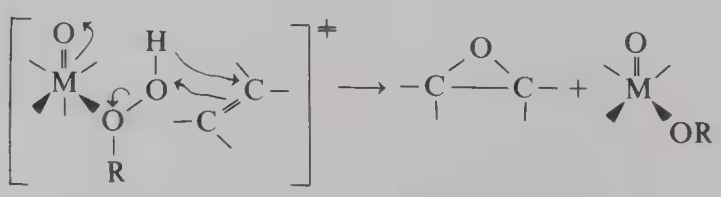

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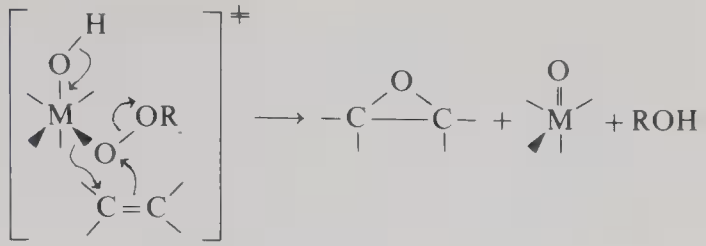

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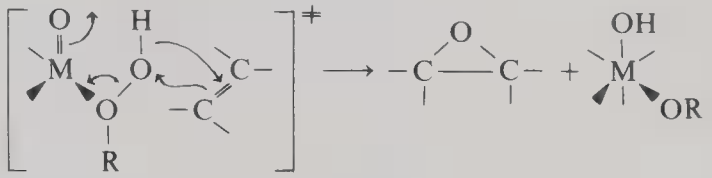

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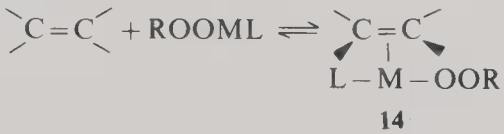
12.[102,103] Evidence has been presented in favor of peroxometal intermediates [**10**, Eqs. (14) and (15)] in the presence of organic bases.[94,114]



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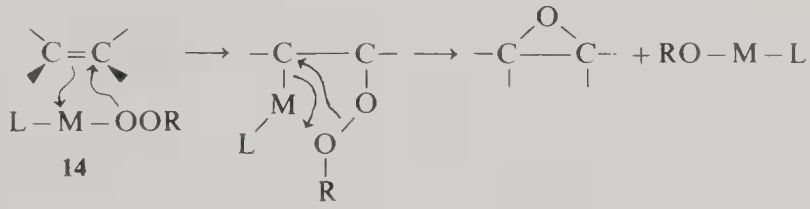
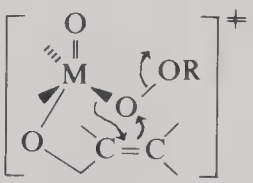


(23)

14 15

Activated complexes **11** and **12** are consistent with the high syn activities and exceptional reactivities observed in the epoxidation of allylic alcohols with vanadium compounds (cf. **16**).[102–113,116,117] A tetrahedral vanadate ester transition state model (**17**) has been proposed to account for the high asymmetric induction involved in the oxidation of



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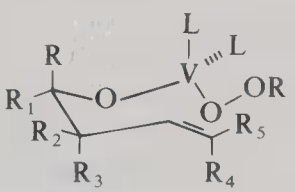
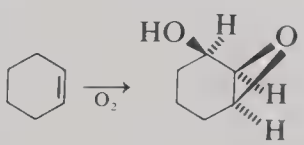


17

homoallylic alcohols.[87] The formation of alcohol–catalyst complexes has a retarding effect on the rate of epoxidation.[100,115]

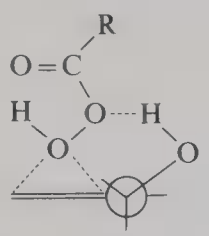
The oxidation of cyclohexene in the presence of $[C_5H_5V(CO)_4]$ gives *cis*-1,2-epoxyclohexen-3-ol (65%) after 10% conversion of the substrate [Eq. (24)].[108] Evidence



(24)

was presented for a reaction pathway which involves the stereoselective epoxidation of 2-cyclohexen-1-ol by cyclohexenyl hydroperoxide. The formation of *cis*-epoxide as the predominant product contrasts sharply with the more conventional results obtained using iron and molybdneum complexes having a similar ligand system.

In contrast to *m*-chloroperoxybenzoic acid (MCPBA), the $VO(acac)_2 - (CH_3)_3COOH$ system epoxidizes cyclic allylic alcohols predominantly to the *syn*-epoxide.[106] However, with conformationally rigid alcohols, the corresponding ketone is formed. A 6,5-membered activated complex (**18**), a 5,5-membered activated complex (**19**), and **20** have been proposed to account for the MCPBA oxidation, *syn*-epoxide formation, and ketone formation, respectively.[106]



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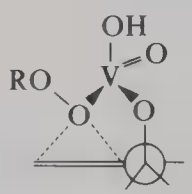

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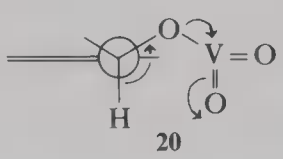


20

2.3. Hydroxy Compounds

2.3.1. Alcohols

The synthetic aspects of the vanadium(V) oxidation of alcohols[130–147] and polyols[148–165] have received limited attention.

The competition between C–H and C–C bond cleavage generally depends on the stability of the radical which is formed and the oxidation potential of the oxidant.[138,139] For example, vanadium(V) selectively oxidizes 2-phenylethanol to phenylmethanal [Eqs. (25)–(27)]. The absence of the α-C–H cleavage product (phenylethanal or

$$C_6H_5CH_2CH_2OH + Va(V) \rightleftharpoons C_6H_5CH_2CH_2OV(V) + H^+ \tag{25}$$

$$C_6H_5CH_2CH_2OV(V) \longrightarrow C_6H_5\dot{C}H_2 + CH_2O + V(IV) \tag{26}$$

$$C_6H_5\dot{C}H_2 + 3Va(V) \xrightarrow{\text{fast}} C_6H_5CHO + 3V(IV) + 3H^+ \tag{27}$$

phenylethanoic acid) suggests that the activated complex for C–C bond fission involves the incipient formation of a benzyl radical by multibond cleavage [Eq. (29)]. Similarly, *tert*-butyl benzyl alcohol gives the *t*-butyl radical and phenylmethanal as the major products and pinacol monomethyl ether affords the relatively stable intermediate α-oxyalkyl radical $(CH_3)_2\dot{C}OCH_3$.[139]

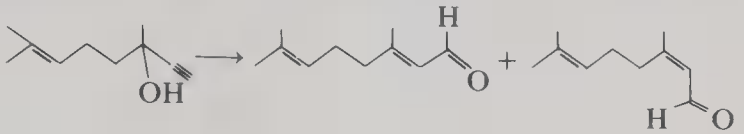
$$C_6H_5CH_2CH_2OH \longrightarrow C_6H_5CH_2\dot{C}HOH \longrightarrow C_6H_5CH_2CHO \longrightarrow C_6H_5CH_2CO_2H \tag{28}$$

$$C_6H_5CH_2CH_2OV(V) \longrightarrow [C_6H_5CH_2 \cdots CH_2O \cdots V]^{\neq} \tag{29}$$

$$C_6H_5\underset{\displaystyle OH}{\underset{|}{C}}HC(CH_3)_3 \xrightarrow{Va(V)} C_6H_5CHO + \dot{C}(CH_3)_3 \tag{30}$$

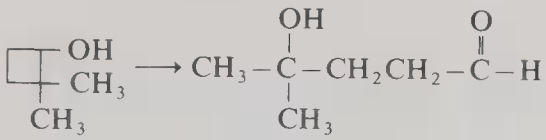
The kinetics of the oxidation of 2-propanol by aquavanadium(V) ions in aqueous perchlorate media[133] and the kinetics of the oxidation of several aliphatic alcohols[134] by vanadium(V) have been reported.

New catalytic systems (silylvanadate catalysts) with silanols or silanediols have been found which effect the isomerization of α-acetylenic alcohols to the corresponding α,β-unsaturated carbonyl compounds with high efficiency.[140] Optimum conditions have been developed for the conversion of dehydrolinalool (**24**) to citral (**25** and **26**).



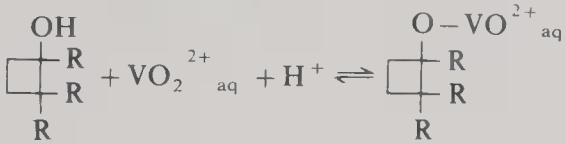
24 **25** **26** (31)

Vanadium(V) in aqueous perchloric acid oxidizes 2-ethylcyclobutanol and 2,2-dimethylcyclobutanol (**27**) to 4-hydroxyhexanal and 4-hydroxy-4-methylpentanal (**28**),

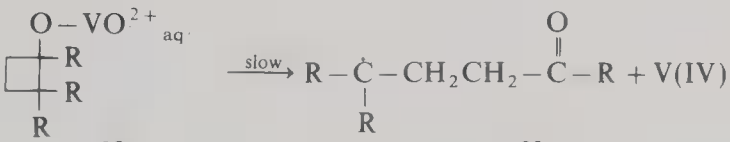


27 **28** (32)

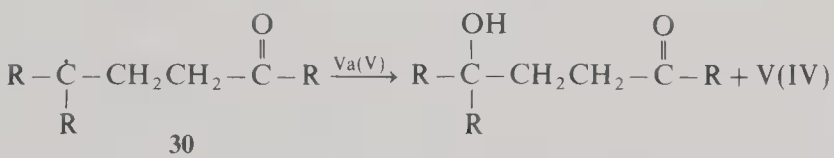
respectively. Ring cleavage occurs at the more substituted carbon atom.[135,136] In $H_2{}^{18}O$, cyclobutanol gives 4-hydroxybutanal with ^{18}O incorporated in the hydroxyl group. The oxidation of the cyclobutanols follows the rate law $v = k[\text{Va(V)}][\text{ROH}]h_0$. (E)- and (Z)-2-ethylcyclobutanol react at the same rate. Methyl cyclobutyl ether is 10^4 times less reactive than cyclobutanol. The overall mechanism of this oxidation is summarized in Eq. (33)–(35).[135]



29 (33)



29 **30** (34)

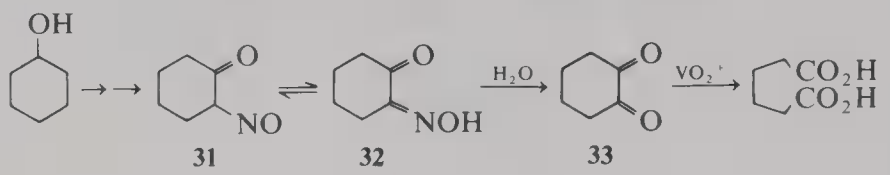


30 (35)

Additional support of the above mechanism includes the observations that 1-methylcyclobutanol reacts about nine times faster than cyclobutanol and 1-deuteriocyclobutanol shows a low deuterium kinetic isotope effect ($k_H/k_D \sim 1.21$). It is also of interest to note that cyclobutanols react with two electron oxidants via carbon–hydrogen bond cleavage to give cyclobutanones and with one electron oxidants [Va(V), Cr(IV), Ce(IV)] via carbon–carbon bond cleavage to give γ-hydroxybutanals.[136]

Although the yields of adipic acid generally exceeds 90%, the mechanisms involved in

the oxidation of a mixture of cyclohexanol and cyclohexanone in a solution of NH_4VO_3 and $Cu(CO_3)_2$ in 45%–50% nitric acid at 70–80°C, in the presence of air, are not known [Eq. (36)].[131,132] It may be that the intermediate diketone (**33**) is stoichiometrically oxidized by two VO_2^+ ions to adipic acid. The vanadium(IV) is reoxidized by nitric acid, which makes the involvement of vanadium catalytic.

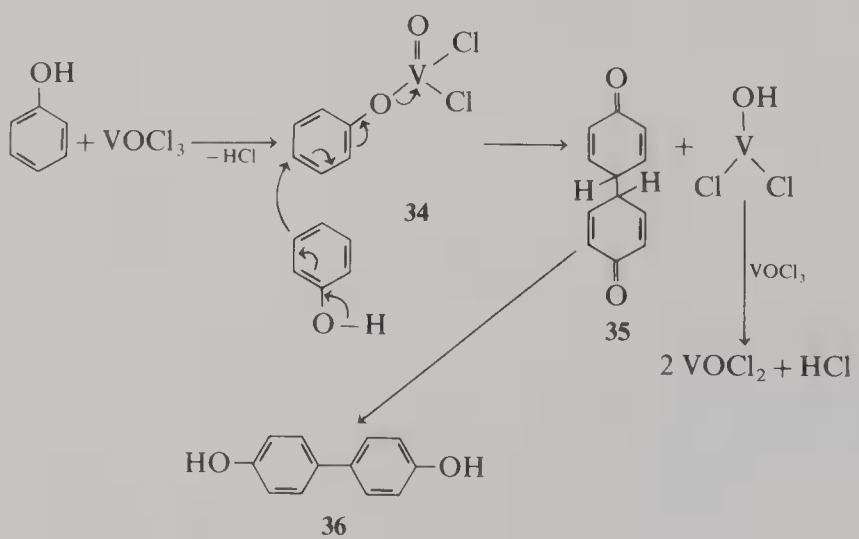


31 **32** **33** (36)

The vanadium(V) oxidation of cyclohexanol follows the kinetic equation[131] $v = k[VO_2^{2+}][ROH][H_3O^+]$. There is evidence for the formation of a complex $[ROH \cdot V(OH)_3^+]$ in acid solution.[132a]

2.3.2. Phenols and Hydroquinones

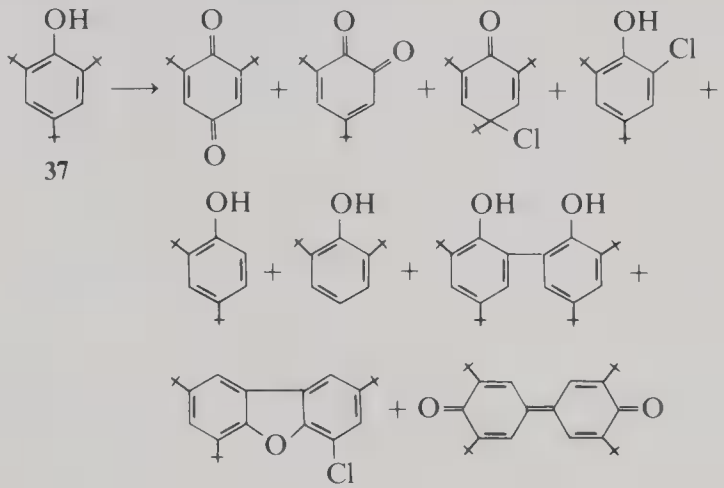
The oxidation of simple phenols and some aniline derivatives with vanadium tetrachloride or vanadium oxychloride affords dimeric products which are coupled predominantly at the para position [Eq. (37)].[166] Phenol itself is not oxidized by $VOCl_3$ under the conditions of vanadium tetrachloride oxidation. The oxidative coupling reaction is believed to occur by a rearrangement of electrons in a complex containing at least two phenoxide (or phenol) residues and at least one metal center. Evidence in support of the existence of vanadium phenoxides was obtained.[166,167] Unfortunately, none of the above data are sufficient to formulate a definitive mechanism for the complex vanadium oxidation of simple phenols. Part of the oxidation pathway may involve a simple NR2 (concerted coupling and electron transfer) mechanism which is nonradical in character [Eq. (37)].[168]



(37)

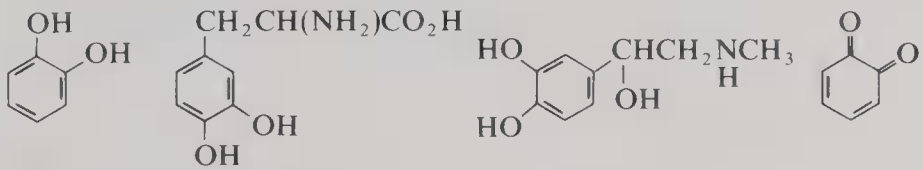
Other kinetic and mechanistic studies of phenol coupling in vanadium(V) oxidations have been reported.[166–170] The oxidation of phenols by vanadium(V) in aqueous solution requires 2 moles of vanadium(V) for each mole of phenol and the order of reaction is variable (between one and two) for vanadium(V) and first order with respect to the concentration of phenol.[169] An intermediate vanadium–phenol complex was proposed as an intermediate. In another study,[170] the rate law $v = k[\text{phenol}][\text{Va(V)}]$ was observed with a rho value of -4.3. These data appear to be consistent with a nonradical mechanism in which an activated complex with considerable positive charge is involved.

The oxidation of 2,4,6-tri-*tert*-butylphenol (**37**) and several other alkyl and halophenols by chromyl chloride and vanadyl chloride has been studied.[171] The products of the $VOCl_3$ oxidation, which depended on the **37**:$VOCl_3$ ratio, are quinones, diphenoquinones, and major amounts of dealkylated phenols and C–C coupled dimers [Eq. (38)]. The product distribution was interpreted in terms of a mechanism involving phenoxy radicals, ligand transfer from metal to radical, and either phenoxonium ions or metallate esters.[171]



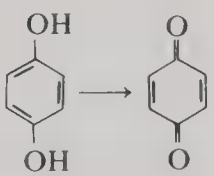
(38)

The kinetics of the oxidation of catechol (**38**) and a series of catechol derivatives, i.e., 1,2,3-trihydroxybenzene (pyrogallol),[174] 1,2,4-trihydroxybenzene,[175] β-(3,4-dihydroxyphenyl)alanine (**39**, L-Dopa),[174] and epinephrine (1-adrenaline, **40**)[163] have been studied. Product identification suggested *o*-benzoquinone (**41**) is the initial product of the Va(V)



38 **39** **40** **41**

oxidation of catechol (**38**).[174] The mechanism most consistent with the data and the chemistry of the catechol system involves reversible formation of a complex between vanadium(V) and the reductant, followed by a rate determining reaction of this complex and vanadium(V).[174] Vanadium(V) rapidly oxidizes quinol (**42**) to 1,4-benzoquinone in perchlorate media.[172,176,177] Stopped-flow techniques showed that the oxidation is an inner-sphere reaction, of first order in [Va(V)] under all conditions, of first order in [**42**] at low acidities, and less than first order in [**42**] at high acidities, and that the rate increases with



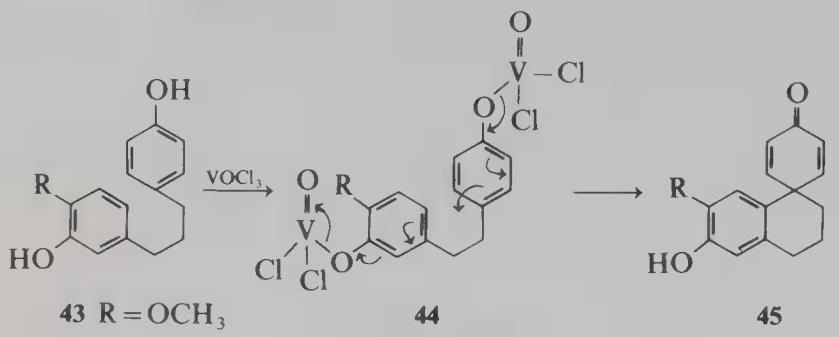
(39)

42

increasing acidity. These data are consistent with the decomposition of two aquovanadium(V) ions which are related by a protonation equilibrium.[172]

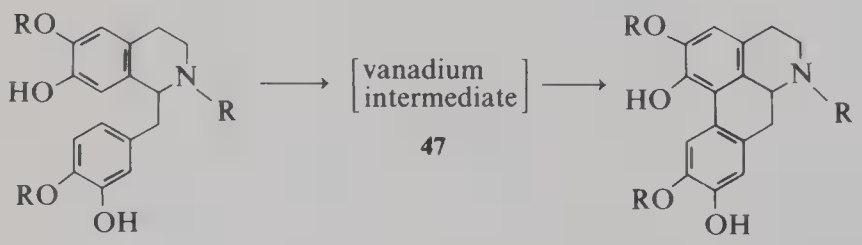
Many phenols can be intramolecularly coupled [cf. Eq. (37), (38)] in moderate to excellent yields with vanadium tetrachloride, vanadium oxytrichloride, or other vanadium compounds.[166,167,178–191] The high yield with vanadium oxychloride has been attributed to

the formation of a phenoxyvanadium intermediate which does not promote the formation of polymeric materials to the same extent as initially added oxidants such as ferricyanide or ferric chloride [Eq. (40); cf. Eq. (37)].[166]



43 R = OCH_3 44 45 (40)

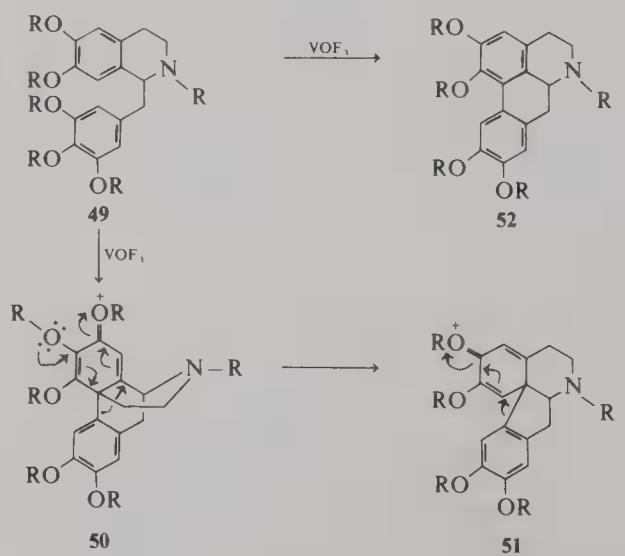
The vanadium oxychloride oxidation of *N*-substituted norreticuline derivatives (**46**) [Eq. (41)] proceeds via the mechanism shown in Eq. (40).[166]



46 47 48 (41)

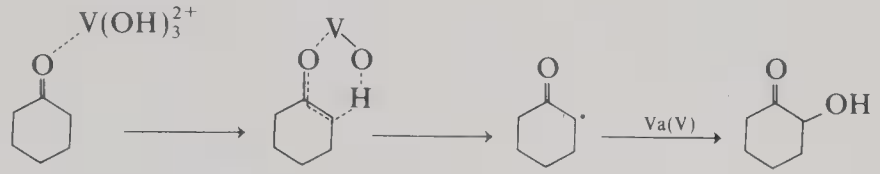
The vanadium oxyfluoride oxidation of laudanosine derivatives (**49**) to glaucine derivatives (**52**) may involve intermediate derivatives of morphinandienone (**50**) and proerythrinadienone (**51**) (Scheme I).[55] The anodic oxidation of **49** in trifluoroacetic acid–trifluoroacetic anhydride also gives **52** (80%).

SCHEME I



2.4. Carbonyl Compounds: Ketones and Quinones

The initial products from the vanadium(V) oxidation of ketones are sometimes difficult to identify owing to their ease of oxidation.[31,48,69,192–205] Ketones with α-hydrogens are readily oxidized by pervanadyl ion. The oxidation of cyclohexanone to α-hydroxycyclohexanone [Eq. (42)] probably involves homolytic decomposition of a cyclic complex (**54**) to yield resonance stabilized radicals.[193–195] A kinetic isotope effect of 4.2 at 50°C is consistent with the proposed mechanism, which suggests initial coordination of the oxidant with the carbonyl oxygen atom [Eq. (42)]. In the coordination process the oxidant behaves as a Lewis acid.



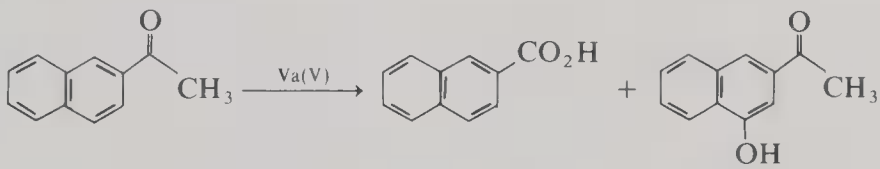
53 **54** (42)

The kinetics of the vanadium(V) oxidation of acetophenone and substituted acetophenones to benzoic acids in perchloric acid solution have been studied.[199–200] The rate expression

$$v = k_3[\text{ketone}][\text{Va(V)}][HClO_4] \tag{43}$$

was obtained.[197] Since the rate increases with increasing acidity, the species $V(OH)_2^{3+}$ and $V(OH)_3^{2+}$ may be important in the oxidation of acetophenones.

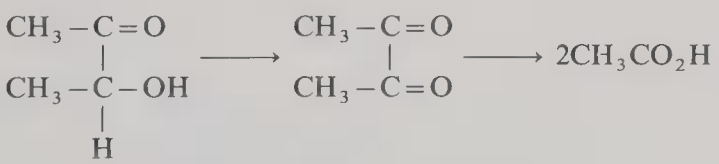
The kinetics of the vanadium(V) oxidation of 1-acetyl- and 2-acetylnaphthalene to the corresponding naphthoic acids and naphthols [Eq. (44)] in aqueous ethanoic acid have been studied.[201] The formation of naphthols suggests attack of oxidant at the double bond of acetylnaphthalene.



(44)

The kinetics and mechanisms of the vanadium(V) oxidation of 4-methylpentan-2-one,[193] cyclopentanone,[195] cycloheptanone,[195] cyclooctanone,[195] aromatic ketones,[196] oxanones,[201] and α-halo ketones[202] have been studied.

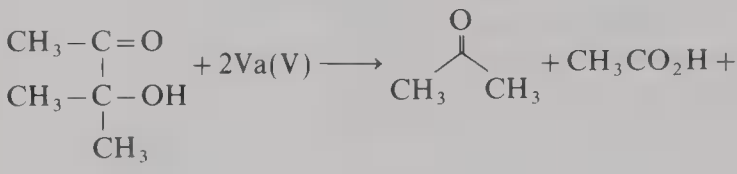
3-Hydroxy-2-butanone (acetoin, **55**) consumes four equivalents of vanadium(V) per mole and gives 2,3-butanedione (biacetyl, **56**), which is oxidized faster than **55**. Ethanal, which is oxidized more slowly than **55**, is not an intermediate. A solvent isotope effect ($k_{D_2O}/k_{H_2O} = 1.3$) was observed. A mechanism involving carbon–hydrogen bond cleavage of **55** is consistent with the observed kinetic and product data.



55 **56** (45)

Vanadium(V) in perchloric acid oxidizes 3-hydroxy-3-methyl-2-butanone (**57**) to

propanone and ethanoic acid. A mechanism involving carbon–carbon bond cleavage of a cyclic complex satisfactorily accounts for the process.[204]



(46)

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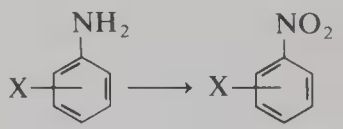
2.5. Nitrogen Compounds

Although the vanadium catalyzed oxidation of nitrogen compounds has not been extensively explored,[170,206–220] several useful synthetic procedures have been described. The kinetics of the vanadium oxidation of amines,[170] piperidinols,[217] benzoylhydrazines,[218] nicotinoyl hydrazide,[218] isonicotinoyl hydrazide,[219] and phenylethanoic acid hydrazide[220] have been studied.

Benzenamine is oxidized by *tert*-butyl hydroperoxide to nitrobenzene in the presence of catalytic quantities of vanadium compounds.[211, 212] The rates correlate reasonably well with

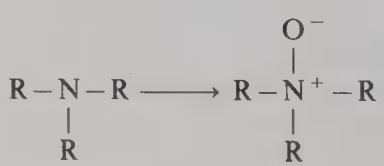


(47)

both Hammett σ constants and Brown–Okamoto σ^+ constants and give rho values of -1.63 and -1.42, respectively. The postulated mechanism involves a rapid complex formation between peroxide and catalyst, preceding a rate-limiting heterolysis of the oxygen–oxygen bond of this complex.[212]

N,N-Disubstituted anilines are oxidatively coupled at the *para* position by vanadium tetrachloride.[166] The mechanism for the coupling is similar to the ones proposed for the reaction of vanadium tetrachloride and phenols [Eqs. (37), (40), (41)].

A novel reaction of tertiary amines with organic hydroperoxides in the presence of vanadium compounds to give excellent yields of amine oxides has been reported.[213–215] An ionic mechanism has been proposed for this vanadium catalyzed hydroperoxide oxidation of tertiary amines to amine oxides (see also Chapter 16 on peroxide–metal compound oxidations).[213,214]

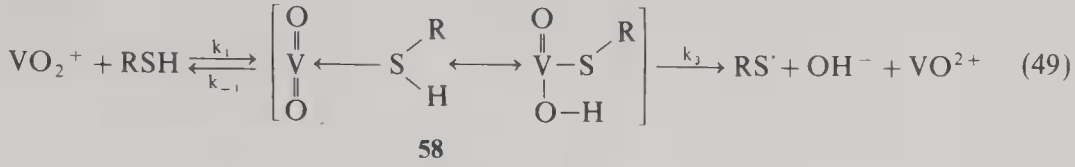


(48)

2.6. Sulfur Compounds

2.6.1. Oxidation of Thiols

The oxidation of 2-mercaptosuccinic acid (thiomalic acid, RSH) to the corresponding disulfide[221,222] by the oxyions of vanadium(V) has been studied in the pH range 2.4–4.4 via spectrophotometric stopped flow techniques.[221] The reaction proceeds via the formation of a colored intermediate complex (**59**) followed by a slower electron transfer step. Reaction of the intermediate leads to the formation of the disulfide [Eqs. (49)–(52)].[221]



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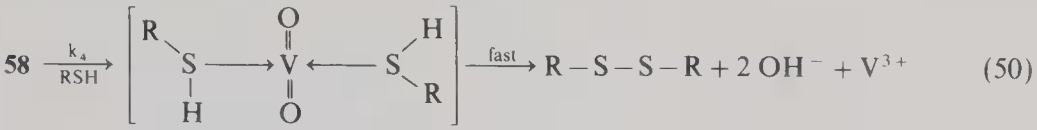


(50)

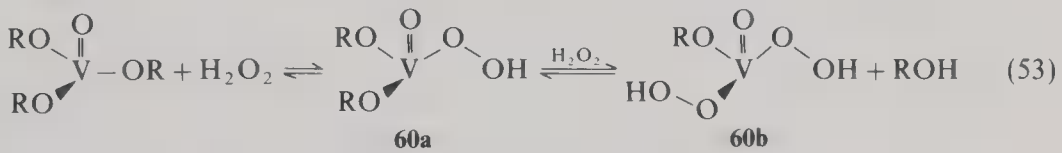
(51)

(52)

2.6.2. *Oxidation of Sulfides and Sulfoxides*

The vanadium catalyzed oxidation of sulfides to sulfoxides and sulfoxides to sulfones by *t*-butyl hydroperoxide has been studied in considerable detail.[223–243]

The oxidation of 4-chlorophenyl methyl sulfide and a series of substituted aryl methyl sulfides with hydrogen peroxide in the presence of catalytic amounts of bisacetylacetonatooxovanadium(IV) [$VO(acac)_2$] in ethanol at 25°C afforded the sulfoxides in quantitative yield.[226] Oxidation rates were little affected by substitution in the phenyl ring of the sulfide. The catalyst associates more strongly with hydrogen peroxide than with *t*-butyl hydroperoxide to form the peroxyvanadate **60a**. The diperoxovanadate (**60b**), which is also

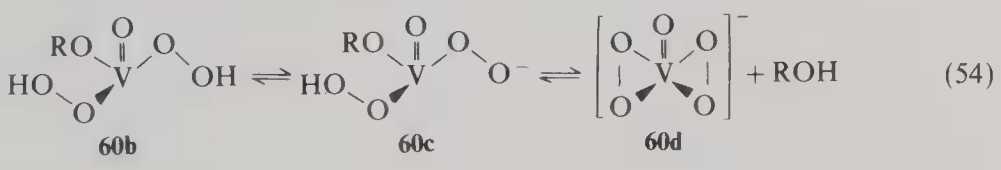


(53)

60a 60b

formed, is a less effective oxidant since it is a strong acid and exists mainly in its anionic form (**60c**), which is a poor nucleophile. The vanadium(V) catalyzed autodecomposition of hydrogen peroxide is a major factor in preventing this system from epoxidizing olefins *(vide supra)*.

More recent studies[229,234–236] on the vanadium(V) catalyzed oxidation of sulfides by hydrogen peroxide in ethanol or dioxane–ethanol have shown the presence of monoperoxo- (**60b**) and diperoxovanadium(V) species (**60c**). Evidence concerning the nature of peroxometal intermediates in the vanadium catalyzed oxidation of organic substrates by hydrogen peroxide or *t*-butyl hydroperoxide has been critically reviewed.[236]



(54)

60b 60c 60d

3. SCOPE AND LIMITATIONS

3.1. Oxidation of Alkanes

Low valent metal ions [Cu(I), Sn(II), Ti(III), V(III)] and dioxygen stoichiometrically oxidize alkanes to alcohols in relatively low yields.[239]

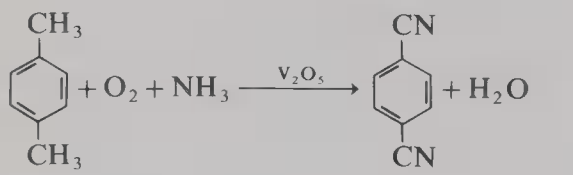
Allylic carbon–hydrogen bonds are oxidized by moderate oxidants such as Mo(IV) and Se(IV), while stronger oxometals [Cr(VI), Mn(VII), Ru(VII), and Va(V)] react at the double bond and at the allylic position.

3.2. Oxidation and Ammoxidation of Alkylaromatics

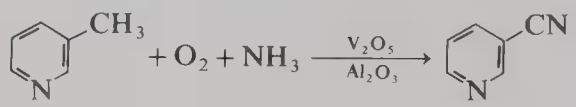
Vanadium compounds oxidize a wide variety of aromatic hydrocarbons under diverse experimental conditions.[45–56]

The vanadium oxidation of alkylbenzenes containing electron attracting groups to the corresponding substituted benzoic acids occurs in near quantitative yields.[45]

Methylbenzenes[57–60] and methylpyridines[61] undergo direct ammoxidation to nitriles with a mixture of ammonia and dioxygen in the presence of V_2O_5 at elevated temperatures. An imidovanadium species may be an intermediate in the direct ammoxidation or oxidative ammonolysis of alkylaromatics.[60,62–65]



(55)

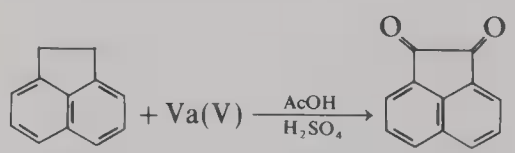


(56)

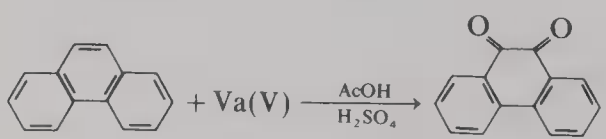
3.3. Oxidation of Aromatic Compounds

Vanadium(V) compounds can effect oxidation of carbon–hydrogen bonds [Eqs. (57–59)] or cleavage of carbon–carbon bonds [Eq. (60)] in aromatic compounds.

Although aqueous vanadium(V) does not attack benzene itself, it oxidizes naphthalene and other polycyclic aromatic hydrocarbons in the presence of acetic acid and sulfuric acid [Eqs. (44), (57), (58)].[31,48]

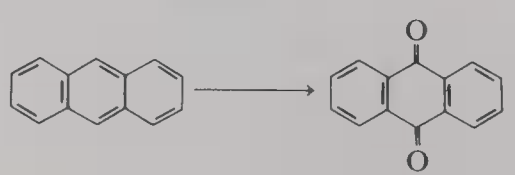


(57)



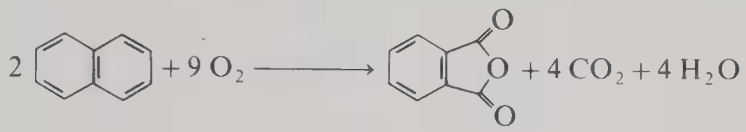
(58)

Although the sodium chlorate–vanadium pentoxide mixture, which is not very powerful, oxidizes hydroquinone (**42**) to 1,4-benzoquinone and anthracene to 9,10-anthraquinone, respectively, it is not suitable for the oxidation of acenaphthene, fluorene, naphthalene, and phenanthrene.[51]



(59)

The vapor phase oxidative cleavage of naphthalene to phthalic anhydride generally involves V_2O_5 supported on silica.[46,50]

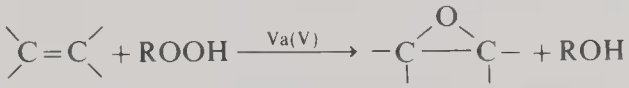


(60)

3.4. Oxidation of Carbon–Carbon Double Bonds

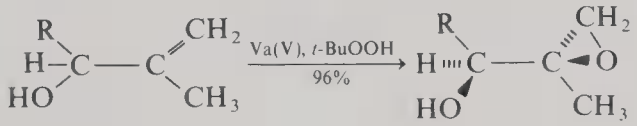
Vanadium(V) compounds can oxidize carbon–carbon double bonds to oxiranes, to aldehydes, or to mono- and dicarboxylic acids.

Although vanadium(V), vanadium(IV), and vanadium(III) complexes are inert to alkyl hydroperoxides, in the presence of nucleophiles such as amines, olefins, phosphines, and sulfides a catalytic reaction involving oxygen transfer occurs.[119] With alkenes, the epoxidation is stereospecific and proceeds in high yield. The industrial synthesis of 1,2-epoxypropane uses vanadium compounds.[56]

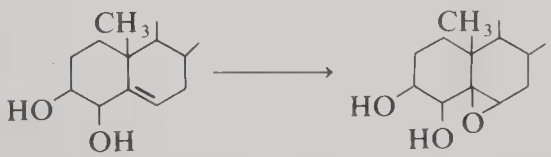


(61)

The vanadyl acetylacetonate [$VO(acac)_2$] catalyzed epoxidation of olefins may be performed at 0 or at 20–24°C. Allylic, homo-, and bishomoallylic alcohols are epoxidized much faster than the simple unsaturated hydrocarbon.[86,87,121–123] The vanadium(V) catalyzed epoxidations of allylic alcohols afford products with the epoxide *syn* to the hydroxyl group [Eqs. (12)–(14), (62), (63)].[118] The key step in the synthesis of the juvenile hormone *dl*-C_{18} Cecropic from farnesol involves the vanadium catalyzed epoxidation of two allylic alcoholic groups in the presence of an unactivated double bond.

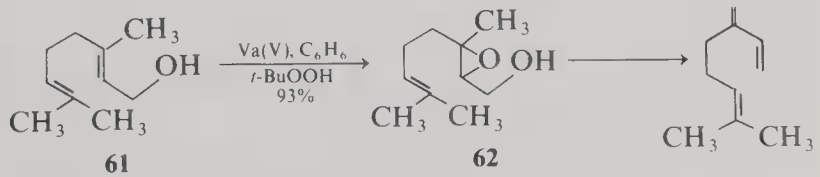


(62)



(63)

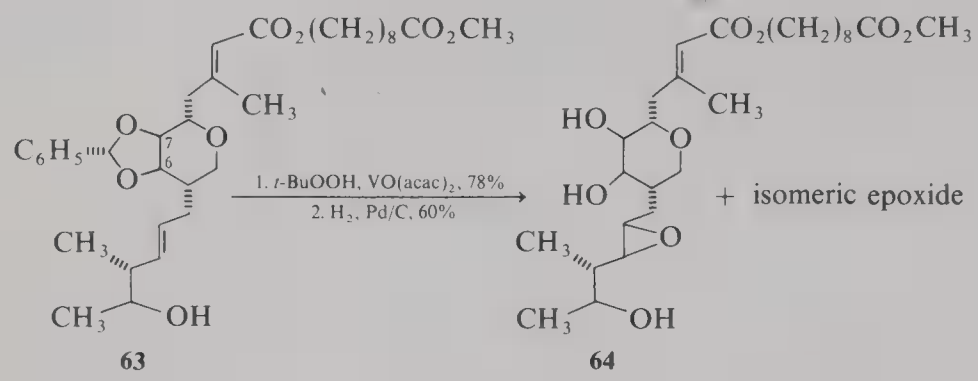
The catalyzed epoxidation of geraniol (**61**) occurs at the double bond closer to the hydroxyl group, whereas peroxy acids preferentially epoxidize the other double bond. Compound **62** is easily converted to a conjugated 1,3-diene [Eq. (64)].[121]



(64)

61 **62**

The antibiotic methyl pseudomonate A (**64**) is obtained at a 1.5:1 ratio with its isomeric epoxide from the *t*-BuOOH/$VO(acac)_2$ oxidation of methyl pseudomonate C (**63**). The reaction becomes more stereoselective if the 6,7-*cis*-diol unit in **63** is protected. Using protected **63**, the ratio of **64** to its isomer is 3:1, presumably because the *cis*-6,7-diol can no longer form a complex with the metal catalyst.[240]

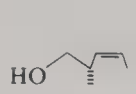
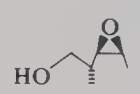
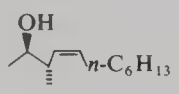
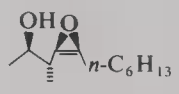
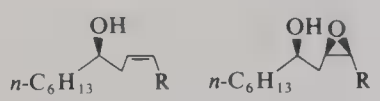
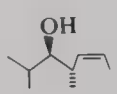
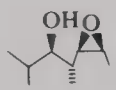
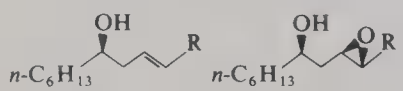
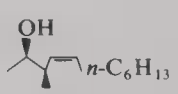
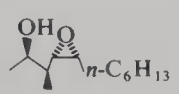
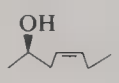
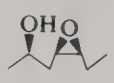
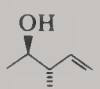
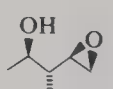
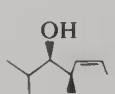
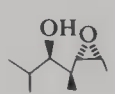
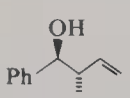
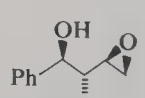
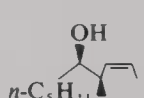
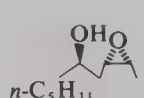
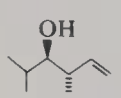
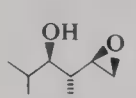
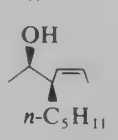
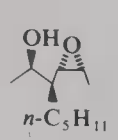
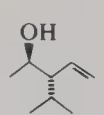
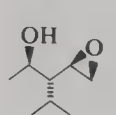


63 64 (65)

Table I summarizes some of the results from the [Va(V)/TBHP] epoxidation of homoallylic alcohols.[87b]

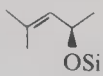
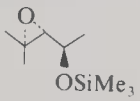
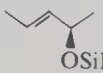
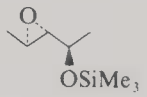
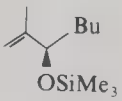
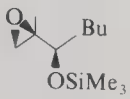
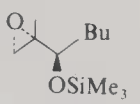
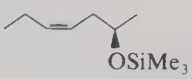
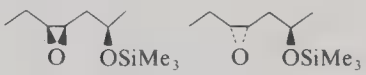
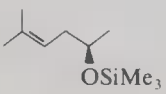
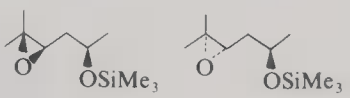
Trimethylsilyl ethers of allyl and homoallyl alcohols are epoxidized with *t*-butyldioxytrimethylsilane and a catalyst system consisting of vanadyl acetoacetate and tris-(trimethylsilyl)phosphate (Table II).[241] Stereoselectivities of the oxidation are similar to the epoxidation of allyl alcohols with vanadium-*t*-BuOOH catalyst.

TABLE I. Vanadium(IV) Oxide bis(2,4-pentanedionate)-*t*-Butyl Hydroperoxide Epoxidation of Homoallylic Alcohols[a]

Alcohol	Major epoxy alcohol	Selectivity	Yield (%)	Alcohol	Major epoxy alcohol	Selectivity	Yield (%)
		>400:1	90			104:1	92
 R = $(CH_2)_7CO_2CH_3$		24:1	93			>400:1	97
		1.4:1	99			70:1	73
		12:1	83			85:1	70
		4.6:1	50			2.1:1	91
		4.8:1	98			15.9:1	81
		3:1	88			211:1	95
		5:1	88				

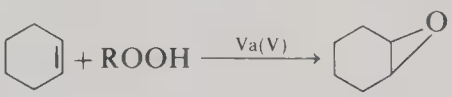
[a] Reference 87b.

TABLE II. Epoxidation of Allyl (or Homoallyl) Trimethylsilyl Ethers[a]

Allyl (or homoallyl) trimethylsilyl ether	Yield (%)	Epoxide(s) (ratio)
	85	 :  87–90 : 10–13
	78	 :  46 : 54
	21	 :  35 : 65
	60	 87 : 13
	56	 89 : 11

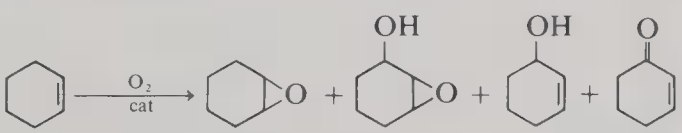
[a] Reference 241.

Cyclohexene epoxide can be prepared in quantitative yield by the vanadyl acetylacetonate (vanadium oxyacetylacetonate) catalyzed *t*-butyl hydroperoxide reaction with cyclohexene.[120] Vanadium octoate [$V(oct)_3$] or $V(acac)_3$ may also be used.



(66)

Vanadyl acetylacetonate–azobisisobutyronitrile [$VO(C_5H_7O_2)_2$–AIBN] is an effective catalyst for oxygenation of cyclohexene mainly to the *cis*-α, β-epoxy alcohol [Eq. (67)].[242] The system is comparable to $CpV(CO)_4$. Other cycloalkenes react in the same way [Eq. (67); cf. Eq. (24)], except for cyclooctene, which affords only the epoxide.



(67)

28 : 41 : 15 : 16

Table III shows a comparison of the stereoselectivities of the epoxidation of 2-

TABLE III. Stereoselectivity in the Metal-Catalyzed *t*-Butyl Hydroperoxide Epoxidation of 2-Cyclohexen-1-ol[a]

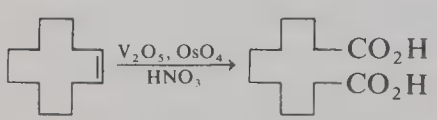
Catalyst	Reaction time (h)	Conversion of *t*-BuOOH (%)	Conversion of ene-ol	Yield of Epoxyol (%) *cis*	*trans*	(*cis*:*trans*)	Yield of *t*-BuOH (%)
$V(acac)_3$	2.0	100	70	96	1	(99)	89
$VO(acac)_2$	2.5	83	69	99	1	(99)	98
$Mo(acac)_3$	3.0	75	49	39	21	(1.9)	61
$MoO_2(acac)_2$	2.0	63	45	40	19	(2.1)	76
$Mo(CO)_6$	1.5	52	36	64	29	(2.2)	87
$W(CO)_6$	9.5	45	40	54	23	(2.3)	82

[a] Reference 108.

cyclohexen-1-ol by *t*-butyl hydroperoxide in the presence of complexes of vanadium, molybdenum, and tungsten.[108] It was shown that the low valent vanadium complex $[C_5H_5V(CO)_4]$ gave higher yields of cyclohexenyl hydroperoxide than $VO(acac)_2$, $V(acac)_3$, and vanadium naphthenate. Moreover, cyclohexene oxidations run in the presence of $[C_5H_5V(CO)_4]$ do not exhibit the long induction periods which can occur when vanadium(III) and vanadium(IV) complexes are used.[108,111]

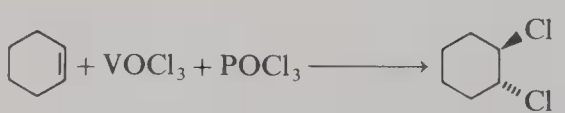
A heterogeneous catalyst system consisting of a mixture of vanadium pentoxide and Pd(II) is used for the commercial preparation of ethanal[76] or ethanoic acid[77] from ethene.

Cycloalkenes are oxidized to the corresponding dicarboxylic acids with aqueous nitric acid in the presence of NH_4VO_3 or V_2O_5.[70–74] A more efficient oxidation system involves use of 25%–50% aqueous nitric acid, V_2O_5, and a nearly stoichiometric amount of osmium tetroxide.[75] In this system, which probably involves glycol intermediates which are cleaved by HNO_3 and V_2O_5, cyclohexene, cyclooctene, and cyclododecene are oxidized to 1,6-hexanedioic (89%), 1,8-octanedioic (82%), and 1,12-dodecanedioic (86%) acids, respectively.[70,71,75]



(68)

Exploratory work has shown that vanadyl chloride ($VOCl_3$) can react with olefins in the presence of Lewis acids such as BF_3 or $POCl_3$.[31,69] The reaction of cyclohexene with $VOCl_3$ in the presence of $POCl_3$ gives an 80% yield of mostly *trans*-1,2-dichlorocyclohexane. The use of $VO(OAc)_3$ in acetic acid in the presence of acetyl chloride gives the corresponding acetylated product.[31,69]



(69)

3.5. Oxidation of Alcohols

3.5.1. Primary Alcohols

Methanol was oxidized to methanal using vanadium pentoxide as a catalyst and stannic oxide as a promoter.[243]

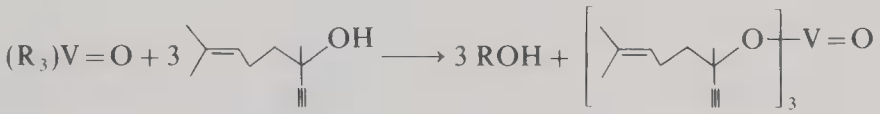
The oxidation of 1-propanol over a modified vanadium pentoxide catalyst at 210°C gives propanal in 94%–96% selectivity.[137]

The vanadium(V) oxidation of 2-phenylethanol to phenylmethanal is described above [Eqs. (25)–(27)].[138,139]

3.5.2. α-Acetylenic Alcohols

α, β-Unsaturated carbonyl compounds are important intermediates in the manufacture of carotenoids, fragrances, and vitamins. They have been obtained by reactions of α-acetylenic alcohols in the Meyer–Schuster[141] and Rupe[142,143] type rearrangements which often lead to complex mixtures of products.[140,144–147] A new efficient procedure for effecting these isomerizations makes use of silated vanadates, particularly tris(triphenylsilyl)vanadate(V), as catalysts.[140]

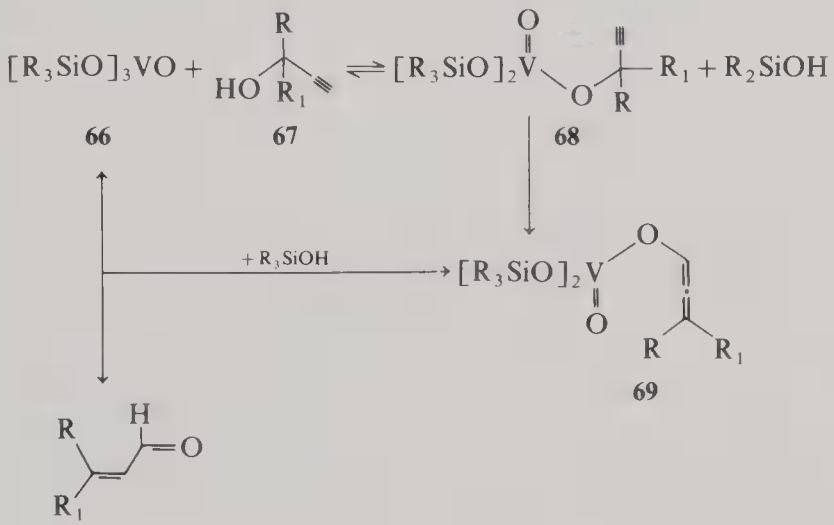
Readily available alkylvanadates are easily esterified with successive replacement of the three alkyl groups by dehydrolinalyl groups. The dehydrolinalylvanadates (**65**) decompose at elevated temperatures to give citral [**25** and **26**; Eq. (31)]. Tris(triphenylsilyl)vanadate(V)



(70)

24 **65**

and **24** in various solvents at 140°C for 5–10 min gave citral in 78% yield and over 90% of the silylvanadate crystallized unchanged from the reaction mixtures. Addition of a carboxylic acid (e.g., benzoic or lauric acid) increased the yields to 85%–90% over a 30 min reaction period. Addition of more **24** repeats the cycle [Eq. (71)].[140]



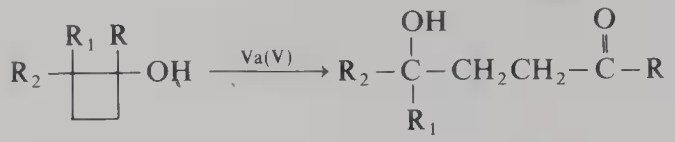
(71)

66 **67** **68** **69**

Table IV summarizes some of the yields of α, β-unsaturated carbonyl compounds from the rearrangement of α-acetylenic alcohols in catalytic systems composed of silylvanadates and silanols or silanediols.[140]

3.5.3. Cyclobutanols

Vanadium(V) in aqueous perchloric acid oxidizes cyclobutanols to the corresponding γ-hydroxy aldehydes and ketones.[135,136]



(72)

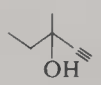
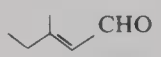
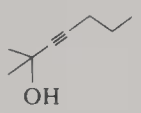
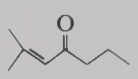
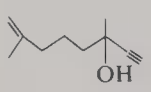
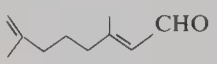
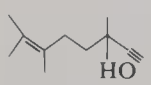
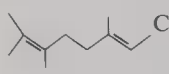
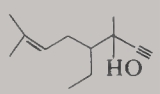
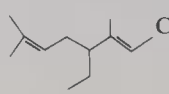
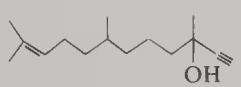
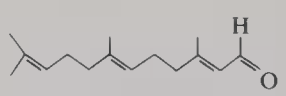
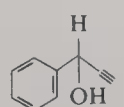
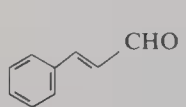
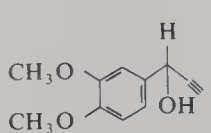
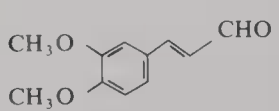
$R = R_1 = R_2 = H$ 94%
$R = CH_3$, $R_1 = R_2 = H$ 76%
$R = R_1 = H$, $R_2 = C_2H_5$ 74%
$R = H$, $R_1 = R_2 = CH_3$ 73%

3.5.4. Phenols and Phenyl Ethers

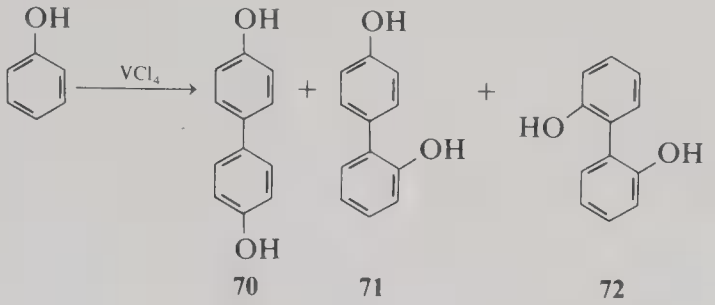
The vanadium(V) oxidation of hydroquinones to quinones is used as an analytical method.[176,177]

Vanadium tetrachloride is useful for the oxidative coupling [cf. Eqs. (37), (38)] of phenols [Eq. (73), 55%–65%] and 1- or 2-naphthols [Eq. (74)].[166]

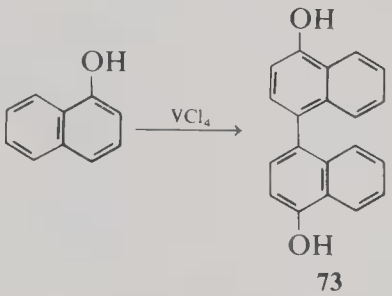
TABLE IV. α,β-Unsaturated Carbonyl Compounds from the Silylvanadate Isomerization of α-Acetylenic Alcohols[a]

α-Acetylenic alcohol	α,β-Unsaturated carbonyl compound	Yield (%)	*Cis/trans*
		95	0.5
		92	
		92	
		95	0.84 to 1
		85	1.2 to 1.4
		85	1.0
		93	
		87	

[a] Reference 140.

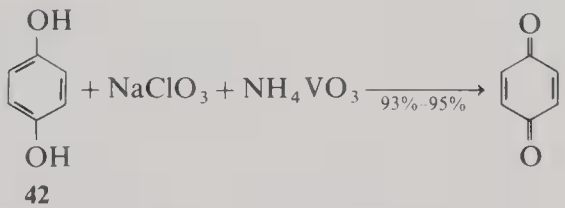


(73)



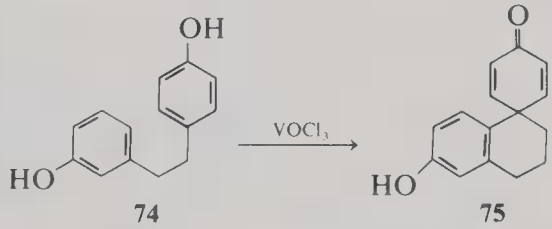
(74)

It was suggested[190] that ammonium metavanadate (NH_2VO_3) may be a better catalyst for the oxidation of 1,4-dihydroxybenzene (**42**) to 1,4-benzoquinone than the conventionally used vanadium pentoxide catalyst [Eqs. (39), (75)].[51] After the catalyst was added to the cooled mixture, the reaction was over in less than 0.5 h, about 12% of the normally required time. 1,4-Benzoquinone is also prepared by the oxidation of 4-aminophenol with V_2O_5 in aqueous sulfuric acid at ca. 100°C.[191]



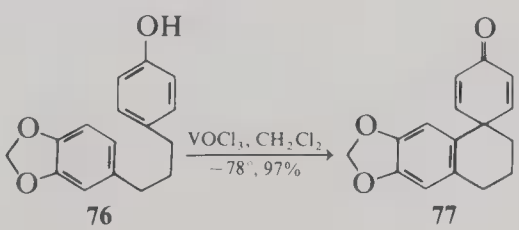
(75)

Examples of oxidative coupling of phenol by vanadium compounds are shown in Eqs. (37)–(41).[166,167,178–192] 1,3-Bis-(hydroxyphenyl)propane (**74**) is converted to the dienone **75** (76%) by reaction with vanadyl chloride in refluxing ether [cf. Eq. (40)].[167] The use of

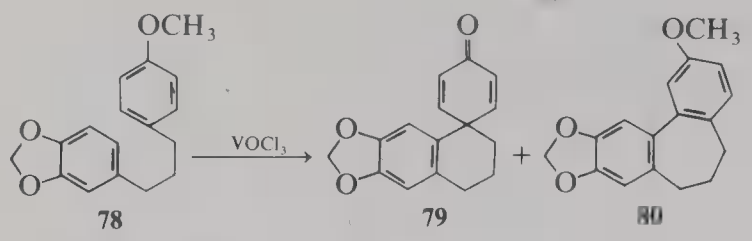


(76)

alkaline potassium ferricyanide, ferric chloride, or manganic tris(acetylacetonate) gave yields of less than 10%. Improved yields of $VOCl_3$ over $K_3[Fe(CN)_6]$ are shown in the preparation of Amarylldaceae alkaloids *(vide infra)*.



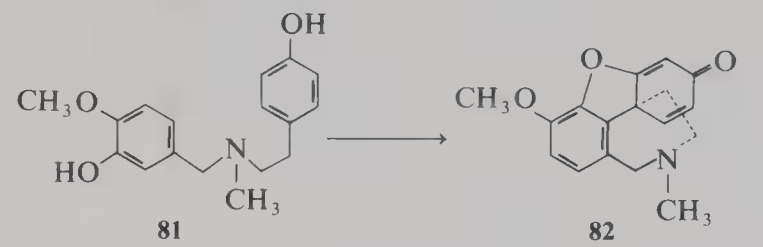
(77)



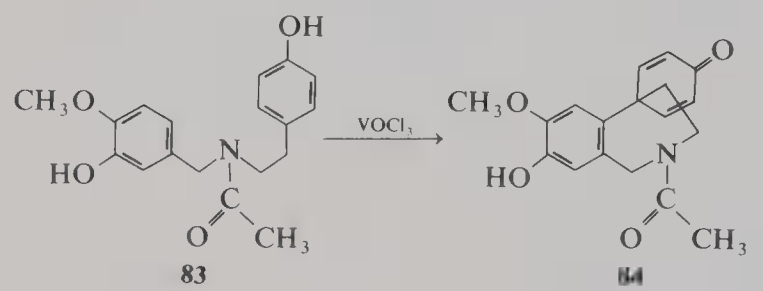
(78)

Vanadyl trichloride has been found to be effective for intramolecular coupling of diphenolic, monophenolic, and nonphenolic 1,3-diarylpropanes [Eqs. (40), (76)–(78)].[182]

The oxidation of **81** with $K_3[Fe(CN)_6]$ gives (±)-narwedine (**82**) in 1.4% yield.[178] The vanadyl chloride oxidation of **83** to **84** (24%) is a key step in a biogenetic type synthesis of the Amaryllidaceae alkaloid (±)-maritidine.[179]

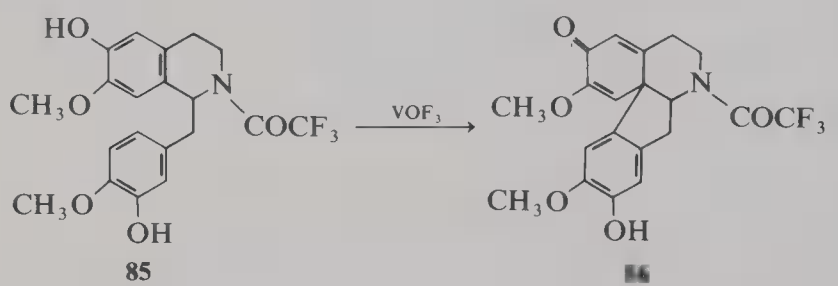


(79)



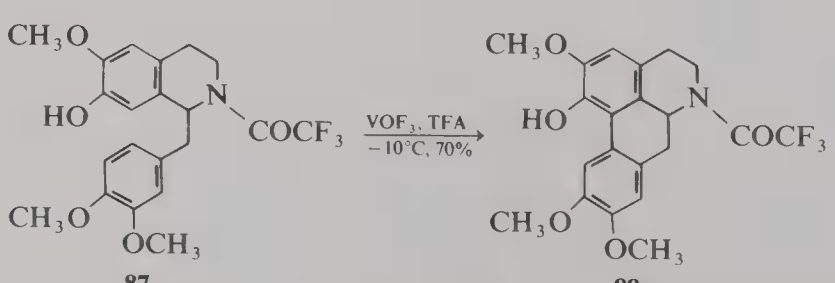
(80)

Oxidative coupling of the norprotosinomine derivative **85** to dienone **86** (40%) occurs under controlled conditions with vanadyl fluoride.[187] Compound **86** is an important intermediate in the biosynthesis of erysodienone.



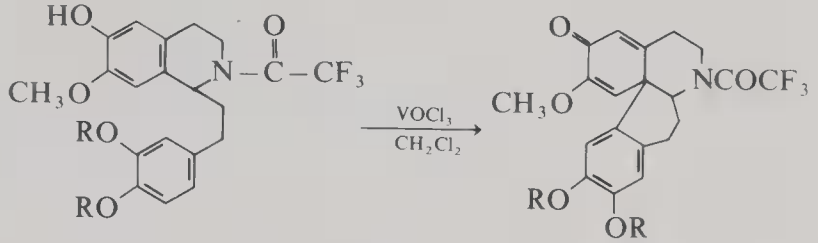
(81)

The oxidative coupling of benzyltetrahydroisoquinolines (**87**) affords aporphines (**88**) in high yields.[186]



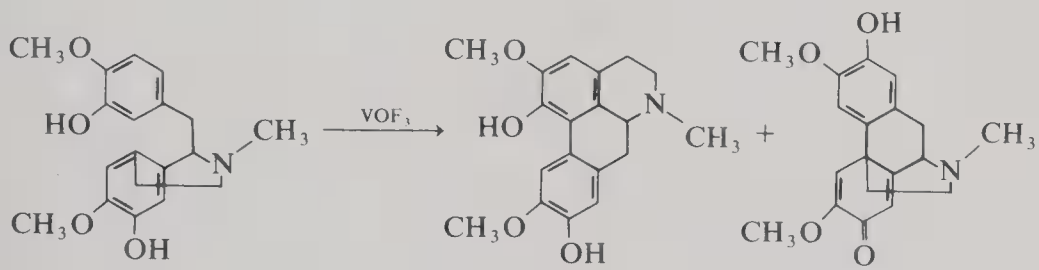
(82)

Oxidation of **89** with $VOCl_3$ gives dienone **90** (35%). This reaction is of interest in the synthesis of Erythrina alkaloids.[181]



89 **90** (83)

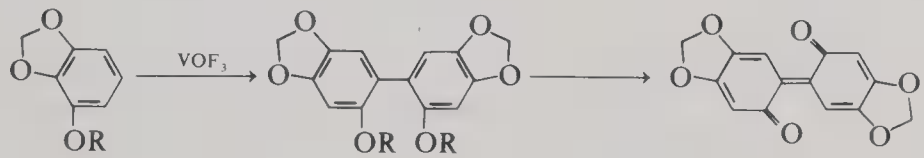
The oxidation of reticuline (**91**) with $VOCl_3$ gives isoboldine (**92**, 1%) and palladine (**93**, 0.3%).[180]



91 **92** **93** (84)

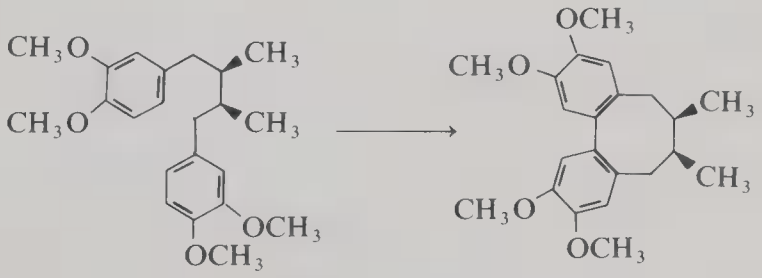
Examples of vanadium catalyzed intramolecular coupling reactions of phenyl ethers are shown in Eqs. (85)–(90).

Oxidation of **94** with vanadyl trifluoride gives **84**, which is an intermediate in the preparation of a dipheno-2,2′-quinone (**96**).[188]



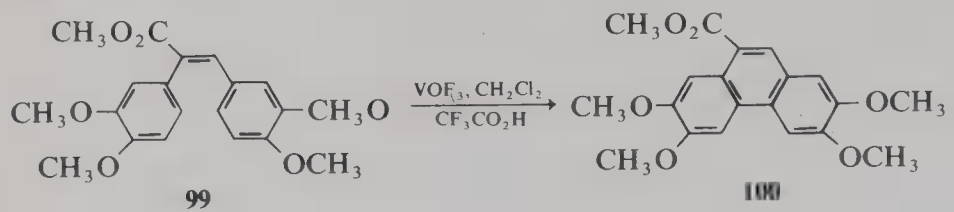
94 $R = C_6H_5CH_2$ **95** **96** (85)

Naturally occurring bisbenzocyclooctadienes (lignans), of which the gomisins, kadsurins, schizandrins, and steganes are representatives, have a wide range of therapeutic activity, notably antileukaemic.[52] The intramolecular oxidation of the 1,4-diarylbutane **97** with vanadyl trifluoride gave the *cis*-dimethyldibenzooctadiene **98**. This reaction was used for the synthesis of a related lignan, (±)-deoxyschizandrin. Similar oxidative coupling reactions with thallium(III) compounds are discussed in Chapter 13.[52]

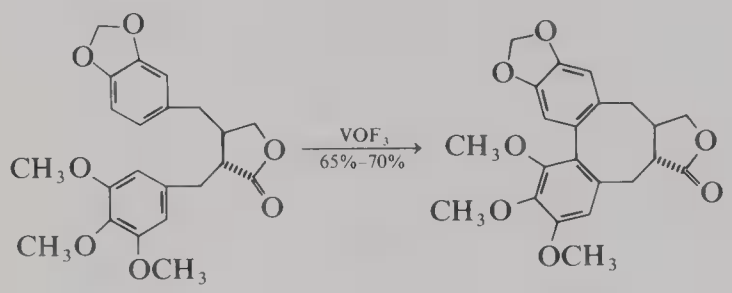


97 **98** (86)

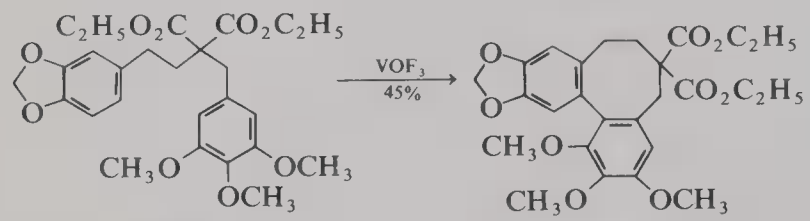
Stilbene derivatives are oxidatively cyclized to phenanthrenes by vanadyl trifluoride at 0°C.[53,54] The yield from the VOF_3 cyclization is higher than the yield from the photocyclization reaction.[54]



99 100 (87)

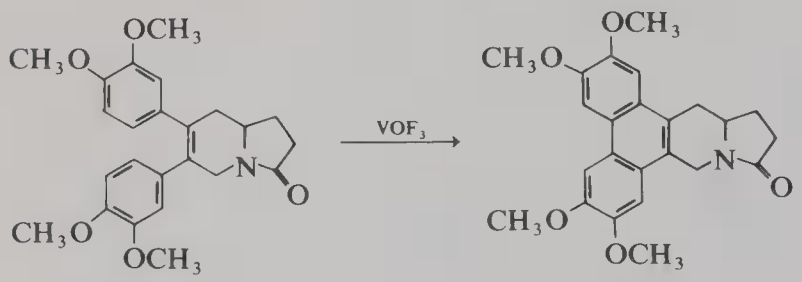


101 102 (88)



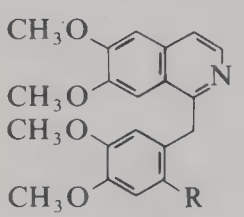
103 104 (89)

Oxidative cyclization is also useful in the phenanthioindolizidine alkaloids. Reduction of the carbonyl group in **106** to a methylene group affords (±)-tylophorine.[53]

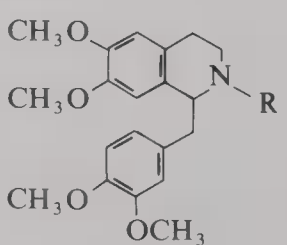


105 106 (90)

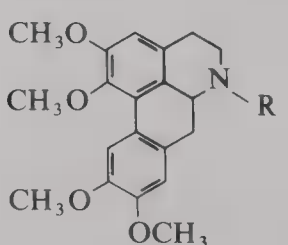
Although papaverine (**107**) gave the aryl-to-aryl intermolecularly coupled product **108** (80%) with VOF_3,[55] (±)-laudanosine **109** and (±)-*N*-formylnorlaudanosine **110** gave the respective intramolecular cyclization products **111** and **112** (cf. Scheme I).[55]



107 R = H
108 R = 6′-papaveryl

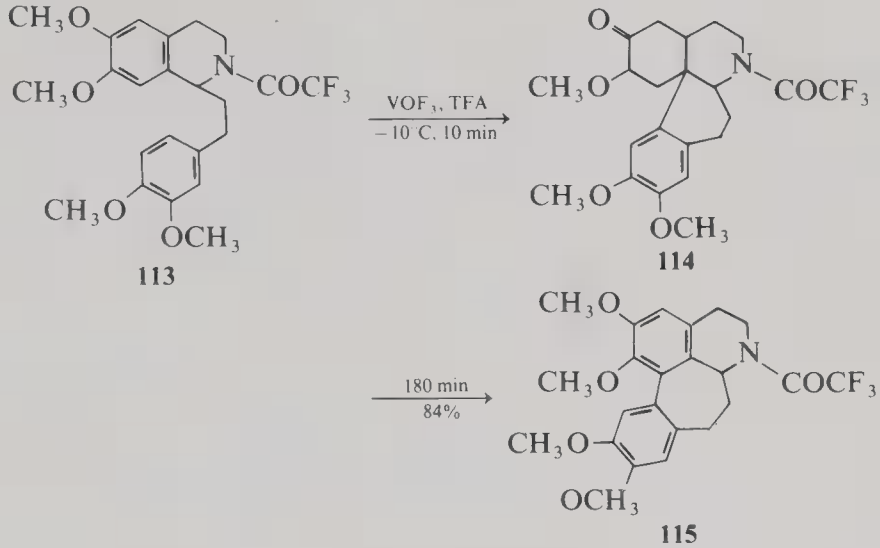


109 R = CH_3
110 R = CHO



111 R = CH_3
112 R = CHO

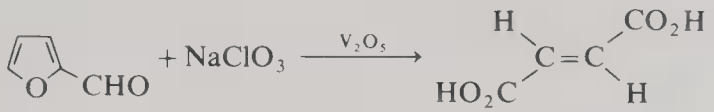
A difference in the coupling properties of $VOCl_3$ and VOF_3 is seen in the comparison of Eq. (83) and (91).



113 114 115 (91)

3.6. Carbonyl Compounds

The sodium chlorate oxidation of furfural to E-2-butenedioic acid (**5**, 74%–78%) is catalyzed by V_2O_5.[244,245] 2-Furoic acid is a possible intermediate.



5 (92)

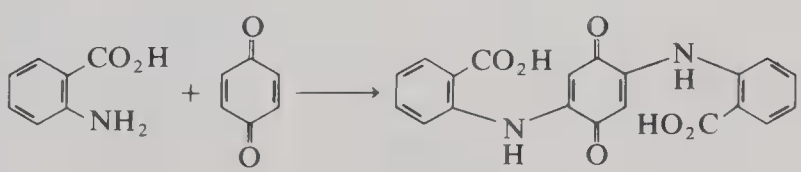
Vanadium pentoxide in sulfuric acid oxidizes propanone to ethanoic and methanoic acids in quantitative yields.[212]

4-Methyl-3-penten-2-one (mesityl oxide) is oxidized by vanadium(V) to propanone and ethanoic acid.[48]

Cyclopentanone is quantitatively converted to methanoic and butane-1,4-dioic acids.[246]

Cyclohexanone is oxidized to hexane-1,6-dioic acid (adipic acid 95%, Eq. 36) by NH_4VO_3 in sulfuric acid.[246,247]

2,5-Bis [2-carboxy-anilino]-1,4-benzoquinone (**116**), which is an intermediate in the preparation of *linear trans*-chinacridochinone, is prepared in 90% yield from the reaction of anthranilic acid, 1,4-benzoquinone, sodium chlorate, and ammonium vanadate [Eq. (113)].[248]



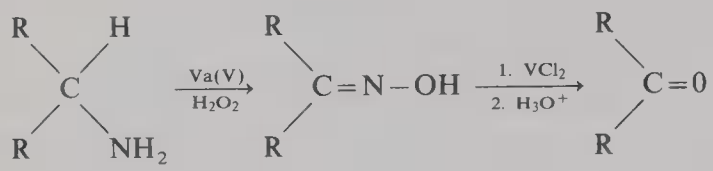
116 (93)

3.7. Nitrogen Compounds

Although it is expected that nitrogen containing functional groups will not be very susceptible to vanadium oxidation in acidic media owing to protonation of the lone pair elec-

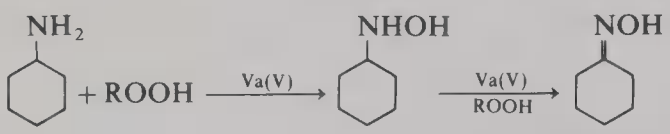
trons, vanadium(V) can oxidize aliphatic and aromatic amines.[69,249] Ethylenediamine tetraacetic acid (EDTA), which forms complexes with vanadium(V), is oxidized by vanadium(V).[250–252] Hydrazine and hydrazone derivatives are also easily oxidized by vanadium(V).[218–220]

Vanadium(V) catalyzes the hydrogen peroxide oxidation of primary amines possessing an α carbon hydrogen bond to oximes.[207–210] Since vanadium(II) chloride in THF is a convenient reagent for deoximation (75%–90%),[253] one can easily prepare carbonyl compounds from primary amines or regenerate aldehydes and ketones from oximes with vanadium compounds.



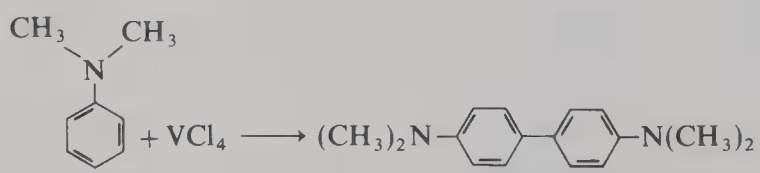
(94)

Alkyl hydroperoxides in the presence of vanadium catalysis in hydrocarbon solvents at 80–100°C selectively oxidize cyclohexylamine to cyclohexanone oxime, which is an intermediate for Nylon 6.[209,210] Cyclohexylhydroxylamine is the major product at 20–25°C.



(95)

N,N-Dimethylaniline and diphenylamine react with vanadium tetrachloride to give *N,N,N′N′*-tetramethylbenzidine (52%) and *N,N′*-diphenylbenzidine (43%), respectively.[166] Under the same conditions, aniline was oxidized to an unidentified black product ("aniline black"?) and 2-methylquinoline failed to produce coupled products.



(96)

A novel reaction of tertiary amines with organic hydroperoxides in the presence of vanadium compounds give excellent yields of amine oxides.[213,215] A comparison of vanadium

TABLE V. Amine Oxides from the Vanadium-Catalyzed *t*-Butyl Hydroperoxide Oxidation of Tertiary Amines[a]

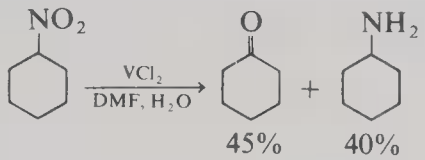
3° Amine	Catalyst	Hydroperoxide	Yield (%) R_3NO
N,N-Dimethyldodecylamine	$VO(acac)_2$	*t*-BuOOH	86
	$V(acac)_3$	*t*-BuOOH	81
	$VOSO_4$	*t*-BuOOH	82
	VCl_2	*t*-BuOOH	88
	V_2O_3	*t*-BuOOH	92
	V_2O_5	*t*-BuOOH	96
Tri-*n*-butylamine	$VO(acac)_2$	Amylene	91
Triethylamine	$VO(acac)_2$	*t*-BuOOH	100
1-Dimethylamino-2-propanol	$VO(acac)_2$	*t*-BuOOH	80

[a] References 213, 214.

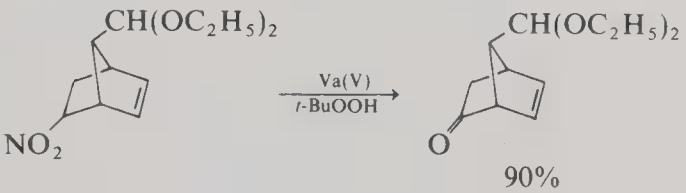
oxyacetylacetonate, vanadium trioxide, and V_2O_5 showed for the oxidation of tertiary amines that organic soluble vanadium complexes are generally the preferred catalysts (Table V).[213]

$$(CH_3CH_2)_3N + t\text{-BuOOH} + VO(acac)_2 \longrightarrow (CH_3CH_2)_3\overset{+}{N}-O^- \qquad (97)$$

Nitroalkanes are converted to carbonyl compounds by the reaction of vanadium(II) chloride in dimethylformamide at pH 0.3[215] or by reaction of the nitronate salt with *t*-BuOOH in the presence of $VO(acac)_2$ catalyst.[216] In contrast to the acidic conditions of the Nef reaction or the VCl_2 procedure, the $VO(acac)_2$ reaction permits the conversion of acid sensitive nitroalkanes to carbonyl compounds. If properly developed, both methods will prove to be as synthetically valuable as the permanganate ion oxidation of nitro compounds.[254–259]

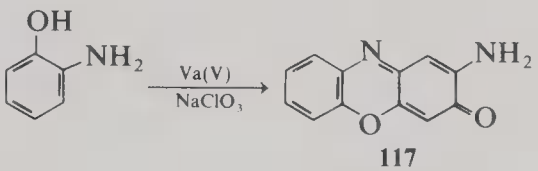


(98)



(99)

The vanadium(V) catalyzed sodium chlorate oxidation of 2-aminophenol to 2-amino-3-phenoxazone (**117**) provides a tensammetric method for the determination of vanadium.[192,260]



117

(100)

3.8. Sulfur Compounds

3.8.1. Thiols

Like other heavy metal ions, vanadium(V) reacts with thiols to give the corresponding disulfides [Eqs. (49)–(52)].[221,222] A deep blue-black solution of vanadium(V) and 8-hydroxyquinoline (oxine) reacts with thiols to give a color change via green to lemon yellow.[261,262]

The oxidation of thiols with *tert*-butyl hydroperoxide in the presence of Va(V) produces sulfonic acids, presumably via the corresponding sulfenic and sulfinic acids as intermediates.[263]

$$R-SH \xrightarrow[t\text{-BuOOH}]{Va(V)} R-S-OH \longrightarrow R-\overset{\overset{O}{\|}}{S}-OH \longrightarrow R-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-OH \qquad (101)$$

3.8.2. Sulfides and Sulfoxides

Sulfides are generally oxidized faster than olefins, and unsaturated sulfides are selectively oxidized at the sulfur atom. In alcohol solvent, hydrogen peroxide is 100 times more effective than *t*-butyl hydroperoxide for the vanadium catalyzed oxidation of sulfides to sulfoxides.[226,227]

Sulfides are oxidized to the corresponding sulfoxides with alkyl hydroperoxides or hydrogen peroxide in the presence of vanadium(V) catalysts.[264–270] The high rates of oxidation and virtually quantitative yields obtained under mild conditions demonstrate the synthetic utility of the vanadium catalyzed oxidation of sulfides to sulfoxides. For example, the oxidation of 4-chlorophenyl methyl sulfide and of a series of phenyl substituted aryl methyl sulfides with hydrogen peroxide in the presence of catalytic amounts of bis-acetylacetonatooxovanadium(IV) [$VO(acac)_2$] in ethanol at 25°C affords the corresponding sulfoxides in quantitative yield.[226] Comparison with the vanadium catalyzed oxidation of sulfides by *tert*-butyl hydroperoxide shows that the Va(V)-H_2O_2 system is more effective than the Va(V)-*t*-BuOOH system.[226]

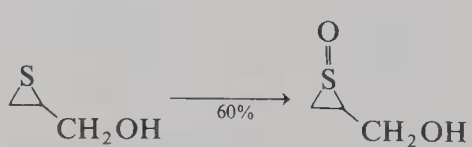
$$\mathrm{Ar-S-R} \longrightarrow \mathrm{Ar-\overset{\overset{O}{\|}}{S}-R} \longrightarrow \mathrm{Ar-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-R} \tag{102}$$

The reactive rates for oxidation by $VO(acac)_2$-*t*-BuOOH of di-*n*-butyl sulfide, butyl phenyl sulfide, di-*n*-butyl sulfoxide, and cyclohexene are 100, 58, 1.7, and 0.2, respectively.[228]

Milas reagent, which is a mixture of V_2O_5, H_2O_2, and *t*-BuOH, oxidizes α-chlorosulfides,[265] sulfides, and thiirans[265] in the presence of disulfides[266,267] and vinyl sulfides.[268]

$$\mathrm{C_{12}H_{25}-S-CH_2Cl} \xrightarrow[69\%]{} \mathrm{C_{12}H_{25}-\overset{\overset{O}{\|}}{S}-CH_2Cl} \tag{103}$$

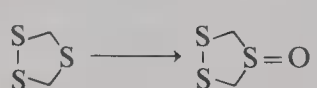
$$\mathrm{(CH_3)_3C-S-CH=CHCH_3} \xrightarrow[69\%]{} \mathrm{(CH_3)_3C-\overset{\overset{O}{\|}}{S}-CH=CHCH_3} \tag{104}$$



(105)

A chiral vanadate ester [$VO(OR)_3$] has been postulated as the catalytic species responsible for the asymmetric oxidation observed when an unsymmetrical sulfide was reacted with $VO(acac)_2$-*t*-BuOOH in a mixture of benzene and a chiral alcohol.[233] Although asymmetric induction was observed, enantiomeric excesses were low (5%–10%).

1,2,4-Trithiolane (**118**) is selectively oxidized to the antibacterial natural product **119** with V_2O_5-H_2O_2 in *t*-BuOH-THF at −30°C.[266–270]



118 **119** (106)

Sulfoxides can be oxidized by equimolar amounts of organic hydroperoxides to sulfones in almost quantitative yields. For example, oxidation of dimethyl sulfoxide with cumyl α-hydroperoxide in the presence of vanadium pentoxide gives dimethyl sulfone (91%).[271,272]

$$CH_3-\overset{\overset{O}{\|}}{S}-CH_3 \longrightarrow CH_3-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-CH_3 \qquad (107)$$

Vanadium oxychloride oxidizes diethyl sulfide to S-ethyl ethanesulfonothioate in 40% yield [Eq. (108)].[273]

$$CH_3CH_2-S-CH_2CH_3 \xrightarrow{VOCl_3} CH_3CH_2-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-S-CH_2CH_3 + S \qquad (108)$$

Unsaturated sulfides such as allyl *n*-butyl sulfide or dialkyl sulfide can be oxidized selectively to the corresponding unsaturated sulfone via the respective sulfoxides.[271] Organic hydroperoxides in the presence of molybdovanadic acid catalyst oxidize sulfides to sulfoxides below 55°C or to sulfones above 55°C.[274]

β-Hydroxy sulfoxides, which are synthetically useful intermediates, are prepared by adding a catalytic amount of V_2O_5 or $VO(acac)_2$ to a reaction mixture of olefin and thiophenol [Eq. (113)].[275]

$$R-CH=CH_2 + Ar-SH \xrightarrow[O_2]{h\nu} R-\underset{\underset{OOH}{|}}{CH}CH_2-S-Ar \xrightarrow{V_2O_5} R-\overset{\overset{OH}{|}}{CH}-CH_2-\overset{\overset{O}{\|}}{S}-Ar \qquad (109)$$

3.8.3. Disulfides

The hydrogen peroxide–vanadium pentoxide reagent may be used to oxidize disulfides to thiosulfinates and/or thiosulfonates.[265] Vanadium oxychloride in the presence of oxygen converts diethyl disulfide to the thiosulfonate in 85% yield [Eq. (110); cf. Eq. (108)].[273]

$$CH_3CH_2-S-S-CH_2CH_3 \xrightarrow[VOCl_3]{O_2} CH_3CH_2-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-S-CH_2CH_3 \qquad (110)$$

4. EXPERIMENTAL CONSIDERATIONS AND PROCEDURES

4.1. General Considerations

Covalent vanadium(V) compounds, especially the oxychloride, are highly toxic when they are absorbed through the skin and when the vapors are inhaled.[9,31]

4.2. General Procedures and Typical Detailed Procedures

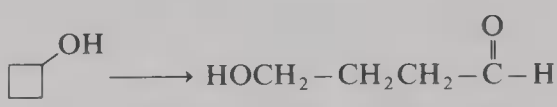
4.2.1. Epoxidation of Carbon–Carbon Double Bonds

*Oxidation of E-Geraniol and its 2,2-Epoxide (**62**) by the Vanadyl Acetylacetonate Catalyzed tert-Butyl Hydroperoxide Epoxidation Procedure [Eq. (63)].*[123] To a solution of E-

geraniol (**61**, 20 g, 0.129 mol) and of vandyl acetylacetonate (0.5 g, 1.8 mmol) in 150 ml of refluxing benzene is added dropwise over a period of 20 min *tert*-butyl hydroperoxide (17.6 g, 0.142 mol). The initially colorless solution turns bright green upon addition of $VO(acac)_2$. The color fades as the reflux temperature is approached and then turns deep red as *t*-BuOOH is added. The deep red color turns to yellow and then to light green as the reaction goes to completion over a 4-h period. The organic phase is washed with aqueous bisulfite and then concentrated to give the epoxy alcohol **62** in 98% yield. Since this alcohol decomposed upon attempted distillation, it was acetylated *in situ* in order to facilitate isolation of the pure product.[123]

4.2.2. Oxidation of Alcohols

Oxidation of Cyclobutanol to 4-Hydroxybutanal by Ammonium Metavanadate. A Typical Procedure.[135,136] A solution of 0.07985 g (0.680 mmol) of NH_4VO_3, 0.0224 g (0.3114 mmol)



(111)

of cyclobutanol, and 1 ml of 5 *M* H_2SO_4 were diluted with H_2O to 5 ml and allowed to react at 20–24°C in the dark. After completion of the reaction, the solution was allowed to react overnight with a slight excess of a solution of 2,4-dinitrophenylhydrazine. The precipitate (4-hydroxybutanal 2,4-dinitrophenylhydrazone) was collected, washed, dried, and weighed. The aqueous layer was extracted three times with CH_2Cl_2, which was then neutralized, dried, and evaporated. The 2,4-DNP and residue were analyzed by TLC (ether-benzene, 3:1).

*Preparation of Triphenylsilanol (***120***).*[140] Silicon tetrachloride (57 ml) and ether (4 liters) in dried apparatus under nitrogen were stirred vigorously at 3–5°C, and freshly

$$SiCl_4 + C_6H_5Li \longrightarrow (C_6H_5)_3SiOH \qquad (112)$$

120

prepared phenyllithium (126 g in 600 ml of ether) was added over 2.5–3 h. The mixture was stirred overnight at 20–24°C and hydrolyzed below 25°C by the addition of 2 liters of H_2O. After neutralization to phenolphthalein with aqueous ammonia (ca. 50 ml of 37%), separation of the ether layer, and two more extractions with ether (500 ml), the combined ether solutions were dried (Na_2SO_4) and decolorized by stirring with charcoal (4 g Darco G 60) for 5 min. The filtered solution was evaporated and the residue dissolved in boiling ligroin (bp 80–105°C, 2.5 liters). Slow cooling to 25°C and refrigeration at 5°C gave white crystals, which were filtered, washed with petroleum ether (bp 40–45°C, 200 ml) in several portions, and dried at 60°C and 20 Torr. The crystals of **120** (124 g, 90%) melted at 153°C.

*Preparation of Tris(triphenylsilyl)vanadate(V) (***121***).*[140] Vanadium pentoxide (22.2 g), **120** (165.8 g), 1-butanol (44.5 g), and 1,4-dimethylbenzene (700 ml) were refluxed for 7 h.

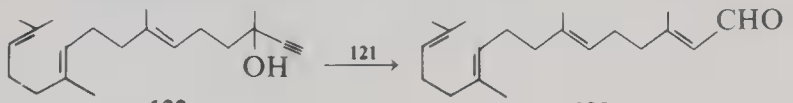
$$(C_6H_5)_3SiOH + V_2O_5 \longrightarrow [(C_6H_5)_3SiO]_3V=O \qquad (113)$$

120 **121**

The water was continuously removed with a Dean-Stark apparatus. Black material (6 g) was filtered off, washed with boiling xylene (5 × 25 ml), and dried. The combined filtrates were allowed to cool, the crystals filtered off, washed with xylene (2 × 25 ml) and hexane (2 × 50 ml), and dried to give 138.5 g (77.2%) of **121**, mp 225–227°C. A second crop (24.8 g, 13.8%) of **121** was obtained by concentrating the 1,4-dimethylbenzene mother liquors.

Compound **121** can also be prepared from **120** and vanadium oxychloride.[140]

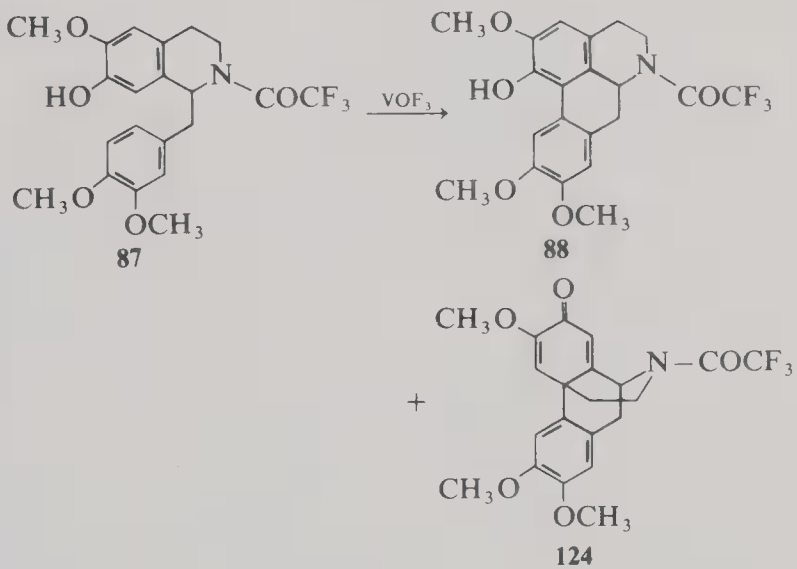
*Rearrangement of 3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yn-3-ol (**122**) to Geranylcitral (**123**) with **121** (Table IV).*[140] Benzoic acid (0.5 g), **121** (6.5 g), and geranyldehydrolinalool (**122**, 75 g) in xylene (500 ml) were boiled under reflux for 45 min. The solvent was removed under reduced pressure and the residue extracted with hexane (400 ml) to leave unchanged **122** (5.6 g, mp 223–226°C). The hexane was evaporated and the residue (**123**, 77.9°C) was distilled to obtain pure **123** (55%, bp 145–149°C at 0.25 Torr).



122 **123** (114)

4.2.3. Intramolecular Oxidative Coupling of Phenols

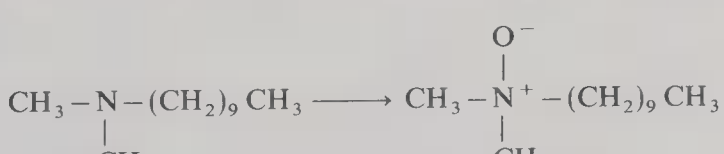
*Intramolecular Oxidative Coupling of (±)-N-trifluoroacetylnorcodamine (**87**) to (±)-N-trifluoroacetylwilsonirine (**88**) and morphinandienone(**124**).*[189] In a typical procedure 1 mmol of **87** [0.05 *M* in CH_2Cl_2 containing 20% TFA-TFAA (20:1 by weight)] was treated with 2.5 molar equivalent of VOF_3 dissolved in a minimum volume of a 1:1 solution of ethyl acetate and TFA-TFAA (20:1 by weight) at −10°C for 10 min. Aqueous workup gave ▩ (70%, mp 196.5–196°C) and **124** (8%, mp 179.4–181.5).



87 **88** **124** (115)

4.2.4. Oxidation of Nitrogen Compounds

*Vanadium Catalyzed Oxidation of N,N-Dimethydodecylamine (**125**) to N,N-Dimethyldodecylamine N-oxide (**126**).*[213] *Procedure A.* A solution of 21 g (0.1 mol) of practical grade *N,N*-dimethyldodecylamine (**125**), 4.6 g (0.05 mol) of *t*-butyl hydroperoxide (94% purity), 0.05 g of vanadium oxyacetylacetonate, and 27 g of *t*-butyl alcohol was added



125 **126** (116)

to a round-bottom flask equipped with a thermometer and reflux condenser. The reaction was refluxed at 90°C for 15 min and cooled. The hydroperoxide was determined by iodometric titration. There was complete conversion of the hydroperoxide. The amine oxide was determined by standard hydrochloric acid titration after reaction of the excess amine with methyl iodide. The titration analysis showed an 86% yield of amine oxide. The titration was confirmed by NMR analysis. For the NMR analysis, dichloromethane was used as an internal standard and TMS as the reference compound. The methyl groups on the nitrogen of the amine and the oxide appeared at τ 7.87 and 6.8. The amine oxide was isolated by flash evaporating of the solvent, dissolving the residue in ether, and extracting the amine oxide into water. The water was flash evaporated. The resulting gel was dissolved in a minimum of acetone and cooled. This yielded 6.3 g (57% yield) of crystals, mp 120–122°C. Alternatively, 30 ml of pentane was added to the residue after flash evaporation of the solvent. This precipitated the amine oxide (**126**) (6.4 g, 58% yield), mp 120–124°C.

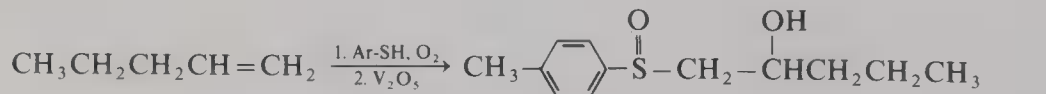
Procedure B. A solution of 21 g (0.1 mol) of practical grade *N,N*-dimethyldodecylamine (**125**), 9.2 g (0.1 mol) of *t*-butyl hydroperoxide (94% purity), 0.05 g of vanadium oxyacetylacetonate, and 27 g of *t*-butyl alcohol was treated as above. The hydrochloric acid–methyl iodide titration showed a 97% yield of amine oxide. The solvent was flash evaporated and gave 20 g of solid, mp 123–125°C. The solid was triturated with 50 ml of pentane, filtered, and dried under vacuum. This yielded 17.7 g (80% yield) of anhydrous amine oxide (**126**), mp 128–130°C. The infrared and ^{1}H NMR spectra were identical with those of an authentic sample.

Mild Oxidative Nitro to Carbonyl Conversion—General Procedure.[216] A mixture of 1 mmol of the nitro compound and 1.1 equivalents of *t*-BuOK in 2 ml of benzene are stirred for 15 min at 20–25°C. A solution of 0.3 ml of 90% *t*-BuOOH, 3.5 mg of $VO(acac)_2$, and 0.7 ml of benzene is added over a 15-min period. After 20 min the mixture is diluted with diethyl ether, washed with water and brine, dried, and concentrated under reduced pressure to give a product which is further purified as appropriate.

(117)

4.2.5. Oxidation of Sulfur Compounds

4.2.5a. Synthesis of β-Hydroxysulfoxides. Preparation of 2-Hydroxypentyl p-Tolyl Sulfoxide by Cooxidation of α-Olefins and Arenethiols with Oxygen in the Presence of Vanadium Pentoxide.[275] A solution of *p*-toluenethiol (1.00 g, 8.05 mmol) and 1-pentene (1.29 g, 18.4 mmol) in 200 ml of hexane–ethyl acetate (4:1) was stirred in a 500-ml flask under the atmosphere of oxygen and the irradiation of a black-light fluorescent lamp overnight. Then the solution was stirred with ca. 30 mg of V_2O_5 for 5 h. The solvent was removed under vacuum to give an oil, which was chromatographed with benzene. The elution with benzene–ethyl acetate (8:2) furnished 1.23 g (67%) of 2-hydroxypentyl *p*-tolyl sulfoxide. The product crystallized on standing and was recrystallized from benzene–hexane.



(118)

*4.2.5b. Oxidation of Sulfides. Oxidation of 4-Chlorophenyl Methyl Sulfide (**127**) to 4-Chlorophenyl Methyl Sulfoxide (**128**) with Hydrogen Peroxide in the Presence of Catalytic Amounts of Bisacetylacelacetonatooxovanadium(IV) [acac)$_2$].*[226] In a typical experiment,[226] **128** (0.67 g, 4.25 mmol) and $VO(acac)_2$ (0.056 mmol) were dissolved in absolute ethanol under dry nitrogen. To this solution, 5 ml of an ethanolic solution containing H_2O_2

(4.23 mmol) was added and the resulting mixture kept at 25°C for 1 h. After removal of most of the solvent *in vacuo*, the residue was treated with warm *n*-hexane and filtered. The filtrate was chromatographed (silica gel) eluting with *n*-hexane-chloroform. Sulfoxide **128** (0.65 g, 3.95 mmol, ~93%) was isolated. The product was further purified by recrystallization from benzene, mesitylene, or xylene.

$$\underset{\textbf{127}}{4\text{-}ClC_6H_4\text{-}S\text{-}CH_3} \longrightarrow \underset{\textbf{128}}{4\text{-}ClC_6H_4\text{-}\overset{\overset{O}{\|}}{S}\text{-}CH_3} \qquad (119)$$

Oxidation of Thiiran to Thiiran 1-Oxide by Hydrogen Peroxide–Vanadium Pentoxide Reagent.[265] To a stirred solution of thiiran (18 g) in *t*-BuOH (180 ml) at 20°C was added portionwise the hydrogen peroxide-*t*-butyl alcohol reagent (170 ml, 6%) containing vanadium pentoxide (0.35 g). After addition the mixture was stirred for a further 30 min, and then *t*-BuOH was removed under reduced pressure. The residue was dissolved in chloroform (100 ml) and the resulting solution, after decolorization with charcoal, was distilled. The fraction (13.4 g) boiling between 35 and 38°C at 5 mm consisted of pure thiiran 1-oxide.

(120)

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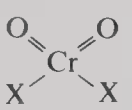
2

Oxidation by Oxochromium(VI) Compounds

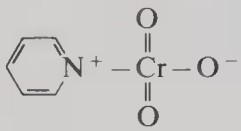
Fillmore Freeman

1. INTRODUCTION

Oxochromium(VI) reagents are some of the most extensively used oxidants for introducing oxygen into organic molecules.[1–16] These versatile, sometimes selective, and synthetically useful oxidants react with almost all types of oxidizable groups. This chapter will discuss mechanisms, scope and limitations, and experimental procedures for chromic acid (**1**), chromyl acetate (**2**),[17–19] chromyl chloride (**3**),[13,15,20–22] *tert*-butyl chromate (**4**),[23,24] chromium trioxide-pyridine complex (Sarett reagent, **5**),[23,25–28] dipyridine chromium(VI) oxide (Collins reagent, **6**),[29–31] pyridinium chlorochromate (PCC, **7**),[32] pyridinium



1 X = OH
2 X = OAc
3 X = Cl
4 X = O – *t* – Bu



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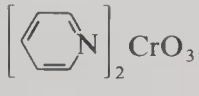

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dichromate (PDC, **8**),[33–35] 2,2′-bipyridinium chlorochromate (BiPy · $HCrO_3Cl$, **9**),[36,37] tetraalkylammonium chromates,[38] supported chromium(VI) oxidants,[39–41] and other

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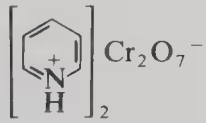

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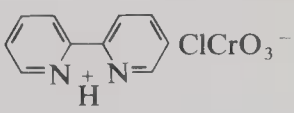

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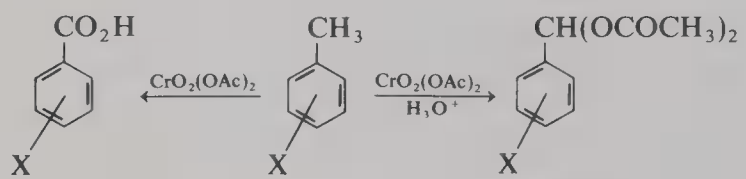
chromium(VI) oxidants. A short background review, which describes in general terms the characteristics of some of the more commonly used oxochromium(VI) oxidants, is given below.

Aqueous chromic acid (**1**), which is prepared from potassium or sodium dichromate and dilute sulfuric acid,[3,42,43] is a potent oxidant. Chromic acid (**1**) may also be used in acetic acid, aqueous acetic acid, or aqueous acetone (Jones reagent).[44,45] Other variations of chromic acid (**1**) oxidants include the Kiliani reagent (H_2CrO_4, H_2SO_4, H_2O) in acetic acid,[42,43] two-phase oxidations ($Na_2Cr_2O_7 \cdot 2H_2O$, H_2SO_4, AcOH-benzene[46]; $Na_2Cr_2O_7 \cdot 2H_2O$, H_2O-ether[47]), chromium trioxide in aqueous acetic,[48] chromium trioxide in anhydrous acetic acid (Fieser reagent),[49,50] and chromium trioxide in concentrated sulfuric acid.[51]

The reaction medium has a dramatic effect on the course of chromic acid (**1**) oxidations.[52,53] The Jones reagent generally oxidizes secondary alcohols containing double or triple bonds to ketones without attacking the unsaturated linkage.[54] This reagent will also oxidize primary allylic or benzylic alcohols to aldehydes in high yields.[55] In the presence of catalytic amounts of mercuric acetate, terminal olefins are oxidized to methyl ketones by the Jones reagent in 80%–90% yields.[56] On the other hand, acidic chromic acid (**1**) solutions will oxidize the alkyl group of an alkylbenzene to a carboxyl group,[3] or an allylic carbon–hydrogen bond to a carbonyl group. Moreover, although ring degradation can occur with acidic chromic acid (**1**) solution, aqueous sodium dichromate oxidizes side chains of polynuclear aromatic systems to carboxyl groups with negligible ring degradation.[57–59]

Chromyl acetate (**2**) is a potent oxidant which is produced from chromium trioxide and acetic anhydride.[16–18] In the absence of mineral acids, **2** oxidizes methylbenzenes to the corresponding benzoic acids.[60] However, in the presence of sulfuric acid (Thiele reagent), the products are benzylidene diacetates (**10**).[61–63] In addition to oxidizing alcohols, unsaturated centers, sulfides, and other functional groups, **2** oxidizes benzylic carbon atoms to carbonyl groups or to tertiary alcohols in excellent yields.[22,60,64–66]



(1)

10

Chromyl chloride (**3**) is a powerful oxidant which is used in nonaqueous solvents. It also oxidizes a wide variety of functional groups. In contrast to **1**, chromyl chloride (**3**) oxidizes alkylbenzenes to aldehydes and ketones.[13,15,17]

tert-Butyl chromate (**4**),[22,23] in nonpolar organic solvents with added acetic anhydride, oxidizes allylic carbon atoms to carbonyl groups.*[,68–77] Carbon–carbon double bonds are not usually attacked and oxidation may occur at both sides of the double bond. *tert*-Butyl chromate (**4**) is also useful for oxidizing primary[73] and secondary alcohols.[74]

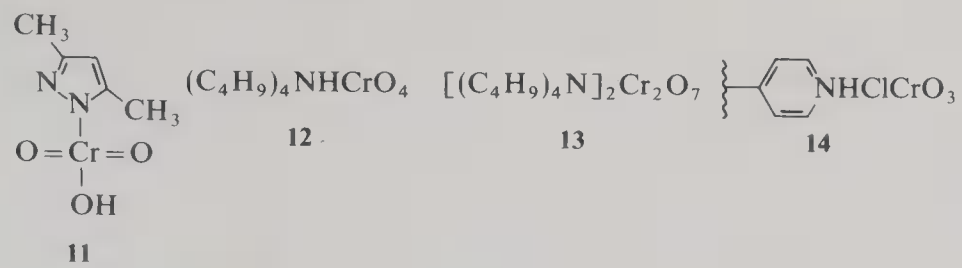
Among the mild, versatile, and selective reagents for the oxidation of alcohols to carbonyl compounds are **6**–**9**, chromic acid supported on Amberlyst A-26, Amberlyst A-29, Amberlite IRA 400, or Amberlite 904,[39] chromyl chloride supported on silica–alumina (SiO_2–Al_2O_3),[†,40,78] chromium trioxide intercalated in graphite ("Seloxcette),[41,79] chromic anhydride-3,5-dimethylpyrazole complex (**11**),[‡,80–83] chromic anhydride–hexamethylphosphoric triamide,[§,84,85] chromic anhydride–diethyl ether,[86] chromic acid–silica

* There is controversy[75–77] concerning the reproducibility of the initial report.[70]

† Ester, ethers, lactones, and nitriles are inert, but alkenes are cleaved.[78]

‡ This complex (**11**) also oxidizes allylic[82] and benzylic[83] carbon–hydrogen bonds.

§ CAUTION: Add CrO_3 in small portions to HMPT with stirring at 20°C. A violent decomposition can result if crushed CrO_3 is added to HMPT.



11 12 13 14

gel (H_2CrO_4–SiO_2),[87] chromium trioxide–pyridine–dichloromethane,[88] chromium trioxide–pyridine–water (Cornforth reagent),[89,90] chromium trioxide–pyridine complex formed *in situ*,*[,28,88,91] chromium trioxide-dimethylformamide,[†,92–94] tetrabutylammonium chromate (**12**),[‡,38] bis(tetrabutylammonium)dichromate (**13**),[95,96] and polymer supported pyridinium chlorochromate (PVPCC, **14**).[97]

2. MECHANISMS

2.1. Carbon–Hydrogen Bonds

Although the chromium(VI) oxidation of alkylbenzenes has received considerable study, very little has been reported concerning the synthetic aspects of the oxidation of alkanes. Chromic acid (**1**), chromyl acetate (**2**),[17–19,65,98–104] chromyl chloride (**3**),[13,15,20–22,105–109] *tert*-butyl chromate (**4**),[§,23,24,75–77] **11**,[†,80–83,110] and dry chromium trioxide pyridine complex[111] are some of the chromium(VI) oxidants which have excellent potential for oxidizing carbon–hydrogen bonds to oxygenated compounds.

2.1.1. Alkanes and Cycloalkanes

The kinetic and mechanistic data for the chromic acid (**1**) oxidation of alkanes and cycloalkanes in aqueous acetic acid have been summarized.[112] The available kinetic data are partially consistent with a hydride transfer, hydrogen atom abstraction, or an insertion mechanism. The kinetic data from the chromic acid (**1**) oxidation of carbon–hydrogen bonds are difficult to interpret owing to the variety of reactions which may follow the initial oxidation step and a dearth of systematic experimental data.

The chromic acid (**1**) oxidation of primary carbon–hydrogen bonds is very slow. Secondary carbon–hydrogen bonds are converted to alcohols which may be subsequently oxidized to ketones, and tertiary carbon–hydrogen bonds lead to tertiary alcohols.[3]

Although the kinetics of the chromyl acetate (**2**) and chromyl chloride (**3**) oxidation of alkanes have not been reported, these reagents show promise of some regiospecificity in the oxidation of carbon–hydrogen bonds.[§,3,5,13,22,113–116]

*CAUTION: The chromium trioxide–pyridine complex can be prepared *in situ* in CH_2Cl_2. This procedure appears to be safer than the method for preparing Sarett reagent.[23,25–28]

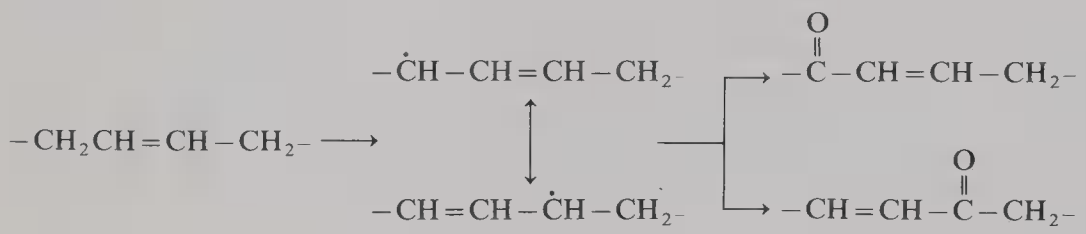
† CAUTION: In order to avoid a fire, powdered CrO_3 must be added in small portions in a nitrogen atmosphere to ice-cooled DMF.[93]

‡ This yellow orange solid (**12**) is very soluble in $CHCl_3$ and CH_2Cl_2. The main advantages are homogeneous conditions and the requirement for only a slight excess of **12**.[38]

§ There is some question as to the nature of the actual chromium(VI) oxidizing species in a solution of CrO_3, acetic anhydride, and acetic acid.[65,100,101,113]

2.1.2. Allylic Oxidations

The oxidation of an allylic carbon hydrogen bond to a carbonyl group can be performed in good to excellent yields with several chromium(VI) oxidants. Although limited kinetic and mechanistic data are available concerning the chromium(VI) oxidation of allylic carbons,[117] it appears that a hydrogen atom or hydride ion is removed from the alkene giving a resonance stabilized allylic radical or carbocation, which is ultimately converted to the unsaturated ketone [Eq. (2)]. However, initial attack by oxidant at the double bond is also possible.[81]



(2)

2.1.3. Benzylic Oxidations

The kinetics and mechanism of the chromic acid (**1**) oxidation of diphenylmethanes in 95% aqueous acetic acid have been studied using an acid catalyst.[118] The reaction followed the rate law, $v = k[CrO_3][\text{diphenylmethane}]h_0$, where h_0 is the Hammett acidity function. The order of reactivity found was triphenylmethane > diphenylmethane > ethylbenzene > toluene > methylcyclohexane > cyclohexane. A kinetic isotope effect of 6.4 and a ρ^+ of -1.40 were observed with diphenylmethanes. These data, the oxidation of alkylbenzenes by **1** in glacial acetic acid[119,120] and the oxidation of toluene and ring-substituted toluenes by chromium trioxide in acetic acid,[121,122] are consistent in many respects with an activated complex involving hydrogen atom abstraction, a hydride transfer, or an insertion mechanism.

Although the kinetics and mechanisms of the chromic acid (**1**) and chromyl acetate (**2**) oxidation of alkylbenzenes remain to be elucidated, Freeman and co-workers[22,65,98–101] have shown that chromium(V) is involved in the chromyl acetate (**2**) (k_1) oxidation of alkylbenzenes [Eqs. (3) and (4)]. A relatively stable chromium(IV) appears to result from the chromium(VI) oxidation (k_2). The relative rates of oxidation for toluene, ethyl-, propyl-, and *i*-propylbenzene are 1:27:16:74 and 1:6:2.5:6 for k_1 and k_2, respectively. Primary kinetic deuterium isotope effects were obtained for *i*-propylbenzene. Rho values of -1.09 and -0.98 were obtained for k_1 and k_2, respectively, with toluenes containing electron withdrawing groups.

$$C_6H_5-CH_2-R + \underset{\mathbf{2}}{CrO_2(OAc)_2} \xrightarrow{k_1} C_6H_5-\dot{C}H-R + Cr(V) \tag{3}$$

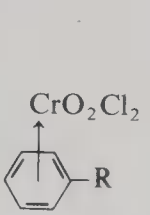
$$C_6H_5-CH_2-R + Cr(V) \xrightarrow{k_2} C_6H_5-\dot{C}H-R + Cr(IV) \tag{4}$$

The kinetics and mechanisms of the chromyl acetate (**2**) oxidation of toluenes to benzylidene diacetates (**10**) appear not to have been studied.[22]

The chromyl chloride (**3**) oxidation of alkylbenzenes to carbonyl compounds is first order in each reactant.[123–127] The order of reactivity for toluene, diphenylmethane, and triphenylmethane is approximately 1:100:1000. A kinetic isotope effect was observed.[128] The oxidation, which may involve prior charge transfer complex formation (**15**),[129] invariably leads to the Étard complex (**16**).[3,130,131]

The kinetics of the oxidation of several sodium *p*-alkylbenzenesulfonates by aqueous dichromate have been studied from pH 5.4 to 7.0.[132] The data suggest that the only active

oxidant under these conditions is the acid chromate ion, $HCrO_4^-$. A free radical mechanism was proposed for this oxidation process.[132,133]



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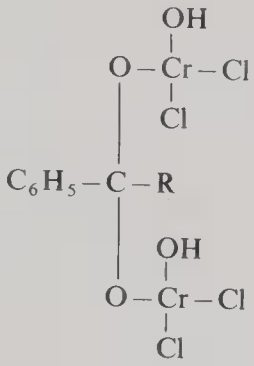


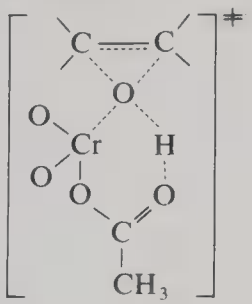
16

It is surprising that despite the apparent synthetic utility of the oxochromium(VI) oxidation of alkylbenzenes, very little is known about the mechanistic details of these important oxidative procedures.[5,22,65,100,101,118]

2.2. Carbon–Carbon Double Bonds

The oxochromium(VI) oxidation of alkenes can lead to several different products including carboxylic acids, carbonyl compounds, glycols, ketols, and oxiranes (epoxides). However, it is possible to obtain good to excellent yields of desired products if the appropriate chromium(VI) oxidant and experimental conditions are selected. The mechanisms involved in the transition metals oxidation of alkenes have generated considerable controversy.[134–136]

Alkenes are oxidized by chromic acid (**1**) in acetic acid media with a rate which is first order in both alkene and **1**.[137] The oxidation product is a mixture of diacetates, monoacetates, diols, and epoxides. The rate of oxidation is little affected by steric factors and is increased by increasing the number of alkyl substituents. Activated complex **17** has been proposed for oxidation in acetic acid and activated complexes **18** and **19** have been suggested for oxidation in aqueous media.[136–139]



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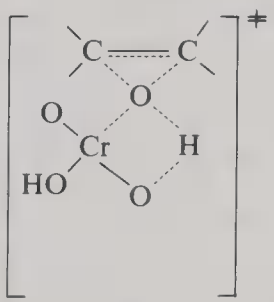

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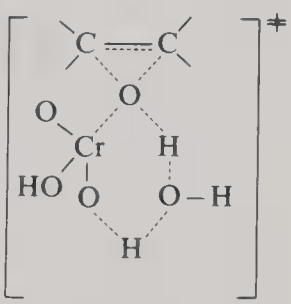
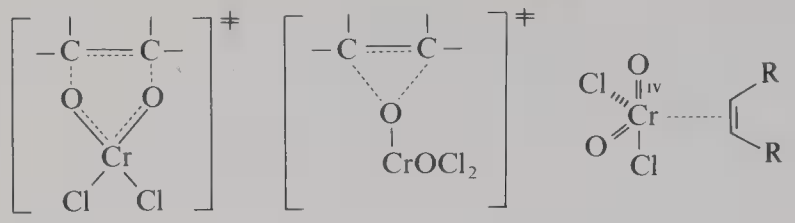


19

The kinetics of the oxidation of cinnamic acid by dichromate ion in acidic media have been reported.[140,141]

Freeman and co-workers[142–150] have examined the chromyl chloride (**3**) oxidation of alkenes in carbon tetrachloride and dichloromethane solution. Although charge transfer complex formation may occur prior to the oxidation step,[22,136,147] the simple rate law $v = k[\mathbf{3}][\text{alkene}]$ was observed.[144,146,149,150] Although a five-membered cyclic activated complex (**20**) has been considered, a three-membered cyclic activated complex (**21**) may be involved.[13,22,136,144,146,150–156]



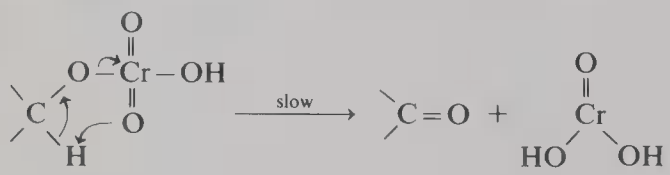
20 21 22

The above studies, and others,[157,158] have shown that oxidation of olefins with **3** at low temperatures basically affords three products: oxiranes which can rearrange to carbonyl compounds,[142–150] α-chloroalcohols, α-chloroketones, and vicinal dichlorides. These data conspire to suggest that the initial step in the chromyl chloride (**3**) oxidation of alkenes involves the organometallic intermediate **22** which may subsequently rearrange to a metallocycle. *Ab initio* molecular orbital calculations have also been reported for the chromyl chloride (**3**) oxidation of ethene.[159,160]

2.3. Hydroxy Compounds

2.3.1. Alcohols

The major use of chromium(VI) oxidants in synthetic chemistry is in the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively.[161–195] Table I summarizes some of the extensive kinetic and mechanistic studies of the chromium(VI) oxidation

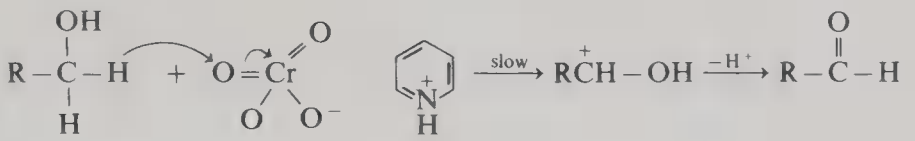


(5)

TABLE I. Kinetic and Mechanistic Studies of the Chromium(VI) Oxidation of Alcohols

Alcohol	Oxidant	Reference
Primary and secondary	H_2CrO_4	161, 172
	PCC (7)	173, 174, 194
Benzyl alcohols	H_2CrO_4	175
	$Na_2Cr_2O_7$	176
	PCC (7)	177, 194
Cyclopropanols	H_2CrO_4	178, 179
Cyclobutanol	H_2CrO_4	180
Cycloalkanols	PCC (7)	181, 194
Adamantanol	H_2CrO_4	182
Benzhydrols	H_2CrO_4	183, 184
Deoxybenzoin	H_2CrO_4	185, 186
Benzoin	H_2CrO_4	187
Camphor	H_2CrO_4	188
Tertiary	H_2CrO_4	189
Triterpenoids	H_2CrO_4	190
Steroids	PCC (7)	191, 194
Three-electron oxidations	H_2CrO_4[Cr(V)]	193, 195

of a wide variety of alcohols. Alcohol oxidation with chromium(VI) oxidants involves the rate determining step shown in Eq. (5). On the basis of the experimental data, Eq. (5) or (6) can be proposed for the pyridinium chlorochromate (PCC, **7**) oxidation of alcohols.[174–177]

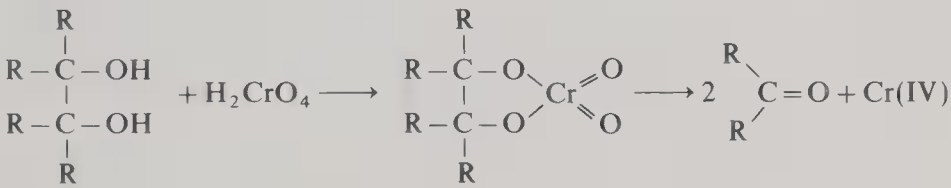


(6)

7

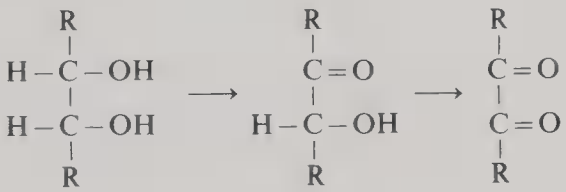
2.3.2. *Diols*

Although the kinetics of the chromic acid (**1**) oxidation of glycols have received some study,[196–200] there appears to be a paucity of data concerning the synthetic aspects of these oxidations. Intermediate **23** [Eq. (7)] may be involved or the oxidation might be stepwise involving α-ketols as intermediates [Eq. (8)].



(7)

23

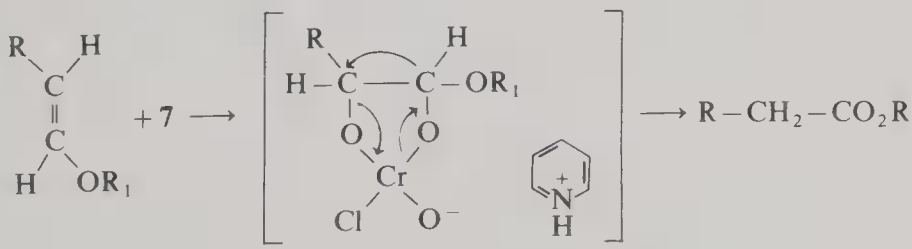


(8)

2.4. Ethers

The oxidation of dioxane was first order in dichromate and the rate constants decreased with increasing ionic strength. The effect of solvation on E_a was discussed.[201]

A possible reaction mechanism for the PCC (**7**) oxidation of linear and cyclic enol ethers to esters and lactones could involve initial attack upon the olefin to afford unstable intermediate **24** (cf. **20** and **23**). Heterolytic cleavage of the Cr–O bond, accompanied by a 1,2-hydride shift, can then give the products [Eq. (9)].

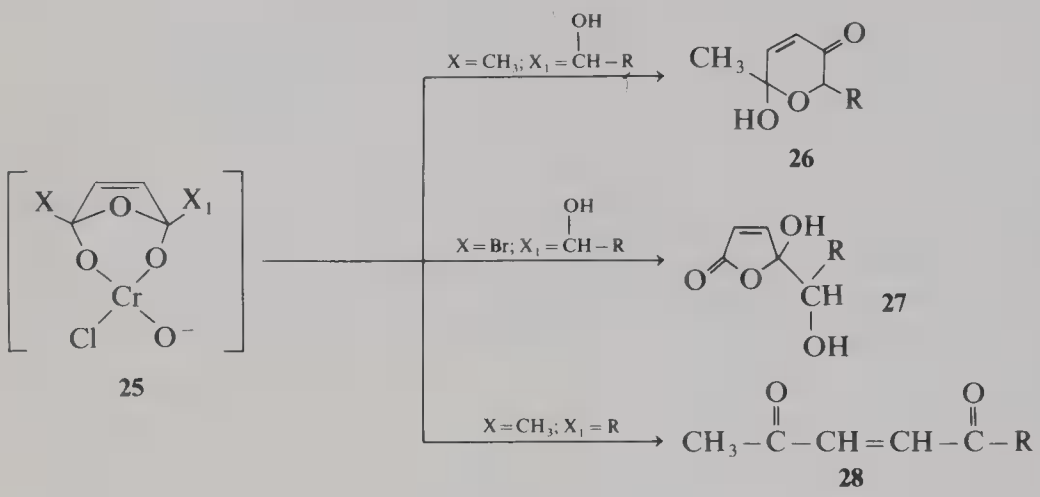


(9)

24

A general mechanism for the oxidation of furan derivatives by **7** has been proposed.[194,195] The experimental data are in agreement with an initial 1,4-electrophilic

attack by the chlorochromate anion to give **25**. Subsequent decomposition of **25** to the final products (**26**, **27**, and **28**) depends on the nature of substituents X and X_1. Moreover, the formation of **26** implies a nucleophilic participation of the side chain hydroxyl groups in the heterolysis of **25**.[194,195]



(10)

2.5. Carbonyl Compounds

2.5.1. Aldehydes

Although the kinetics and mechanisms of the chromium(VI) oxidation of aldehydes have been investigated,[203–211] this is not a highly useful method for synthetic purposes since aldehydes are generally more difficult to obtain than the corresponding acids. However, oxochromium(VI) oxidants may be used to oxidize nonenolizable aldehydes in good yields.

2.5.2. Ketones

As with aldehydes, the oxochromium(VI) oxidation of ketones is not a synthetically useful procedure. The oxidation of an enolizable ketone generally leads to carbon–carbon bond cleavage with the formation of two carboxylic acids. Limited kinetic studies of the chromium(VI) oxidation of ketones have been reported.[212]

2.6. Carboxylic Acids

The chromium(VI) oxidation of carboxylic acids has not been developed as a useful synthetic procedure. The oxidation generally leads to degradation of the carbon chain via bond cleavage. The kinetics and mechanisms of the chromium(VI) oxidation of carboxylic acids have been reported by several investigators.[213–218]

2.7. Nitrogen Compounds

Although the use of chromium(VI) oxidants in synthetic procedures for the oxidation of organic compounds containing nitrogen remains an area to be explored, the kinetics of the chromium(VI) oxidation of ethanolamines,[219] hydroxylamine,[220] aniline,[221] azo compounds,[222] lower aliphatic amines,[223,224] triphenylamines,[225] hydrazine,[226–230] phenylhydrazine,[231] and penicillamine[232] have been reported.

2.8. Sulfur Compounds

The kinetics of the chromium(VI) oxidation of thiols,[233] glutathione,[232] L-cysteine,[234] methionine,[235] thioureas,[236,237] and methyl phenyl sulfoxides[238] have been investigated.

2.9. Organic Halides

The chromic acid oxidation of benzyl chloride to phenylmethanal in aqueous acetic acid is first order with respect to halide, oxidant, and hydronium ion.[239]

3. SCOPE AND LIMITATIONS

3.1. Oxidation of Alkanes and Cycloalkanes

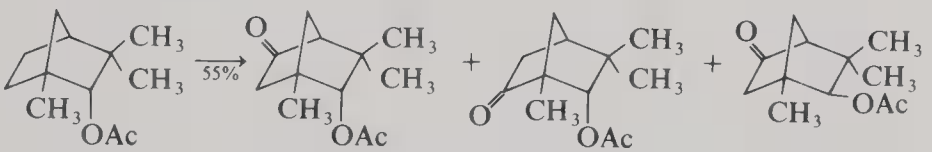
The carbon–hydrogen bonds in alkanes and cycloalkanes may be converted to alcohols, aldehydes, and ketones with strong chromium(VI) oxidants. The primary products of alkane and cycloalkane oxidations can be oxidized further to carboxylic acids via cleavage of C–C bonds [Eq. (11)]. However, as will be seen below, use of specific chromium(VI) oxidants under controlled experimental conditions can produce good to excellent yields of desired oxygenated products.

$$R-CH_2-CH_2-R_1 \longrightarrow R-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-R_1 \longrightarrow R-\overset{\displaystyle O}{\overset{\|}{C}}-CH_2-R_1$$

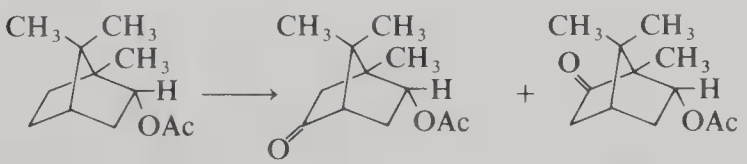
$$\longrightarrow RCO_2H + R_1CO_2H \qquad (11)$$

It can be seen in Table II that chromyl acetate (**2**) oxidations can be rather selective.[5,113] With the smaller bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane systems only ketones and secondary acetates are formed, without attack at the bridgehead position. On the other hand, attack at the bridgehead predominates in larger systems.[5,100,113]

Other examples of regioselectivity in the chromyl acetate (**2**) oxidation of bicyclic systems, which is probably a result of greater accessibility at the C_5 position, is seen in the oxidation of *endo*-fenchyl acetate (**29**),[5] (−)-bornyl acetate (**33**),[102] and (−)-isobornyl acetate (**36**).[114] This regioselectivity is useful in the synthesis of (+)-6-exo-hydroxycamphene nojigku alcohol (**39**) from **36**.[114]

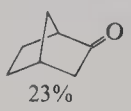
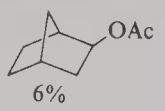
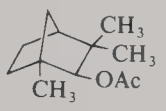
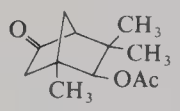
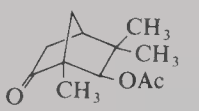
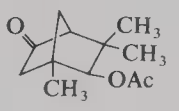
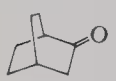
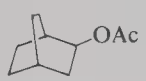
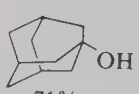
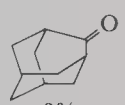


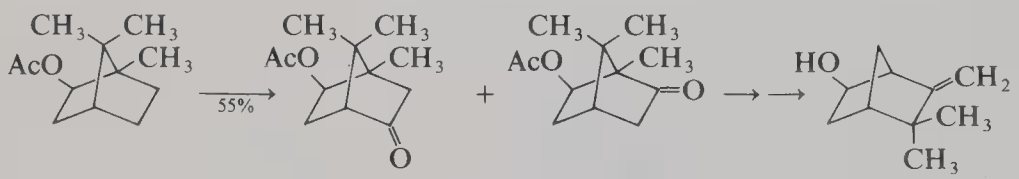
29 **30** (50%) **31** (4%) **32** (1%) (12)



33 **34** (40%) **35** (16%) (13)

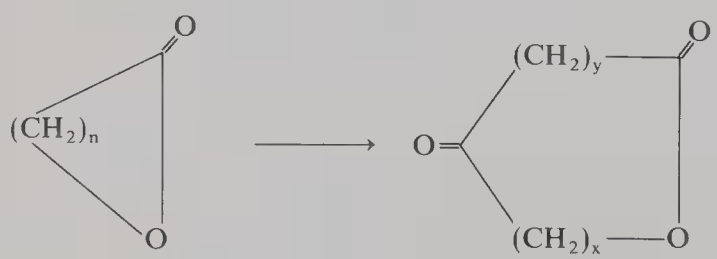
TABLE II. Oxidation of Cycloalkanes with Chromyl Acetate (**2**)

Cycloalkane	Products	Reference
	 23%  6%	113
	 43%  6.2%  3.1%	5
	 40%  4%	113
	 71%  9%	113



36 **37** (4:1) **38** **39** (14)

Direct remote oxidation of macrocyclic lactones (**40**) to a mixture of monoketo lactones (**41**, 35%–40%) can be accomplished with partial regiospecificity using **2** in acetic acid at 25°C for 48h.[103] Presumably the preferred conformation of **40** determines the possible oxidation sites.



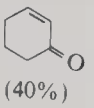
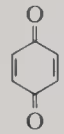
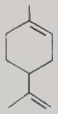
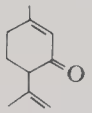
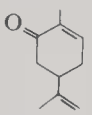
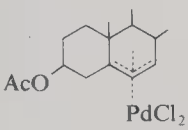
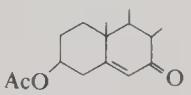
40, n = 11, 14, 15 **41**, x + y = 10, 13, 14 (15)

3.2. Oxidation of Allylic Carbon–Hydrogen Bonds

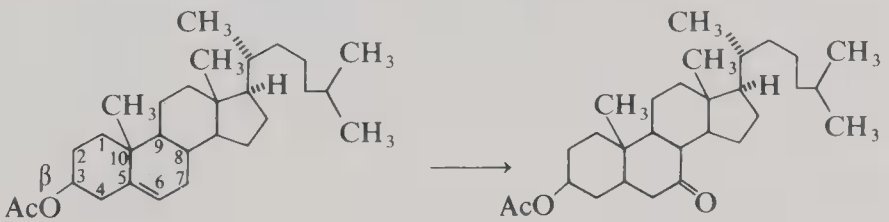
Table III shows the allylic products from some chromium(VI) oxidations. Additional examples are described below.

Ratcliffe's reagent (CrO_3 · pyridine complex[91]) can be used for allylic oxidations [e.g.,

TABLE III. Allylic Products of Chromium(VI) Oxidations

Substrate	Oxidant	Products	Reference
	$(t\text{-BuO})_2CrO_2$	 (40%)  (24%)	70
	Sarett reagent	 (68%)  (10%)	5
	Sarett reagent	 (31%)  (36%)	5
	CrO_3 in N,N-dimethylformamide	 (96%)	94

cholesteryl acetate (**42**) or (**44**] without isolation of the crystalline complex if all reagents are kept dry.[111] However, *tert*-butyl chromate (**4**) gives **43** in 90% yield.[70,75–77]



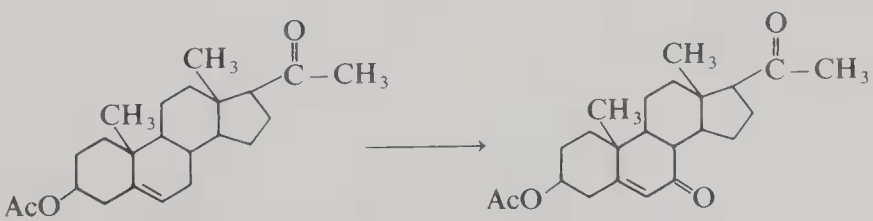
(16)

42 **43** (72% – 76%)

(17)

44 **45** (70%)

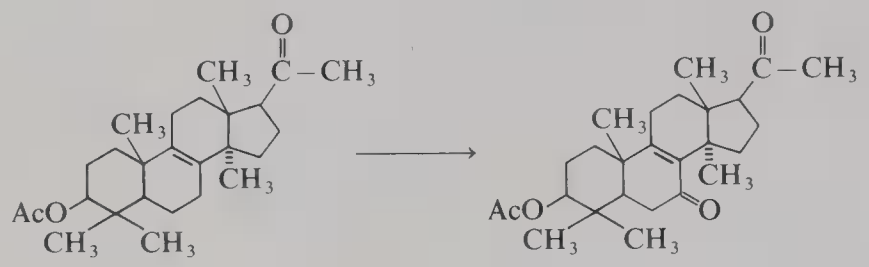
Sodium dichromate in acetic acid oxidizes the steroidal alkene **46** to **47** in 79% yield.[240]



(18)

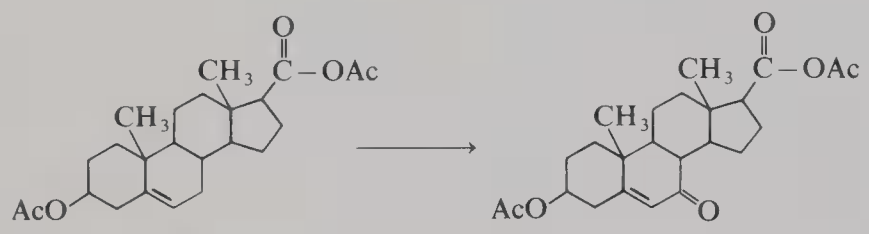
46 **47**

Although oxidation of the Δ^8-pregnene derivative **48** may lead to different carbonyl groups at C_7 and C_{11}, chromium trioxide in acetic acid converts **48** to **49** in 75% yield.[241] *tert*-Butyl chromate (**4**) oxidizes **50** to **51** in 71% yield.[240]



(19)

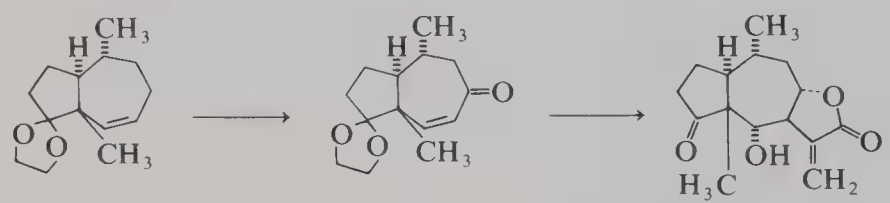
48 **49**



(20)

50 **51**

Chromic anhydride-3,5-dimethylpyrazole complex (**88**) oxidizes **52** to **53**, which is an intermediate in the total synthesis of the antibacterial helenanolide (+)-carpesiolin (**54**).[82] The oxidation of cholesteryl benzoate and Δ^6-cholestene-3β,5α-diol to the corresponding Δ^5-7-ketones (70%–75%) by **11** is rapid.[81]



(21)

52 **53** (60%) **54**

3.3. Oxidation of Carbon–Hydrogen Bonds Adjacent to Triple Bonds

A new method for the synthesis of conjugated acetylenic ketones (**56**), which provides these compounds in a single step from readily available alkynes (**55**), involves oxidation with chromium trioxide–pyridine complex or anhydrous sodium chromate in solution of acetic acid and acetic anhydride (Table IV).[242]

(22)

55 **56**

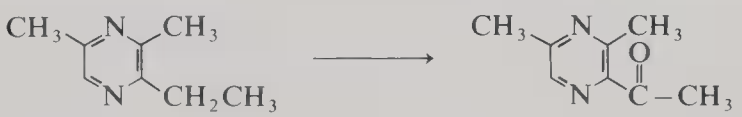
TABLE IV. Acetylenic Ketones from Chromium(VI) Oxidations[a]

Alkyne	Product	Yield (%)	
		CrO_3(pyridine)$_2$	Anhydrous Na_2CrO_4
1-Phenyl-1-butyne	$CH_3-\overset{\overset{O}{\|}}{C}-C\equiv C-C_6H_5$	40	17
4-Octyne	$CH_3CH_2-\overset{\overset{O}{\|}}{C}-C\equiv C-(CH_2)_2CH_3$	42	19
1-Decyne	$CH\equiv C-\overset{\overset{O}{\|}}{C}-(CH_2)_6CH_3$	0	0
2-Decyne	$CH_3-C\equiv C-\overset{\overset{O}{\|}}{C}-(CH_2)_5CH_3$	31	18
5-Decyne	$CH_3(CH_2)_2-\overset{\overset{O}{\|}}{C}-C\equiv C-(CH_2)_3CH_3$	46	20

[a] Reference 242.

3.4. Oxidation of Alkylbenzenes

Alkylbenzenes may be oxidized to a wide variety of oxygenated products depending on which chromium(VI) oxidant is used. Acidic chromic acid (**1**) oxidizes the alkyl group of an alkylbenzene to a carboxyl group (Table V).[243–260] This procedure provides the basis for the determination of the orientation and number of alkyl groups in substituted benzenes or heterocycles.[3,261,262] Experimental conditions may be adjusted so some selectivity is obtained in polyalkyl-substituted compounds. For example, the ethyl group in 2-ethyl-3,5-dimethylpyrazine (**57**) is selectively oxidized to an acetyl group (**58**) in 50%–70% yield by hot chromic acid (**1**).[263]



57 **58** (23)

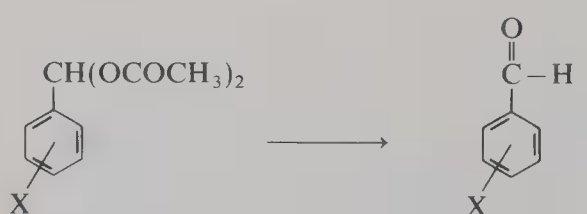
The use of dichromate ion in nearly neutral aqueous solution, where the oxidant is mainly in the form of acid chromate ion, results in almost exclusive attack of alkyl side chains.[57–59,132,133,263–265] The yield of carbonyl or carboxylic acid product is generally superior (Table VI) to that obtained using chromic acid (**1**), and the isolation procedure is simpler.[57,264] One of the major advantages of the dichromate procedure is the oxidation of side chains on polynuclear aromatic hydrocarbons without attack on the aromatic rings (Table VII).[57]

The oxidation of substituted toluenes with CrO_3 in acetic anhydride in the presence of sulfuric acid or methanesulfonic acid gives the corresponding benzal diacetates (**10**) in fair to

TABLE V. Products of the Chromic Acid (1) Oxidation of Alkylbenzenes

Alkylbenzene	Oxidant	Products	Yield (%)	Reference
Methylbenzene	H_2CrO_4	Benzoic acid		243
1,3-Dimethylbenzene	H_2CrO_4 HNO_3	Isophthalic acid		244
1,4-Dimethylbenzene	H_2CrO_4 HNO_3	Terephthalic acid		244
1,2,4-Trimethylbenzene	CrO_3 HOAc	Trimellitic acid	23	245, 246
Ethylbenzene	H_2CrO_4 H_2SO_4	Benzoic acid	80–85	247
Propylbenzene	H_2CrO_4 H_2SO_4	Benzoic acid	50–60	247
i-Propylbenzene	H_2CrO_4 HOAc	2-Phenyl-2-propanol Phenylethanone		248, 249
sec-Butylbenzene	H_2CrO_4 HOAc	Benzoic acid Phenylethanone		250
Octylbenzene	H_2CrO_4	Benzoic acid		251
Tetralin	H_2CrO_4 HOAc	Tetralone		252
Diphenylmethane	H_2CrO_4 HOAc	Diphenylketone		120
Fluorene	CrO_3 HOAc	Fluorenone		122
1,1-Diphenylethane	H_2CrO_4 HOAc	Diphenylketone		253
4-Nitrotoluene	H_2CrO_4 H_2SO_4	4-Nitrobenzoic acid	82–86	254, 255
3,4-Dinitrotoluene	H_2CrO_4 H_2SO_4	3,4-Dinitrobenzoic acid	89	256
2,4,6-Trinitrotoluene	H_2CrO_4 H_2SO_4	2,4,6-Trinitrobenzoic acid	57–69	257
2-Methyl-5-nitropyridine	H_2CrO_4 H_2SO_4	5-Nitropyridine-2-carboxylic acid	80	258
Triphenylmethane	H_2CrO_4 H_2SO_4	Triphenylcarbinol Diphenylketone		259, 260

good yields [Eq. (1), Table VIII].[61–63,267,268] Hydrolysis of **10** gives the corresponding substituted phenylmethanals (**59**).[60,267,268] In the absence of sulfuric acid or methansulfonic acid, the substituted toluenes are oxidized to the corresponding benzoic acids.[60,267]



10 **59** (24)

Chromyl acetate (**2**) oxidizes triphenylmethane to triphenylcarbinol in quantitative yield, and diphenylmethanes to the corresponding ketones in 90%–100% yields.[22,60,64,66]

Chromyl chloride (**3**) oxidizes alkylbenzenes to aldehydes and ketones (Table IX) via

TABLE VI. Oxidation of Alkylbenzenes with Aqueous Sodium Dichromate

Alkylbenzene	Product	Yield (%)	Reference
Ethylbenzene	Methyl phenyl ketone[a,b]	30–70	58
	Benzoic acid	10–40	
i-Propylbenzene	Methyl phenyl ketone	25	266
	Benzoic Acid	11	
	α-Methylstyrene	21	
	2-Phenyl-2-propanol	5	
Fluorene	Fluorenone	99	57
		—	57
3-Fluorotoluene	3-Fluorobenzoic acid	35	57
4-Fluorotoluene	4-Fluorobenzoic acid	55	57
2-Chlorotoluene	2-Chlorobenzoic acid	98	57
4-Chlorotoluene	4-Chlorobenzoic acid	88	57
4-Nitrotoluene	4-Nitrobenzoic acid	94	57
2-Bromo-*p*-xylene	Bromoterephthalic acid	68	57
3-Methoxytoluene	3-Methoxybenzoic acid	70	57
4-Methylbiphenyl	4-Biphenylcarboxylic acid	95	57

[a] The products reported earlier[59] appear to be in error.
[b] It is interesting to contrast this reaction with chromyl acetate (**2**) which gives methyl phenyl ketone[66] and with chromyl chloride (**3**) which gives mainly phenylethanal.

TABLE VII. Aqueous Sodium Dichromate Oxidation of Alkyl Substituted Polynuclear Aromatic Hydrocarbons[a]

Hydrocarbon	Product	Yield (%)
1-Methylnaphthalene	1-Naphthoic acid	95
2-Methylnaphthalene	2-Naphthoic acid	93
1,2-Dimethylnaphthalene	1,2-Naphthalic anhydride	75
2,3-Dimethylnaphthalene	2,3-Naphthalene dicarboxylic acid	93
2-Methylanthracene	2-Anthroic acid	98
1-Methylphenanthrene	1-Phenanthroic acid	91
4-Methylphenanthrene	4-Phenanthroic acid	91
9,10-Dimethylphenanthrene	9,10-Phenanthrenedicarboxylic anhydride	92
2-Methyltriphenylene	2-Triphenylenecarboxylic acid	92
6-Methylchrysene	6-Chrysenecarboxylic acid	88
3-Methylfluorenone	Fluorenone-3-carboxylic acid	88

[a] Reference 57.

TABLE VIII. Chromyl Acetate (**2**) Oxidation of Alkylbenzenes

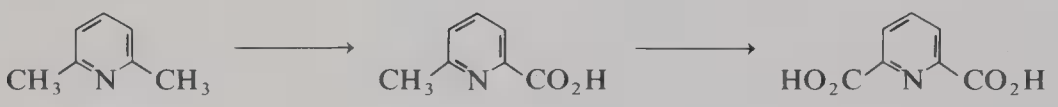
Alkylbenzene	Product	Yield (%)	Reference
2-Nitrotoluene	2-Nitrobenzaldehyde diacetate	36–37	62,267
4-Nitrotoluene	4-Nitrobenzaldehyde diacetate	60–65	62,267
4-Bromotoluene	4-Bromobenzaldehyde diacetate	48–60	269
4-Cyanotoluene	4-Cyanobenzaldehyde diacetate	63	267–269
Methyl *p*-tolyl sulfone	*p* (Methylsulfonyl) benzaldehyde diacetate	52	270
2-Methyl-5-chlorobenzenesulfonyl chloride	4-Chloro-2-chlorosulfonylbenzaldehyde diacetate	34	271
o-Xylene	Phthalaldehyde tetraacetate	14	61
m-Xylene	Isophthalaldehyde tetraacetate	40–50	61
p-Xylene	Terephthalaldehyde tetraacetate	52	61

TABLE IX. Chromyl Chloride (3) Oxidation of Alkylbenzenes

Alkylbenzene	Solvent	Product	Yield (%)	Reference
Toluene	CCl_4	Benzaldehyde	90	15
o-Xylene	CCl_4	*o*-Tolualdehyde	65	67, 106
m-Xylene	CCl_4	*m*-Tolualdehyde	60	67, 106
p-Xylene	CCl_4	*p*-Tolualdehyde	70–80	67, 106
Ethylbenzene	CS_2	Phenylacetaldehyde		272, 273
n-Propylbenzene	CCl_4	Benzyl methyl ketone	11–26	107, 272, 273
		Propiophenone	3–14	
		α-Chloro-*n*-propylbenzene	12–30	272, 273
i-Propylbenzene	CS_2	Hydratropaldehyde		
		Methyl phenyl ketone		
Diphenylmethane	CS_2	Benzophenone	98	106, 131
Triphenylmethane	CCl_4	Triphenylcarbinol	93	106, 274
Fluorene	CCl_4	Fluotenone	35	67
p-Benzyltoluene	CS_2	Phenyl *p*-tolyl ketone	62	275
4-Chlorotoluene	CCl_4	4-Chlorobenzaldehyde	75	106, 276, 277
4-Nitrotoluene	CCl_4	4-Nitrobenzaldehyde	60–70	276, 278

the Étard complex (**16**). With alkyl groups larger than methyl, oxidation occurs preferentially at the benzylic carbon atom.

Oxidation of 2,6-lutidine (**60**) with chromium trioxide gives 6-methyl-2-pyridinecarboxylic acid (**61**) with 60%–66% selectivity [cf. Eq. (22)]. The sodium dichromate oxidation of **60** gives 2,6-pyridinecarboxylic acid (**62**, 62%).[279]

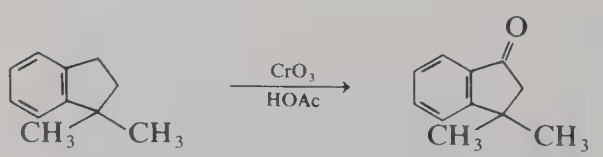


60 **61** **62** (25)

Selectivity in the cyclization of gamma-arylbutanoic acids via chromic acid (**1**) oxidation at the benzylic position has been studied.[280]

3.5. Oxidation of Hydrindacenes, Indans, Tetralins, and Acenaphthenes

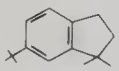
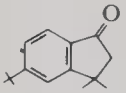
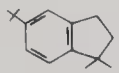
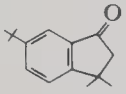
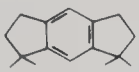
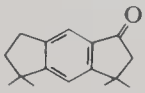
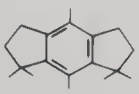
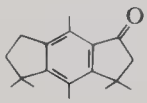
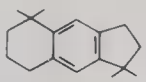
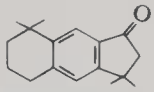
The oxidation of indans and hydrindacenes [Eq. (26), Table X] is an attractive synthesis since the resulting ketones are useful intermediates for preparing indenes and their homologs via reduction and dehydration.[281]



63 **64** (88%) (26)

The chromic acid (**1**) oxidation of a series of mono- and polyalkyl-1,2,3,4-tetrahydronaphthalenes (tetralins) has been investigated (Table XI).[252,282–284] Preferential oxidation occurs at the benzylic methylene position para to an alkyl substituent in the aromatic ring. An alkyl group *ortho* to a benzylic methylene position may enhance or retard

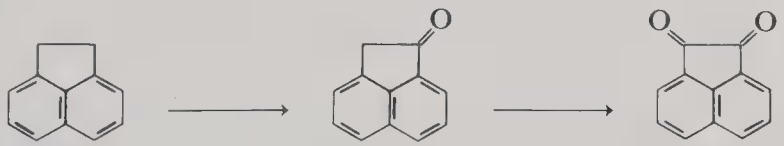
TABLE X. Chromium Trioxide in Acetic Oxidation of Hydrindacenes and Indans[a]

Substrate	Product	Yield (%)
		92
		87
		90
		88
		90

[a] Reference 281.

oxidation at that position, depending upon the degree of steric crowding by the alkyl group. 2-Alkyltetralins undergo preferential oxidation in that 3-alkyl-1-tetralones predominate in the product mixture.

The chromic acid (**1**)[285] and dichromate[286,287] oxidation of acenaphthene (**65**) to acenaphthenone (**66**) or to acenaphthenequinone (**67**)[288] have received some study.



65 **66** **67** (27)

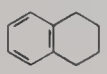
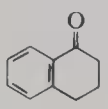
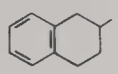
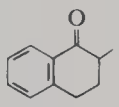
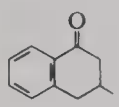
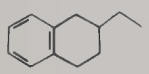
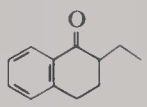
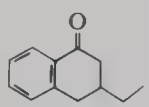
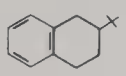
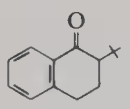
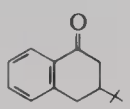
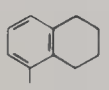
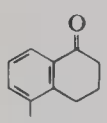
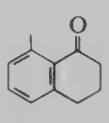
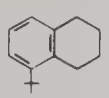
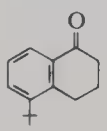
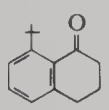
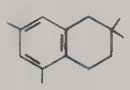
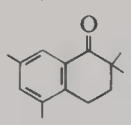
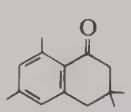
3.6. Oxidation of Aromatic Rings

Chromyl acetate (**2**) and chromyl chloride (**3**) are the first nonenzymatic oxidants to mimic mixed-function oxygenases in all important aspects [(1) stereospecific hydroxylation of aliphatic hydrocarbons, (2) oxidation of olefins and aromatic substances, and (3) hydroxylation of aromatic substrates with concomitant NIH shift].[289] These studies involved the oxidation of naphthalene to 1,4-naphthoquinone.

Table XII shows the yield of quinones from the chromium(VI) oxidation of polynuclear hydrocarbons.[290–293] Other examples include the chromium(VI) oxidation of 2,6-dimethylnaphthalene,[294] 1,2,5-trimethylnaphthalene,[295,296] 1-methylanthracene,[297] 2,6-dimethylanthracene,[298] 1,3,5,7-tetramethylanthracene,[299] phenanthrene,[300,301] 1-methylphenanthrene,[302] and 1-ethylphenanthrene.[303]

A two-stage electrochemical process for the oxidation of anthracene to anthraquinone in

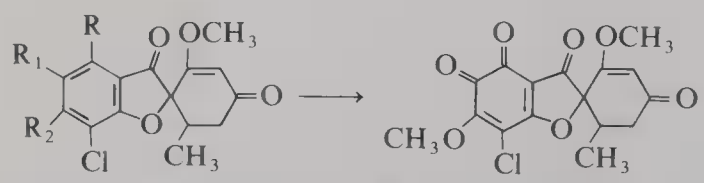
TABLE XI. Chromic Acid Oxidation Products of Tetralins[a]

Tetralin	1-Tetralone products A	1-Tetralone products B	Ratio A:B	Combined yield (%)
				55
			1.0/2.1	72
			1.0/2.1	83
			1.0/5.8	70
			1.0/1.3	60
			2.9/1.0	62
			1.0/6.1	57

[a] Reference 282.

89%–95% yield with dichromate has been reported.[304] The oxidant may be regenerated electrolytically in aqueous sulfuric acid.

Addition of potassium dichromate to griseofulvin (**68**) in concentrated sulfuric acid produced a red color due to formation of the *o*-quinone **69**, which is useful for identification of **68**.[305] Intermediate oxidation products **70** and **71** were obtained with **68** in excess at low temperature.



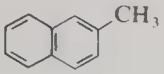
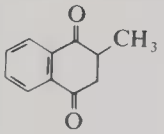
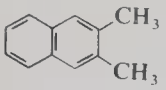
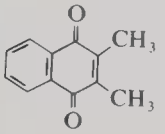
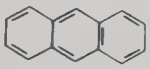
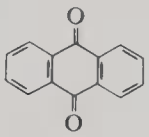
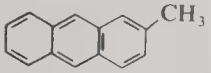
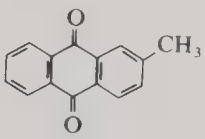
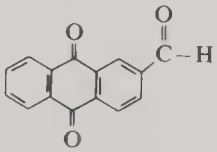
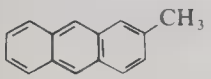
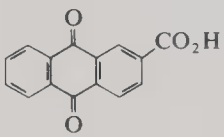
(28)

68, $R = OCH_3$, $R_1 = H$, $R_2 = OCH_3$ **69**

70, $R = R_1 = OH$, $R_2 = OCH_3$

71, $R = OCH_3$ $R_1 = R_2 = OH$

TABLE XII. Chromium(VI) Oxidation of Polynuclear Hydrocarbons

Aromatic compound	Oxidant	Products	Yields (%)
	CrO_3[a] HOAc		25–40
	CrO_3[b] HOAc		60–80
	$Na_2Cr_2O_7$[c]		99
	CrO_2Cl_2, CCl_4[d]	 (42%)  (25%)	
	$Na_2Cr_2O_7$[e] H_2SO_4		100

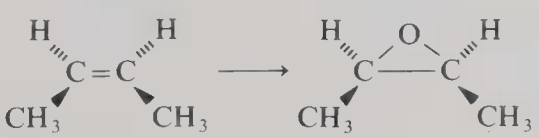
[a] References 291, 292.
[b] Reference 291.
[c] Reference 263.
[d] Reference 133.
[e] Reference 293.

3.7. Oxidation of Unsaturated Systems

3.7.1. Nonfunctionalized Alkenes and Polyenes

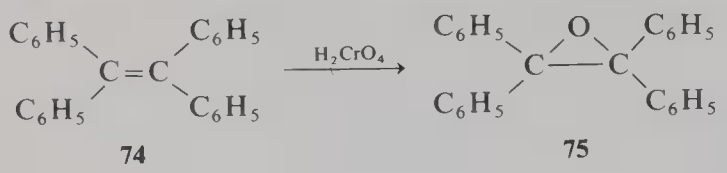
Pyridinium chlorochromate (PPC, **7**) is slightly acidic, but unlike other oxochromium(VI) oxidants, it does not oxidize simple carbon–carbon double or triple bonds.[10,306] However, **7** can bring about E–Z isomerization[32] and oxidize activated carbon–carbon double bonds.[194] A π complex may be involved in the interaction of **7** and olefins.[22,202,307] The first example of the direct conversion of enol ethers to esters or lactones by the PCC (**7**) oxidation of enol ethers is described above [Eq. (9)].[202]

Although the chromic acid (**1**) oxidation of carbon–carbon double bonds does not appear to be synthetically useful at this time, chromyl acetate (**2**)[22,60,64,66] and chromyl chloride (**3**) are useful reagents for oxidizing olefins. Chromyl acetate (**2**) has been reported to form oxiranes from olefins with retention of configuration [Eq. (28)].[308] The syntheses of chiral oxiranes is important because they constitute ideal building blocks for asymmetric syntheses, since subsequent reactions do not generally involve the chiral center.[309]



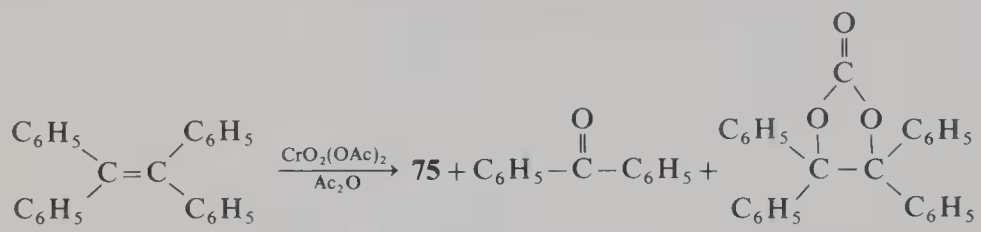
(29)

The chromic acid (**1**) oxidation of tetraphenylethene (**73**) gives mainly epoxide **74**.[310–312] Although chromic acid (**1**) is useful in the Barbier–Wieland side-chain determination,[313–315] it is not generally very useful for synthetic reactions involving carbon–carbon double bonds.



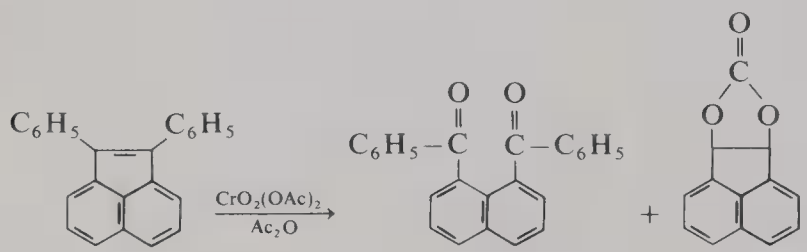
74 **75** (30)

Chromyl acetate (**2**) oxidizes **74** to **75** (20%), benzophenone (5%), and benzopinacol (**76**, 60%).[51] Similar results are obtained with diphenylacenaphthalene [**77**, Eq. (32)]. The



74 **76** (31)

formation of diol carbonates is a nonstereospecific process.[51] Table XIII, which omits the cleavage products, shows that chromyl acetate (**2**) is also useful for converting styrene derivatives to epoxides.[316–319]



77 **78** **79** (32)

Jones reagent (CrO_3–H_2SO_4–H_2O–acetone)[44,45] oxidizes alcohols to ketones efficiently and is relatively unreactive toward alkenes. However, examples of epoxidation during oxidation with Jones reagent have been reported.[320,321]

The oxidation of terminal olefins by Jones reagent in the presence of a catalytic quantity

TABLE XIII. Chromyl Acetate (**2**) Oxidation of Alkenes to Oxiranes

Alkene	Yield of oxirane (%)	Reference
$(C_6H_5)_2C=CH_2$	88	316
$C_6H_5CH=CHCH_3$	28	317
$C_6H_5(CH_3)C=CHCH_3$	39	317
$C_6H_5CH=C(CH_3)_2$	40	317
$Ar(CH_3)C=C(CH_3)_2$	45–56	317
$C_6H_5CH=C(C_6H_5)_2$	53	318
$(Z)-4-ClC_6H_4C(C_6H_5)=C(CH_3)C_6H_5$	62	318
$(E)-4-ClC_6H_4C(C_6H_5)=C(CH_3)C_6H_5$	49	318
$(4-ClC_6H_4)_2C=CH(C_6H_5)$	50	318
$(4-BrC_6H_4)_2C=CH(C_6H_5)$	53	318

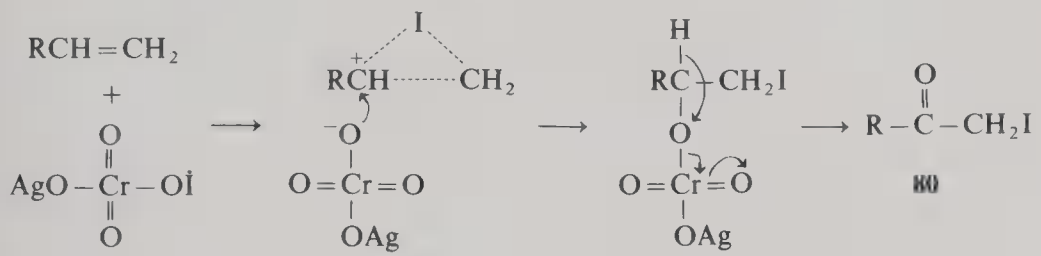
TABLE XIV. Oxidation of Alkenes by Chromium(VI) Oxidants Catalyzed by Mercury(II)[a]

Alkene	Oxidant	Product	Yield (%)
3,3-Dimethyl-1-butene	A[b]	3,3-Dimethyl-2-butanone	86
1-Octene	A	2-Octanone	82
(Z)-2-Octene	B[c]	2-Octanone (64%) 3-Octanone (36%)	56
(E)-2-Octene	A	2-Octanone (63%) 3-Octanone (37%)	54
Undecenylic acid	A	10-Oxoundecanoic acid	82
2-Allylcyclododecanone	B	β-Oxo-2-propylcyclododecanone	70
Styrene	B	Methyl phenyl ketone	26
Cyclohexene	B	Cyclohexanone	41
Cyclododecene		Cyclododecanone	36
Norbornene		Norcamphor	20

[a] Reference 322.
[b] Jones reagent (Refs. 44, 45).
[c] Sodium dichromate–trifluoroacetic acid.

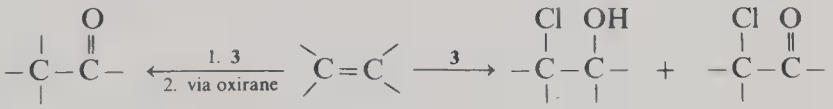
of mercury(II) affords good yields (>70%) of the corresponding methyl ketones (Table XIV).[322] Similar oxidations of 1,2-disubstituted olefins gives fair (20%–70%) yields.

The oxidation of olefins with silver chromate–iodine [Eq. (33)] provides a new and facile synthesis of α-iodo ketones (**80**, Table XV).[323]



(33)

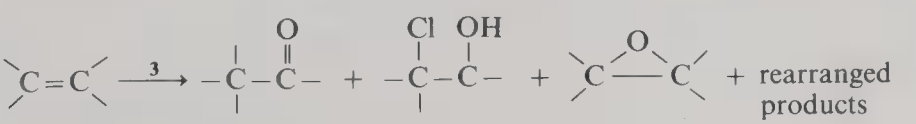
The products from the chromyl chloride (**3**) oxidation of alkenes are strongly dependent on reaction conditions (Tables XVI–XX).[13] For example, Freeman and co-workers[22,142,143,145,148] obtained aldehydes and ketones (Table XVI) from the oxidation of alkenes by **3** in dichloromethane, while Sharpless and co-workers[136,324] obtained α-chloro ketones[108,109,325,326] in acetone (Table XVII). The high stereoselectivity of *cis* addition of the elements of HOCl across the double bond is shown in Table XVIII.[136]



(34)

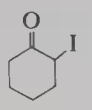
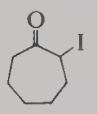
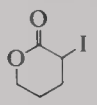
Table XIX[327,328] shows the comparison of products from the chromyl chloride (**3**) oxidation of endocyclic and exocyclic cycloalkenes.[152,153]

Table XX[156] shows the major products from the chromyl chloride (**3**) oxidation of cycloalkenes in carbon tetrachloride under anhydrous conditions [Eq. (35)].[156]



(35)

TABLE XV. Oxidation of Olefins with Silver Chromate–Iodine[a]

Olefin	α-Iodo ketone	Yield (%)
Cyclohexene		60
Cyclooctene		65
1-Octene	$C_6H_{13}-\overset{\overset{O}{\|}}{C}-CH_2I$	74
1-Octadecene	$C_{16}H_{33}-\overset{\overset{O}{\|}}{C}-CH_2I$	65
Styrene	$C_6H_5-\overset{\overset{O}{\|}}{C}-CH_2I$	86
Cinnamyl acetate	$C_6H_5-\overset{\overset{O}{\|}}{C}-CHICH_2OAc$	82
Allyl benzoate	$C_6H_5-\overset{\overset{O}{\|}}{C}-OCH_2-\overset{\overset{O}{\|}}{C}-CH_2I$	49
2,3-Dihydro-4H-pyran		39

[a] Reference 323.

TABLE XVI. Aldehydes and Ketones from the Chromyl Chloride (3) Oxidation of Alkenes in Dichloromethane[a]

Alkene	Product	Yield (%)
2,3-Dimethyl-2-butene	3,3-Dimethyl-2-butanone	50
2,3,3-Trimethyl-1-butene	2,3,3-Trimethylbutanal	35
2,4,4-Trimethyl-1-pentene	2,4,4-Trimethylpentanal	78
4,4-Dimethyl-2-neopentyl-1-pentene	4,4-Dimethyl-2-neopentanal	81
(E)-1-Phenylpropene	1-Phenyl-2-propanone	40
2-Phenylpropene	2-Phenylpropanal	60
1,1-Diphenylethene	2,2-Diphenylethanal	63

[a] References 142, 143, 145, 148.

TABLE XVII. α-Chloro Ketones from the Chromyl Chloride (3) Oxidation of Alkenes in Acetone[a]

Alkene	Procedure	Yields (%)
(E)-Cyclododecene	B	70
(E)-Cyclododecene	A	79
(E)-5-Decene	A	90
(E)-5-Decene	B	81
(Z)-5-Decene	B	65
(Z)-5-Decene	A	68
(E)-2-Octene	A	70
4,4-Dimethyl-(E)-2-pentene	A	60
2-Methyl-2-heptene	A	45
Cyclohexene	A	38
Norbornene	A	58

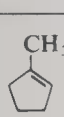
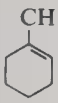
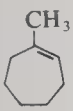
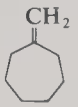
[a] Reference 324.

TABLE XVIII. Chromyl Chloride (3) Oxidation of Disubstituted Alkenes in Dichloromethane[a]

Olefin	Epoxide		Halohydrin		Halo ketone
	Z	E	Erythro	Threo	
(E)-Cyclododecene	2	20	5	60	8
(Z)-Cyclododecene	28	2	25	4	5
(E)-5-Decene	1	15	5	55	7
(Z)-5-Decene	13	2	35	30	5
(Z)-5-Decene	0	0	28	5	35
Cyclohexene	5		15	25	5

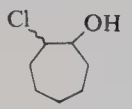
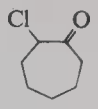
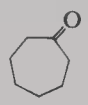
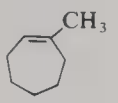
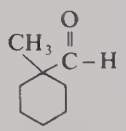
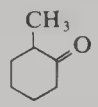
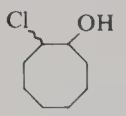
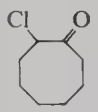
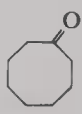
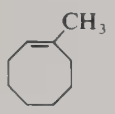
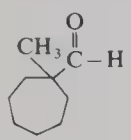
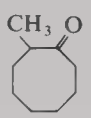
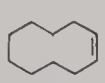
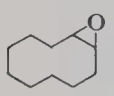
[a] Reference 136.

TABLE XIX. Comparison of Products from the Chromyl Chloride (3) Oxidation of Endocyclic and Exocyclic Cycloalkenes[a]

Endocyclic cycloalkene	Overall yield (%)	(% Yield) Products (% Yield)	Overall yield (%)	Exocyclic cycloalkene
	56	(84.6) 2-Methylcyclopentanone (72.0) (1.4) Cyclopentanecarboxaldehyde (17.5) (4.2) 2-Chloro-2-methylcyclopentanone (4.7) (9.9) 2-Methylcyclopenta-3-one (5.8)	40	
	68	(52.5) 2-Methylcyclohexanone (29.1) Cyclohexanecarboxaldehyde (47.1) (38.5) 1-Methylcyclopentanecarboxaldehyde (23.8) (9.3) 2-Chloro-2-methylcyclohexanone		
	60	(52.8) 2-Methylcycloheptanone (31.5) (3.9) Cycloheptanecarboxaldehyde (28.3) (26.4) 1-Methylcyclohexanecarboxaldehyde (25.3) (11.1) 2-Methylcyclohepten-3-one (5.7) 2-Chloro-2-methylcycloheptanone Cycloheptanone (12.4) Cyclooctanone (2.5)	68	

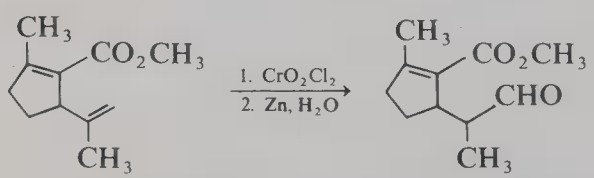
[a] References 13, 327, 328.

TABLE XX. Chromyl Chloride (**3**) Oxidation of Cycloalkenes in Carbon Tetrachloride[a]

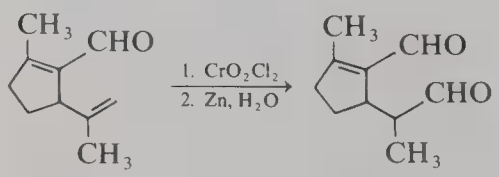
Cycloalkene	Products			
	 (30%)	 (11%)	 (14%)	
	 (28%)	 (6%)	Chlorinated products	
	 (17%)	 (17%)	 (3%)	 23%
	 (30%)	 (18%)	Chlorinated products	
				

[a] Reference 156.

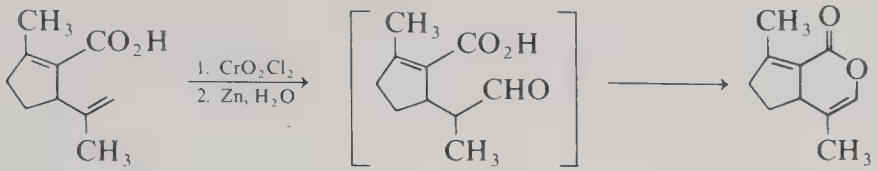
Methyl 2-methyl-5-isopropenyl-1-cyclopenten-1-carboxylate (**81**), the corresponding aldehyde (**83**), and free carboxylic acid (**85**) are selectively oxidized by **3**, according to the procedure of Freeman and coworkers,[148] respectively, to the aldehyde ester **84** (80%), chrysomelidial **85** (69%), and **86**, which was not isolated but cyclized to dienelactone **87**.[329]



81 **82** (36)

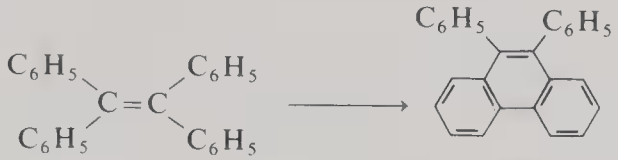


83 **84** (37)



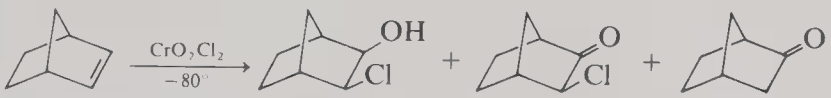
85 86 87 (38)

The chromyl chloride (**3**) oxidation of tetraphenylethene (**74**) results in a novel cyclization reaction giving 9,10-diphenylphenanthrene (**88**) in 70% yield.[330]



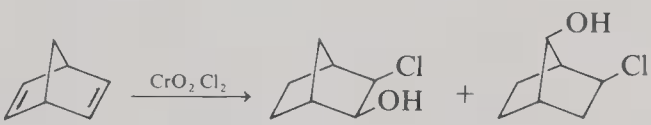
74 88 (39)

Oxidation of norbornene at −80°C with **3** gives 3-exo-chloro-2-exo-hydroxynorbornene (**89**, 63%), 3-exo-chlorononcamphor (**90**, 11%), norcamphor (**91**, 3.1%) and an unidentified aldehyde (1.7%, *cf.* Tables XVI–XX).[151]



89 90 91 (40)

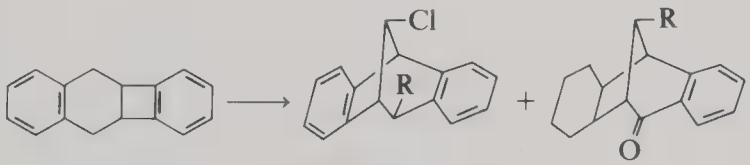
Norbornadiene was oxidized with fresh **3** (1.5 molar equiv, −78°C, CH_2Cl_2, dark 2 h).[157] Analysis indicated the presence of two major products, **92** (50%) and **93** (37%) among no less than 10 products.



92 93 (41)

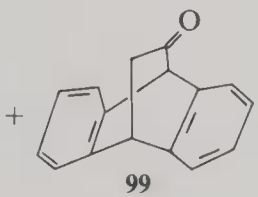
The oxidation of α-pinene with chromyl chloride (**3**) has been investigated and 11 products amounting to 81% of the total reaction have been isolated and identified.[331]

The reaction of dibenzo[c, g]bicyclo[4.2.0]octa-3,7-diene (**94**) with chromyl chloride (**3**) gives a mixture of **95**, **97**, and **99**. The reaction of **95** (R = H) with **3** yielded **96** and **98**.[332]



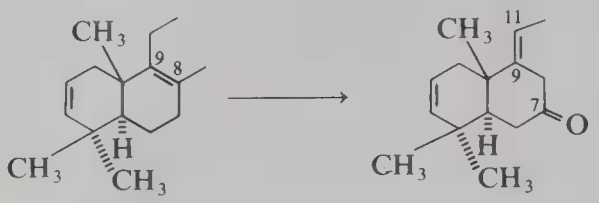
94 95 R = H 97 R = H (42)

96 R = OH 98 R = Cl



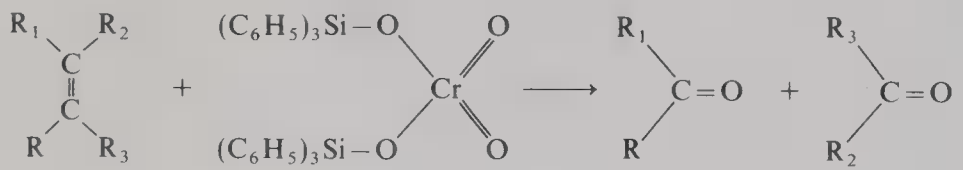
99

Barton and co-workers[333] observed some unusual oxidations of chromyl chloride (**3**) in the lanosterol series. One example is the oxidation of $\Delta^{2,8(9)}$-lanostadiene (**100**) to the $\Delta^{2,9(11)}$ – 7-ketone (**101**).



100 **101** (43)

Bistriphenylsilyl chromate (**102**) oxidatively cleaves olefins, giving the corresponding aldehydes and ketones along with reduced organochromium species.[334] The silyl chromate also polymerizes ethene at high pressure without added catalysts.



102 (44)

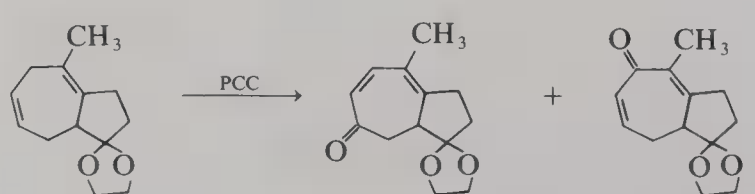
Organoboranes derived from terminal olefins are oxidized by pyridinium chlorochromate (PCC, **7**) to aldehydes in good yields [Eq. (45)].[335] Similarly, organoboranes from cyclic alkenes provide ketones in high yields *(vide supra)*.[336]

$$RCH{=}CHR \xrightarrow{BH_3 \cdot S(CH_3)_2} (RCH_2CHR)_3B \xrightarrow{Py \cdot HCl \cdot CrO_3} RCH_2{-}\overset{\overset{O}{\|}}{C}{-}R \qquad (45)$$

A number of hitherto unknown and unexpected oxidation products have been obtained from the chromic acid (**1**) oxidation of polyenes with terminal β-ionylidene groups.[337]

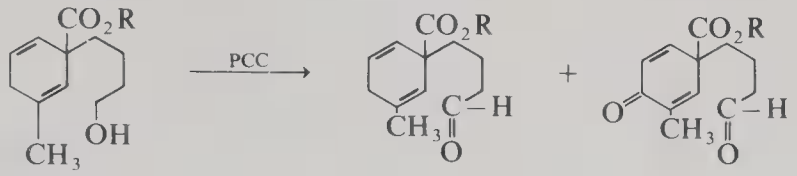
3.7.2. Functionalized Alkenes

Although PCC (**7**) does not effect oxidation of isolated double bonds, propenylbenzene, or diphenylmethane, it is able to oxidize 1,4-dienes to dienones.[338] This chemoselectivity is shown in the oxidation of dienone **103** to dienones **104** and **105**, in a respective ratio of 9:1.



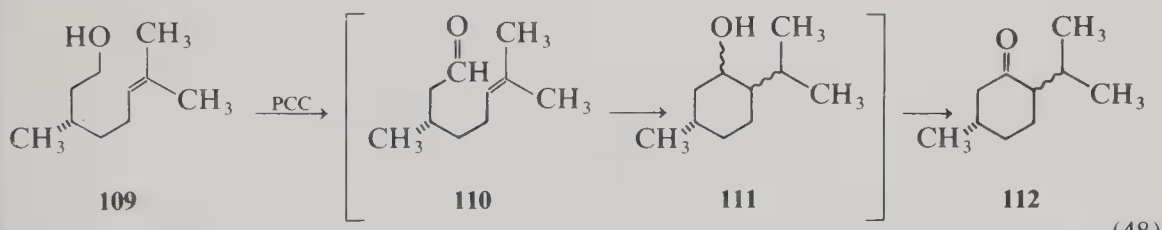
103 **104** **105** (46)

The selectivity (**104**/**105** = 1:3) was reversed using *tert*-butyl chromate (**4**) or chromium trioxide dipyridine (Collins reagent, **6**). The PCC (**7**) oxidation of 1,4-diene **106** has also been reported.[339] The major product **107** resulted from oxidation of the hydroxyl group and the minor product **108** arose from allylic oxidation.



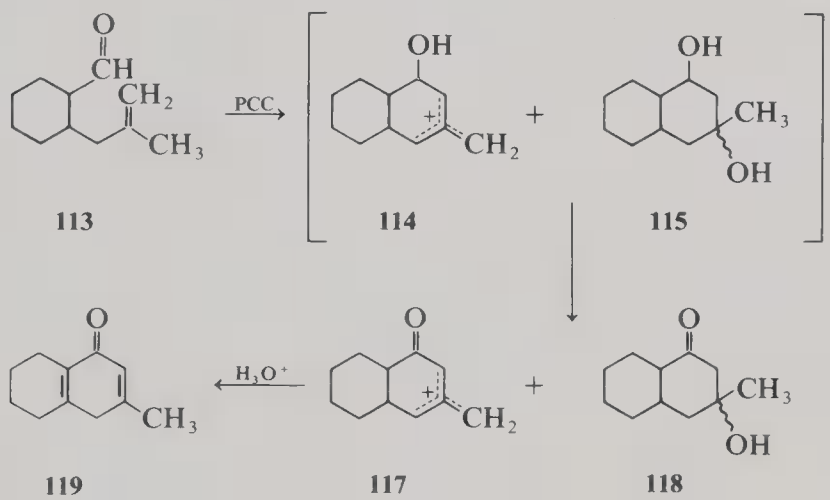
106 **107** **108** (47)

The mildly acidic character of PCC (**7**) may be used to bring about oxidative cationic cyclization reactions. For example, (−)-citronellol (**109**) was converted to (−)-pulegone (**112**, 70%) which is an important reactant for the asymmetric synthesis of prostaglandins.[340–342]



109 **110** **111** **112** (48)

The oxidative cationic cyclization reaction of PCC (**7**) provides a facile method for the preparation of β-disubstituted α, β-unsaturated cyclohexenones (Table XXI).[343] The reaction only proceeds with substrates capable of forming a tertiary carbocation as the initial cyclic intermediate. Attempts to form cyclopentenone derivatives were unsuccessful.[343]



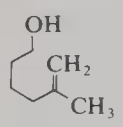
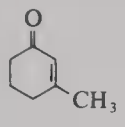
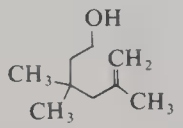
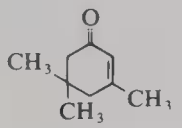
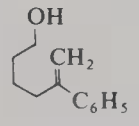
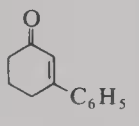
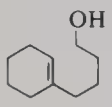
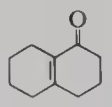
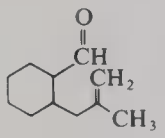
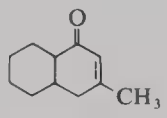
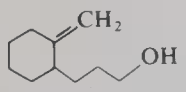
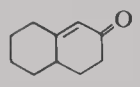
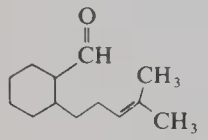
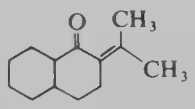
113 **114** **115** **119** **117** **118** (49)

The oxidation of enol ethers [Eq. (9)] and furan ring systems [Eq. (10)] by PCC (**7**) are described below.

3.7.3. Alkynes

It appears that carbon–carbon triple bonds are relatively inert to some chromium(VI) oxidants. The formation of α-acetylenic ketones [Eq. (22), Table IV][242] has been described above and the oxidation of alkynes containing other functional groups will be described below.

TABLE XXI. Products from PCC (7) Oxidative Cyclization Reactions[a]

Substrate	Product	Yield (%)
		68
		65
		69
		55
		78
		62
		41

[a] Reference 343.

3.8. Oxidation of Hydroxy Compounds

3.8.1. Alcohols

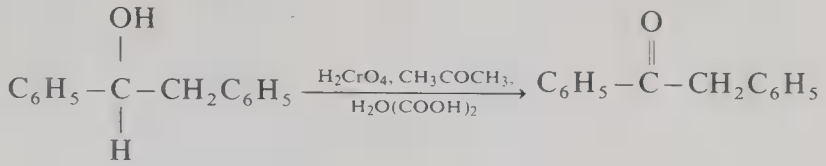
Primary alcohols are oxidized by oxochromium(VI) compounds to aldehydes which may be further oxidized to the corresponding carboxylic acid. Moreover, a side reaction between the aldehyde and unreacted alcohol can lead to ester formation via the hemiacetal.[344]

$$R-CH_2OH + R-\overset{\overset{O}{\|}}{C}-H \rightleftharpoons R-\underset{\underset{OH}{|}}{\overset{\overset{H}{|}}{C}}-OCH_2R \xrightarrow{Cr(VI)} R-\overset{\overset{O}{\|}}{C}-O-CH_2R \qquad (50)$$

The chromic acid (1) oxidation of secondary alcohols to ketones can be complicated by cleavage. It appears that alkyl phenyl carbinols generally give larger amounts of

$$C_6H_5-\underset{\underset{H}{|}}{\overset{\overset{OH}{|}}{C}}-C(CH_3)_3 \xrightarrow{Cr(VI)} C_6H_5-\overset{\overset{O}{\|}}{C}-C(CH_3)_3 + C_6H_5-\overset{\overset{O}{\|}}{C}-H + (CH_3)_3C-OH \qquad (51)$$

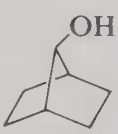
cleavage.[345,346] This cleavage is reduced to 6% when the reaction is conducted in aqueous acetone and is completely surpressed on addition of oxalic acid. This method leads to a



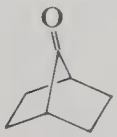
(52)

120

quantitative yield of **120** from the oxidation of 1,2-diphenylethanol and much improved yields of **122** from the oxidation of 7-norbornol (**121**).[345,346]



121



122

The oxidation of tertiary alcohols by chromium(VI) involves initial acid catalyzed dehydration to give the respective alkene, which is then oxidized.[347,348]

Table XXII shows representative examples of the aqueous chromic acid or chromic acid in aqueous acetic acid oxidation of primary alcohols to aldehydes and carboxylic acids.[349–368]

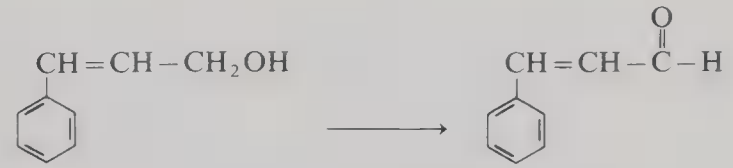
The oxidation of secondary alcohols to ketones with chromium trioxide in acetic acid or aqueous acetic, dichromate ion in aqueous sulfuric acid, and dichromate ion in aqueous sulfuric acid added to the alcohol in acetone solution has been summarized by Wiberg.[369]

The Jones reagent in acetone is a rapid and high yield method for oxidizing alcohols. This procedure oxidizes primary and secondary alcohols in the presence of a double or triple bond without attacking the unsaturated centers [Eqs. (53), (54)].[54] Jones reagent oxidizes benzyl alcohol to phenylmethanal (76%)[55] and cyclooctanol to cyclooctanone (92%–96%)[310] in excellent yields.

Jones reagent cleaves tertiary cyclobutanols to 1,4-ketols or 1,4-diketones [Eqs. (55)–(57)].[371] Fieser's reagent oxidizes cyclic tertiary alcohols to long-chain keto acids in excellent yields.[49b]

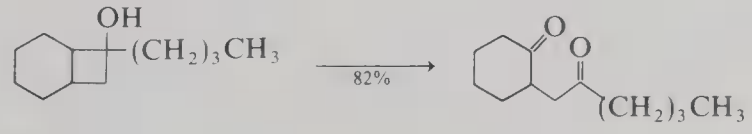
(53)

123 **124**



(54)

125 **126**



(55)

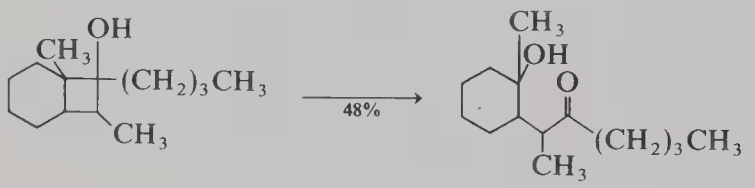
127 **128**

TABLE XXII. Chromic Acid Oxidation of Primary Alcohols

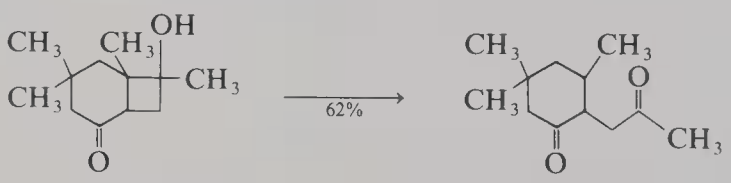
Product	Yield (%)	Ref.	Product	Yield (%)	Ref.
Methanal	72	349	Citral	42	359
Propanal	49	350	3,3,3-Trifluoropropanal	57	360
2-Methylpropanal	64	351	2-Chloro-6-nitrobenzaldehyde	87	369
2-Methylbutanal	52	352	1-Naphthaldehyde	42	362
3-Methylbutanal	60	353	4-Methyl-1-naphthaldehyde	84	363
Pentanal	50	354	2-Thiophenecarboxaldehyde	65	364
Cyclohexanecarboxaldehyde	35	355	3-Fluoropropanoic acid	80	365
2-Pentenal	50	356	4-Fluorobutanoic acid	75	366
2-Hexenal	50	356	2-Methylbutanoic acid	52	367
2-Heptenal	75	356	Heptanoic acid	70	368
4-Octenal	35	358			
2-Nonenal	50	356			
Propargyl aldehyde	46	358			

The Jones reagent oxidations of β-hydroxysteroids,[372] 8-hydroxy-3,4-tetrafluorobenzobicyclo[3.2.1]octadienes,[373] allyl alcohol,[319] and β-ayrin and its acetate[374] have been reported.

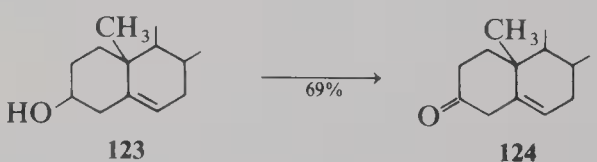
Chromium trioxide (1.0–2.0 equiv) in a mixture of dichloromethane and diethyl ether (3:1) is useful for oxidation of alcohols to carbonyl compounds [Eqs. (58)–(60)].[86] Benzyl alcohol is converted to benzaldehyde in 75% yield by this reagent. The yields are higher and workup simpler if Celite is added.



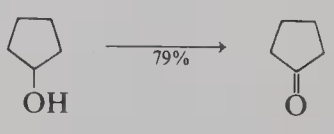
129 130 (56)



131 132 (57)



123 124 (58)

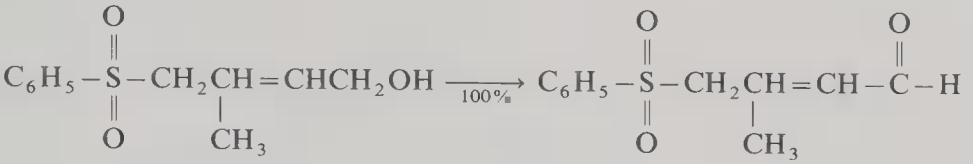


133 134 (59)

135 136 (60)

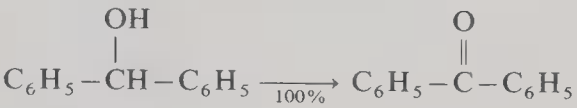
The oxidation of secondary alcohols in diethyl ether with aqueous chromic acid (**1**) is a convenient procedure for the preparation of ketones (85%–97%) in high epimeric purity.[376]

Chromic anhydride–hexamethylphosphoric triamide (HMPT) oxidizes primary (~80%) and secondary alcohols to carbonyl compounds.*,[84] Highest yields are obtained with α,β-unsaturated primary and secondary alcohols and lowest yields are obtained with saturated secondary alcohols. Examples are shown in Eqs. (61) and (62).



(61)

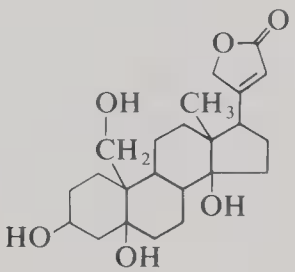
137 **138**



(62)

139 **140**

The final step in the synthesis of strophanthidin requires selective oxidation of the primary hydroxyl group of **141** to an aldehyde group.[85] Although attempts to oxidize **141** with chromic acid (**1**) or PCC (**7**) were unsuccessful, chromic trioxide in HMPT oxidized **141** to strophanthidin in 35% yield.



141

Phenylmethanol and its derivatives are converted to the corresponding phenylmethanals by use of chromic trioxide in dimethyl sulfoxide.[377]

The chromic acid (**1**) oxidations of amino alcohols (to amino ketones),[378] [3,2]propellanols,[379] and some substituted 2-hydroxymethylphenethyl alcohols[380] have been reported.

Chromic acid (**1**) adsorbed on silica gel is useful for oxidation of primary and secondary alcohols to aldehydes and ketones (80%–90%), respectively.[87]

Chromic anhydride intercalated in graphite is a very specific oxidizing agent for converting primary alcohols to the corresponding aldehydes (70%–100%).[41,79] Secondary and tertiary alcohols are not oxidized. 1,2-Diols are oxidized with cleavage to give carbonyl compounds. Residual chromium salts are retained in the lattice of the graphite.

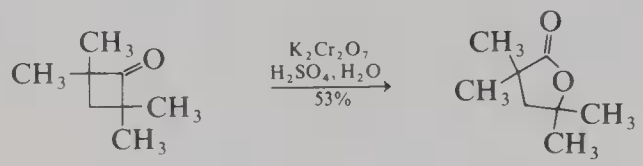
A supported form of chromic acid (**1**) is prepared by reaction of the chloride form of an anion exchange resin in water with chromium trioxide to obtain a hydrogen chromate form of the resin, which oxidizes primary and secondary alcohols in high yield (85%–95%).[39] The chloride form of the resin is regenerated by wash with sodium hydroxide and hydrochloric acid solutions.

The oxidation of unsaturated primary alcohols by coordinated chromium trioxide has been described.[381]

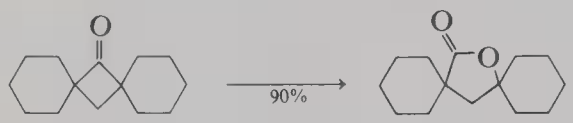
Applications of chromic acid–celite columns to micro- and semimicro preparation of fatty aldehydes have been described.[382]

Potassium dichromate in glacial acetic acid appears to be superior to dichromate in acetic or chromium trioxide for the oxidation of saturated alcohols.[383,384]

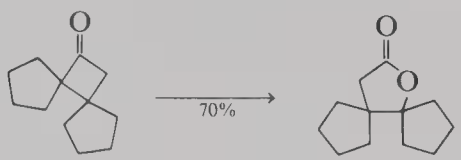
Cyclobutanols and cyclobutanones are oxidized by potassium dichromate in aqueous sulfuric acid to γ-butyrolactones [Eqs. (61)–(63)] in yields of 50%–90%.[385,386] Acetic acid is added if necessary to effect solution and the oxidation is not applicable to larger cyclic ketones.



142 143 (63)



144 145 (64)



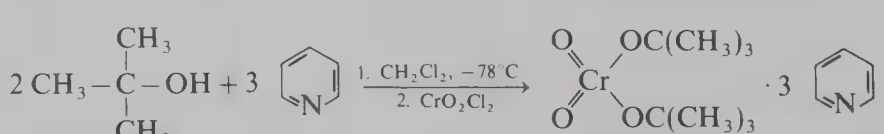
146 147 (65)

A rapid and selective method for the oxidation of primary alcohols to aldehydes by dichromate in two-phase systems[46,47] has been discussed.[290]

Dichromates adsorbed on various inorganic supports (SiO_2, Al_2O_3, Florisil, and MgO) were tested for heterogeneous oxidation of alcohols. Benzylic alcohols are preferentially oxidized as confirmed by the selective oxidation of 1-phenyl-1,3-propanediol to 3-hydroxy-3-phenylpropanal.[387]

Chromyl acetate (**2**) oxidizes benzhydrols to benzophenones in greater than 90% yields.[22,60,64,66]

Chromyl chloride (**3**) and 3 equiv of pyridine in dichloromethane at −78°C oxidized primary saturated alcohols to aldehydes (78%–99%).[73] When this reagent was modified by addition of 2 equiv of *t*-butanol, a new reagent, possibly **4** or its pyridine adduct **148**, was formed. Reagent **148** is a milder oxidant than the chromyl chloride–pyridine complex (Table XXIII). Although **148** is less effective than the Collins reagent for the oxidation of allylic alcohols, it is useful for oxidizing simple saturated primary alcohols.



148 (66)

Chromyl chloride (**3**) absorbed on SiO_2–Al_2O_3 is useful for oxidation of alcohols to carbonyl compounds.[†,78,80] The yields are comparable to those obtained with other oxidants, but has the convenience shown by other chemisorbed reagents on an inert support.

The oxidation of primary and secondary alcohols by *tert*-butyl chromate (**4**) has been

TABLE XXIII. Oxidation of Alcohols to Aldehydes or Ketones by Reagents Derived from Chromyl Chloride[a]

Alcohol	Oxidant, yield (%)	
	CrO_2Cl_2 (3)	148
1-Decanol	—	84
	—	79
I-Dodecanol	94	99
Citronellol	87	93
	—	84
Geraniol	87	100
2-Methyl-2-phenylpropanol	—	86
Phenylmethanol	85	100
Cyclohexylmethanol	90	99
Cyclododecanol	99	97
Cinnamyl alcohol	78	86
Pinocarveol	82	60
3-(Hydroxyphenyl)methanol	0	38

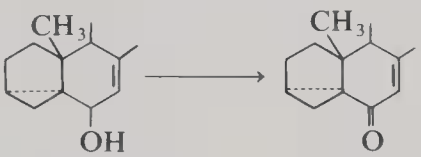
[a] Reference 73.

reviewed.[388] This oxidant in petroleum ether oxidizes, primary alcohols to aldehydes in excellent yield (80%–94%).[70] The oxidation of secondary alcohols also proceed in good to excellent yields.

The chromium trioxide–pyridine complex (Sarett reagent, **5**), which may be hazardous to use, oxidizes alcohols to carbonyl compounds in good to excellent yields without oxidizing other functional groups.[25–27]

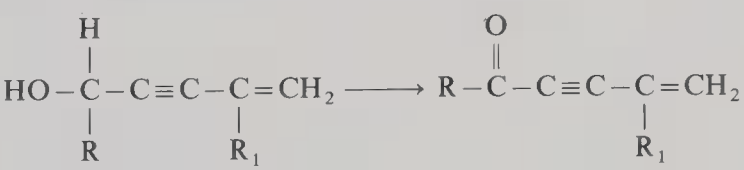
The Cornforth reagent (chromium trioxide–pyridine–water) is less tedious to prepare than the Sarett reagent (**5**) and is useful for oxidizing alcohols to carbonyl compounds.[89]

The oxidation of 3α,5α-cyclocholest-7-ene-6-ol (**149**) to ketone **150** (80%) has been accomplished with chromium trioxide in pyridine–dichloromethane (1:3.6).[88]



149 **150** (67)

A pyridine–hydrogen chloride complex (1:1) with chromium trioxide in dichloromethane oxidizes the unsaturated alcohols (**151**) to the corresponding ketones (**152**) in 44%–78% yield). In **151**, R = Me, Pr, $CH(CH_3)_2$, C_6H_5; R_1 = H, CH_3).[389]

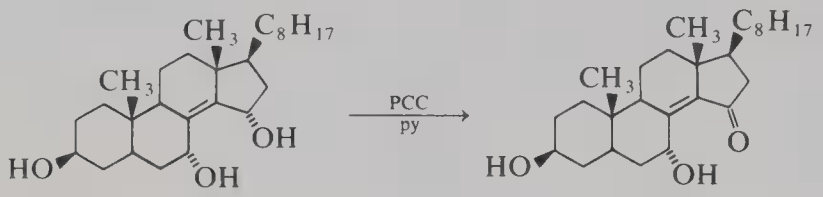


151 **152** (68)

PCC (**7**) oxidizes a wide variety of alcohols to carbonyl compounds in dichloromethane solution with high efficiency.[32] This reagent is more economical and convenient than the Collins reagent which uses 6 times as much solvent and four times as much oxidizing agent.[32]

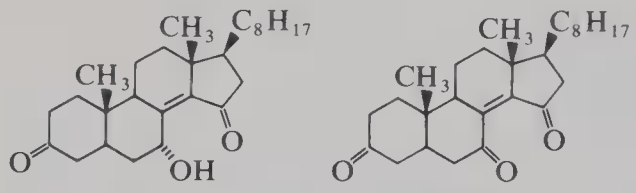
Table XXIV shows a few examples of the PCC (7) oxidation of alcohols. A larger compilation appears in Ref. 193.

PCC in dichloromethane containing 2% pyridine at 2°C selectively oxidizes steroidal allylic alcohols to ketones.[390–392] If experimental conditions are carefully controlled, this procedure may be more desirable than the commonly used manganese dioxide oxidation of allylic alcohols.[393]



153 154 (69)

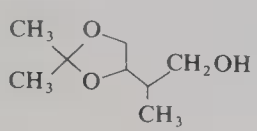
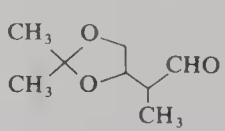
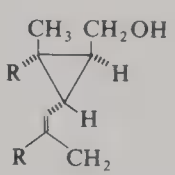
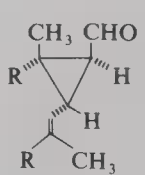
The mildly acidic character of PCC (7) can usually be altered for acid-sensitive groups with powdered sodium acetate. Thus, the oxidation of 5α-cholest-8(14)-ene-3β,7α,15α-triol (**153**) with buffered PCC gives **155** while PCC (7) oxidizes **153** to **156** [cf. Eq. (67)].[390–392]



155 156

PCC (7) converts allylic tertiary alcohols into α,β-unsaturated aldehydes (Table XXV).[307,394,395] The absence of diene products is remarkable in view of the slightly

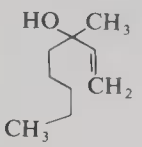
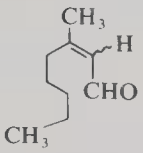
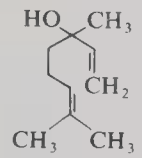
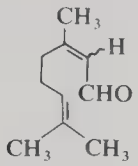
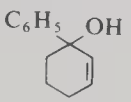
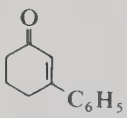
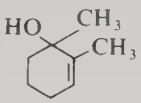
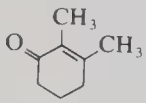
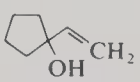
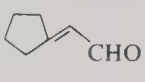
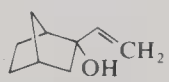
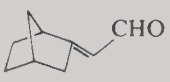
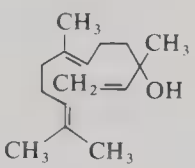
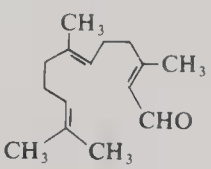
TABLE XXIV. Pyridinium Chlorochromate (PCC, 7) Oxidation of Alcohols[a]

Alcohol	Product	Yield (%)
1-Decanol	Decanal	92
1,6-Hexanediol	Hexanedial	68
Diphenylmethanol	Benzophenone	100
4-*t*-Butylcyclohexanol	4-*t*-Butylcyclohexanone	97
Oct-2-yn-1-ol	Oct-2-ynal	84
1-Heptanol	Heptanal	78
Citronellol	Citronellal	82
(Z)−$HOCH_2CH=CHCH_2OTHP$	(E)−$CHOCH=CHCH_2OTHP$	81
		85
		78

R = $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2^-$
(Presqualene alcohol)

[a] Reference 32.

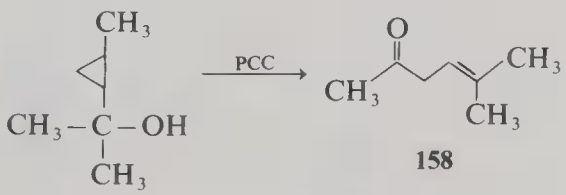
TABLE XXV. Unsaturated Carbonyl Compounds from the Pyridinium Chlorochromate (PCC, 7) Oxidation of Tertiary Allylic Alcohols

Substrate	Product	Yield (%)	Reference
		90[a]	394
		80[a]	307, 394, 395
		90	394
		93	394
		89	394
		79	395
		92	394

[a] Mixture of E, Z diastereomers.

acidic character of **7** and of the sensitivity of tertiary vinylcarbinols towards dehydration. Cyclic tertiary allylic alcohols gave transposed 3-alkyl-α,β-unsaturated ketones which are useful in the synthesis of natural products.[394]

PCC (**7**) oxidizes tertiary cyclopropylcarbinols to the corresponding β,γ-unsaturated ketones [Eq. (68)].[396] The net effect of this oxidative rearrangement is an efficient procedure for obtaining 1,4-carbonyl transposition since the starting tertiary alcohols are available from the addition of cyclopropyl organometallic reagents to ketones.



157 **158** (70)

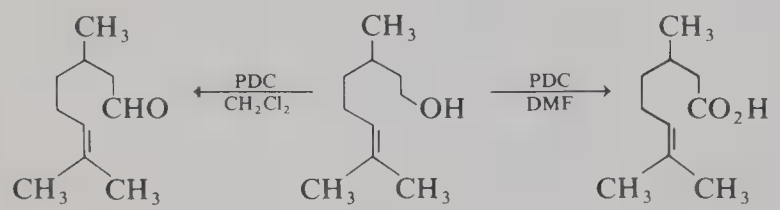
PCC (**7**) absorbed on alumina is a suitable reagent for the oxidation of alcohols to aldehydes and ketones.[397] The workup of this procedure is less difficult than that of **7**. This

easily prepared reagent is a clean oxidant and the workup is a mere filtration. The yields of aldehydes and ketones are high (Table XXVI).

The insoluble reagent poly[vinyl(pyridinium chlorochromate)], PVPCC, **14**), which is prepared easily from cross-linked poly(vinylpyridine) resins by reaction with chromic anhydride and hydrochloric acid, has a capacity of 3.5–3.9 mmol of chlorochromate per gram.[397] It (**14**) is useful in the oxidation of alcohols to carbonyl compounds. This highly efficient oxidant has other advantages which are associated with its insolubility and with the quantitative recovery and regeneration of the spent resin. After several regenerations, the reagent is still as reactive as the original material. The oxidant is effective in the oxidation of various types of alcohols: allylic, benzylic, secondary, or primary, as shown in Table XXVII.

The more neutral character of pyridinium dichromate (PDC, **8**)[33–35,398] is preferable to the mildly acidic PCC (**7**) for oxidations involving acid sensitive products or reactants. This oxidant is probably the oxidizing species present in the Sarett (**5**)[23,25–28] and Cornforth[89,90] oxidizing mixtures. Owing to the unstable character of Collins reagent (**6**),[29–31] which behaves as though it is neither markedly acidic nor basic, PDC (**8**) is the reagent of choice for the oxidation of alcohols to carbonyl compounds, and in some cases, to carboxylic acids (Table XXVIII).[33]

PDC (**8**) may be used in dichloromethane (nonaqueous workup) or dimethylformamide (aqueous workup with extraction). Equation (71) shows that the results of a given oxidation may be different in the two solvents.



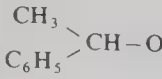
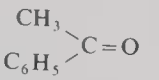
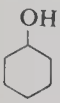
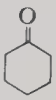
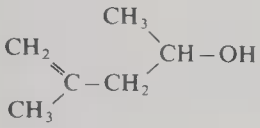
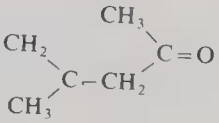
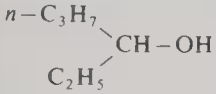
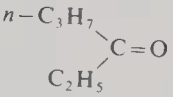
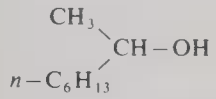
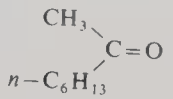
160 **159** **161** (71)

TABLE XXVI. Oxidation of Alcohols to Aldehydes and Ketones with Pyridinium Chlorochromate (**7**) Absorbed on Alumina[a]

Alcohol	Solvent	Ratio of oxidant/ alcohol	Yield (%)	Oxidation by other methods	
				Reagent	Yield (%)
Carveol	$n-C_6H_{14}$	1.6	93	Pyridinium chlorochromate	82
2-Ethylhexanol	$n-C_6H_{14}$	2.5	87		
Furfuryl alcohol	C_6H_6	2.5	45	CrO_3/pyridine complex	46
Menthol	$n-C_6H_{14}$	2.5	94	CrO_3	94
Tetrahydrogeraniol	$n-C_6H_{14}$	2.5	80		
Citronellol	$n-C_6H_{14}$	3	82	Pyridinium chlorochromate	82
2-Methylcyclohexanol	$n-C_6H_{14}$	2.5	83	CrO_3	80
Cinnamyl alcohol	C_6H_6	2	84	CrO_3/pyridine complex	81
Isopulegol	$n-C_6H_{14}$	2.5	81		
Cholesterol	C_6H_6	3	80	CrO_3/pyridine complex	64

[a] Reference 397.

TABLE XXVII. Oxidation of Alcohols to Carbonyl Compounds by PVPCC (**14**)[a]

Substrate	Product	Yield (%)
$n-C_4H_9-OH$	$n-C_3H_7-CHO$	90
$n-C_6H_{13}-OH$	$n-C_5H_{11}-CHO$	91
$C_6H_5-CH_2-OH$	C_6H_5-CHO	95
$C_6H_5-CH=CH-CH_2-OH$	$C_6H_5-CH=CH-CHO$	100
		96
		86
		94
		61
		86
		76

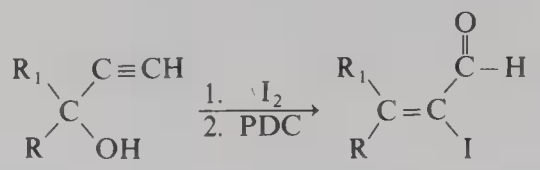
[a] Reference 97.

TABLE XXVIII. Oxidation of Alcohols to Carbonyl Compounds and Carboxylic Acids with PDC (**8**)[a]

Alcohol	Solvent	Product	Yield (%)
1-Decanol	CH_2Cl_2	Decanal	98
1-Hexadecanol	CH_2Cl_2	Hexadecanal	94
Citronellol	CH_2Cl_2	Citronellal	92
Phenylmethanol	CH_2Cl_2	Phenylmethanal	83
4-*t*-Butylbenzyl alcohol	CH_2Cl_2	4-*t*-Butylbenzaldehyde	94
4-*t*-Butylcyclohexanol	CH_2Cl_2	4-*t*-Butylcyclohexanone	97
	DMF	4-*t*-Butylcyclohexanone	94
2-Cyclohexenol	DMF (0°C)	2-Cyclohexenone	86
Cinnamyl alcohol	DMF (0°C)	Cinnamaldehyde	97
Geraniol	DMF (0°C)	Gerianial	92
	DMF (25°C)	3,7-Dimethyloct-7-enoic acid	93
Cyclohexylmethanol	DMF (25°C)	Cyclohexanecarboxylic acid	84

[a] Reference 33.

Under mild and simple conditions, PDC (**8**) oxidizes α-ynol-I_2 complexes to α,β-unsaturated α-iodo-aldehydes (**162**, 30%–66%).[399]



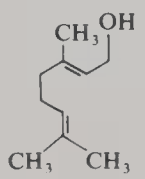
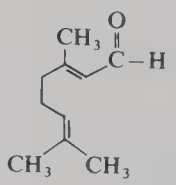
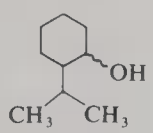
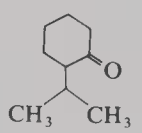
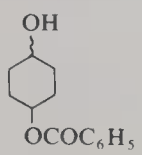
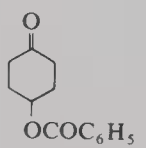
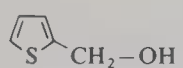
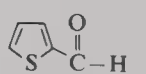
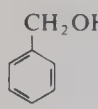
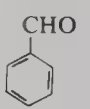
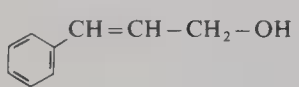
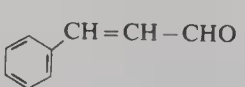
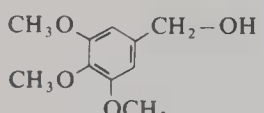
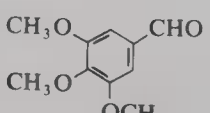
(72)

162

Treatment of a primary or secondary alcohol in dichloromethane or acetone with a 2:1 to 4:1 excess of the 2,2′-bipyridinium chlorochromate complex (BiPy · $HCrO_3Cl$, **9**)[36,37] affords a solution of the corresponding carbonyl compound plus a water-soluble crystalline chromium-containing by-product which can be completely removed by filtration through a 1-cm Celite pad (Table XXIX).[37]

A 2,2′-bipyridine analog of the Collins reagent was also evaluated. The 2,2′-bipyridine-chromic anhydride adduct [BiPy · CrO_3] could be prepared in a manner analogous to the

TABLE XXIX. Oxidation of Alcohols to Aldehydes or Ketones Using 2,2′-Bipyridinium Chlorochromate (BiPy · $HCrO_3Cl$, **9**)[a]

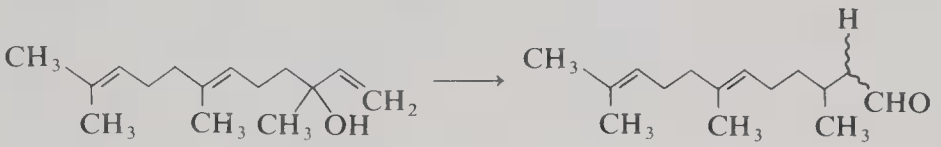
Substrate	Product	Yield (%)
$n-C_7H_{15}-OH$	$n-C_6H_{13}-CHO$	82
$n-C_{12}H_{25}-OH$	$n-C_{12}H_{25}-CHO$	37
		93
		86
		83
		79
		79
		65
		68

[a] Reference 37.

pyridine complex.[37] The resulting brown crystalline adduct appears to be a much milder reagent than the pyridine complex. More polar solvents (ethyl acetate) and long reaction times (48 h) as well as large excesses of reagent (6–8 equiv) are necessary to achieve optimum oxidation.

Oxidation of primary and secondary alcohols with tetra-*n*-butylammonium chromate (**12**)[§,38] provides some interesting features including reactivity, homogeneous conditions, selectivity, and utilization of moderately acidic conditions. This salt (**12**), which is easily prepared, is very soluble in chloroform and dichloromethane. Tetrahydrofuran may be used, but not benzene or ether.[38] Table XXX shows that **12** oxidizes alcohols in good yields.

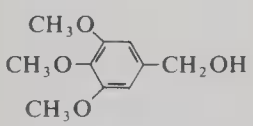
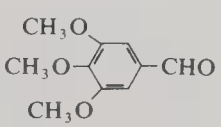
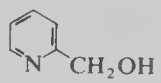
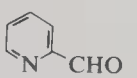
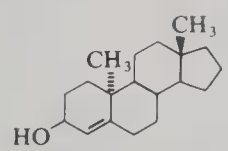
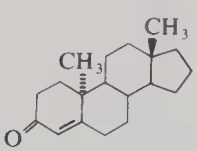
The reaction of **12** with a tertiary allylic alcohol such as nerolidol (**163**) in a 4:1 molar ratio gave rise to a 60:40 mixture of isomeric farnesals (**164**, 87%).[38,307] These results may be compared with the products from the PCC (**7**) oxidation of allylic alcohols [Eq. (69), Table XXV].



163 **164** (73)

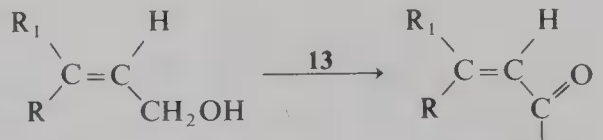
The desire for mild oxidizing agents which are soluble in organic solvents has led to the development of neutral bis-tetra-*n*-butylammonium dichromate (TBADC, **13**).[95,96] TBADC

TABLE XXX. Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds by Tetra-*n*-butylammonium Chromate (**12**) in Chloroform[a]

Alcohol	Product	Yield (%)
$C_6H_5CH_2OH$	C_6H_5CHO	81
$(C_6H_5)_2CH-OH$	$(C_6H_5)_2C=O$	91
$C_6H_5-CH=CH-CH_2-OH$	$C_6H_5-CH=CH-CHO$	90
$C_6H_5-CH=CH-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-OH$	$C_6H_5-CH=CH-\underset{\displaystyle CH_3}{\underset{\vert}{C}}=O$	88
$C_6H_5-CH=CH-\underset{\displaystyle C_6H_5}{\underset{\vert}{CH}}-OH$	$C_6H_5-CH=CH-\underset{\displaystyle C_6H_5}{\underset{\vert}{C}}=O$	92
		75
		43
		76

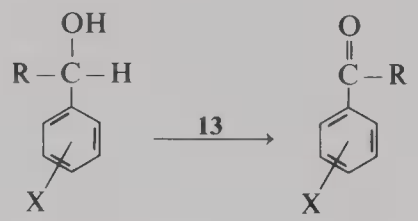
[a] Reference 38.

(**13**) can be used in refluxing dichloromethane for the oxidation of allylic and benzylic alcohols.[96]



(74)

165 $R = C_6H_{11}$, $R_1 = CH_3$ 78%
166 $R = C_{11}H_{19}$, $R_1 = CH_3$ 82%
167 $R = C_6H_5$, $R_1 = H$ 80%



(75)

168 X = R = H 90%
169 X = 4–Cl, R = H 85%
170 X = 4–OCH_3, R = H 80%
171 X = 4–NO_2, R = H 84%
172 X = H, R = CH_3 80%
173 X = H, R = $CO_2C_2H_5$ 86%

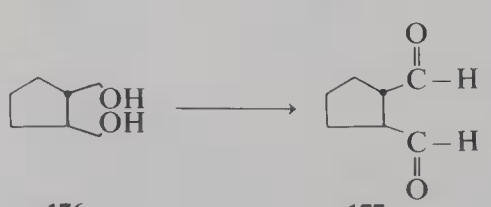
Dichromate in benzene (Orange Benzene) without added acid is a very mild, effective, and selective oxidant in the oxidation of conjugated alcohols to the corresponding carbonyl compounds at 55°C.[400] Aliphatic alcohols are oxidized sluggishly under the same conditions. The respective yield of aldehyde or ketone from the dichromate in benzene oxidation of phenylmethanol, 1-phenylethanol, cinnamyl alcohol, decanol, 2-octanol, and cyclododecanol is 82%, 80%, 91%, 6%, 33%, and 45%.[400]

Although the chromic acid (**1**) oxidation of ethane-1,2-diol gave only 1%–2% cleavage, carbon–carbon bond scission appears to increase with increasing alkyl substitution [Eq. (8)].[196,197]

Aqueous or nonaqueous chromium(VI) oxidizes 1,4-diols (**174**) to γ-lactones (**175**) in good yields. However, the stereochemical barrier in **176** precludes cyclization, and the *trans*-dialdehyde **177** is formed.[401] 1,6-Diols also undergo an oxidative cyclization of this type.[402]

(76)

174 **175** (60%)



(77)

176 **177**

Preliminary studies of the chromyl chloride (**3**) oxidation of benzpinacolyl alcohol, methyl-*t*-butylcarbinol, and *t*-butylphenylcarbinol in different solvents have been

reported.*[16,403] It has been found in dry carbon tetrachloride that chromyl chloride (**3**) reacts with pinacol, benzpinacol, *meso*- and racemic hydrobenzoin to give 1:1 chromyl chloride:glycol adducts.[196]

3.8.2. Carbohydrates

The application of chromium(VI) oxidations to carbohydrates has generally been limited to the use of the chromium oxide–pyridine complex and to chromium oxide in acetic acid.[404] The chromium oxide–pyridine complex has been used with some success for the oxidation of alditol derivatives,[405,407] and in some furanoid and pyranoid systems.[408,410]

Pyridinium chlorochromate (PCC, **7**) has been successfully applied to the oxidation of a hexopyranoside[411] and to the oxidation of isolated secondary hydroxyl groups in both furanoid and pyranoid systems.[412] The use of molecular sieves with PCC (**7**) leads to a quick and complete oxidation of nucleosides.[413] It appears that this new procedure constitutes an alternative to the PCC (**7**) oxidation of carbohydrates in refluxing benzene.[412] The combination of PDC (**8**) and molecular sieves has a wider field of application as shown by the oxidation of small molecules like benzhydrol and veratryl alcohol.[413]

3.8.3. Phenols

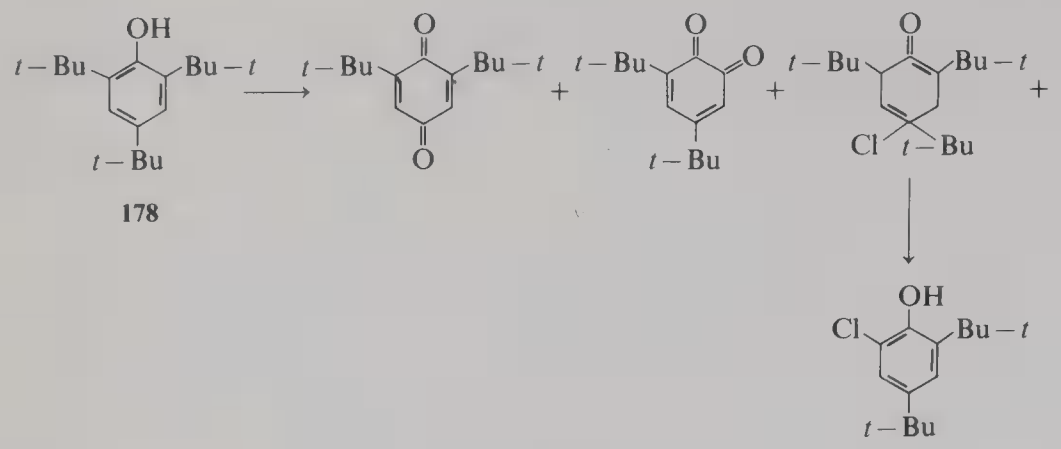
On treatment with aqueous potassium dichromate, *p*-cresol and cresol readily undergo nuclear oxidative coupling. The yields of dimeric and trimeric cresols and of dimeric ketones are the same as those of preparation by one-electron oxidants. The yields are tripled when manganous sulfate is added. The probable mechanism of the coupling reaction of phenols in aqueous potassium dichromate has been discussed.[414]

The reaction of chromyl chloride (**3**) with various phenolic compounds yields brown solids which in general do not have stoichiometric compositions.[415] The hydrolysis of these solids gives tars and/or varying yields of the 1,4-benzoquinones. The presence of chlorine in the positions *ortho* to the phenolic oxygen results in increased yields of the quinone. Thus, while 2,6-dichlorophenol and 2,4,6-trichlorophenol gave good yields of the corresponding 1,4-benzoquinones and pentachlorophenol gave a yield of chloranil in excess of 70%, phenol gave only traces of 1,4-benzoquinone and 2-chlorophenol gave only a small yield of 2-chloro-1,4-benzoquinone.[415]

It has been shown that the oxidation of alkyl phenols with chromyl chloride (**3**) gives 1,4-benzoquinones, in yields which depend on the mole ratio of reactants, the position of the substituent on the ring, and the nature of the alkyl substituent.[416] When the reaction was carried out in carbon tetrachloride or carbon disulfide, a nonstoichiometric solid contained the 1,4-benzoquinone coordinated onto the reduced chromium species was observed.[417] For 2,5-disubstituted phenols the yield of quinone increases across the sequence methyl, 2-propyl, and *t*-butyl (15%, 42%, and 83%, respectively), while for 2,6-disubstituted phenols the increase is smaller (48%, 56%, and 69%, respectively). The presence of an alkyl group in the 4-position does not enhance the formation of *ortho* quinones.

The oxidation of 2,4,6-tri-*tert*-butylphenol (**178**) and several other alkyl and halophenols by chromyl chloride (**3**) has been studied.[418] The products are mostly quinones and diphenoquinones. The product distributions are interpreted in terms of a mechanism involving phenoxy radicals ligand transfer from metal to radical, and either phenoxonium ions or metallate esters where there is sufficient electron withdrawal from the organic group.

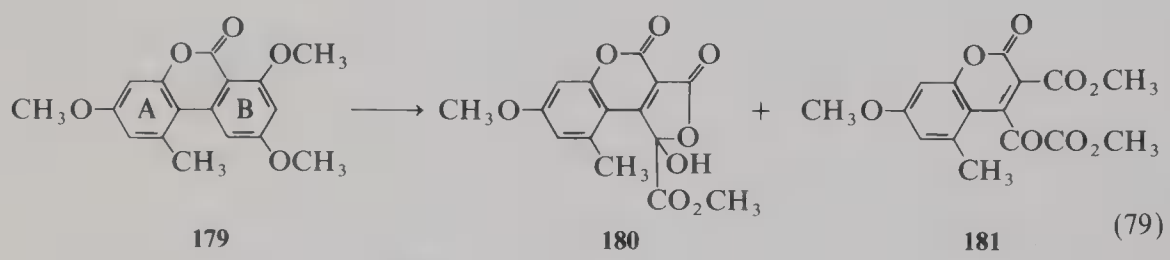
* It has been reported without experimental details that chromyl chloride (**3**) oxidized 1,1,2,2-tetramethylethanol to acetone (4.5%) and to 3,3-dimethyl-2-butanone (23%), and 1,1,2,2-tetraphenylethanol to 9,10-diphenylphenanthrene in 80% yield.[16] *t*-Butyl alcohol is inert to chromyl chloride (**3**).[196]



178 (78)

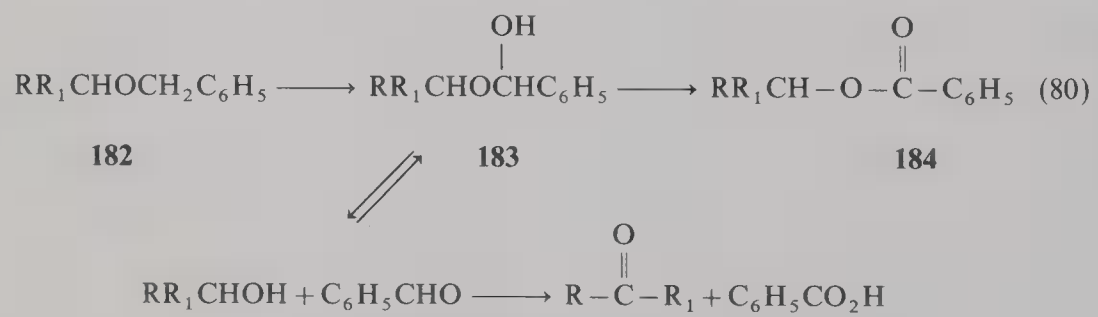
3.9. Oxidation of Ethers

Alternariol trimethyl ether (**179**) undergoes an exothermic reaction with chromium trioxide in glacial acetic acid to give **180** (25%) and **181** (8%).[419] The required selective oxidative loss of a single carbon atom from ring B of **179** appears to constitute a novel addition to the various known types of oxidations of alkyl aryl ethers.[420]



179 **180** **181** (79)

Jones reagent rapidly oxidizes a variety of benzyl ethers (**182**) to ketones, benzoates (**184**), and benzoic acid.[421] The products apparently arise by initial formation of a hemiacetal (**183**), followed by oxidation to the ester, ketone, and benzoic acid [Eq. (80)]. Table XXXI shows the yields of products from the Jones oxidation of benzyl ethers.[421]

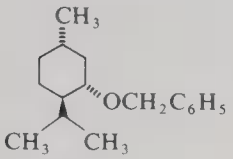
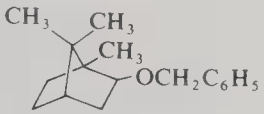
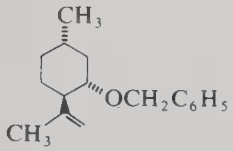


182 **183** **184** (80)

Other chromium(VI) compounds have been examined for the oxidation of benzyl ethers.[421] Although Collins reagent oxidizes alcohols to ketones in 15 min without affecting benzyl ethers,[28] 2-octyl benzyl ether gives 2-octanone (24%), 2-octyl benzoate (20%), and 45% starting material after 15 min. Pyridinium dichromate (PDC, **8**) does not affect the benzyl ether of 2-octanol over a 16 h period,[421] and chromium trioxide in glacial acetic acid yields esters from ethers.[422–424]

Oxidation of 2-methoxy- and 2,7-dimethoxy-10H-phenothiazine (**185** and **186**) with potassium dichromate in glacial acetic acid gave the corresponding phenothiazinones (**187** and **188**).[425] Other methoxyphenothiazines were similarly oxidized.

TABLE XXXI. Jones Oxidation of Benzyl Ethers to Acids, Esters, and Ketones[a]

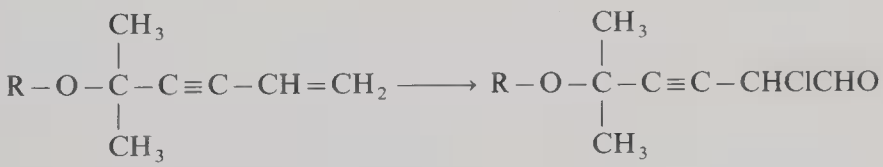
Ether	Products, yield (%)		
	Ketone	Benzoate	Benzoic acid
$CH_6(CH_2)_5CH(CH_3)OCH_2C_6H_5$	79	21	61
	57	28	53
$C_6H_5CH(CH_3)OCH_2C_6H_5$	56	21	52
	63	24	47
	16	40	16
	30	32	31

[a] Reference 421.

185, R = H **187**, R = H
186, R = OCH_3 **188**, R = OCH_3 (81)

The chromyl chloride oxidation of ethers gave various products (ketones, alcohols, chlorides), depending on the nature of the substituents.[426]

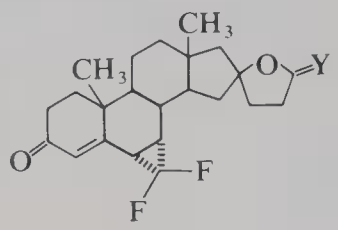
Chromyl chloride (**3**) selectively oxidizes enynes (**189**, R = CH_3, C_2H_5, C_4H_9) to the respective aldehyde derivatives (**190**) in 32%–35% yield.[427]



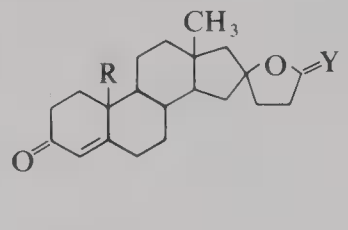
189 **190** (82)

t-Butyl chromate (**4**) oxidizes keto spiroethers (**191**, **192**, **193**) to lactones (**194**, 40%; **195**, 48%; **196**, 30%).[428] Oxidation occurred selectively at the position alpha to the ether

oxygen. The fact that the 19-norsteroid **191** was not noticeably aromatized under the reaction conditions indicates that the method is reasonably specific.

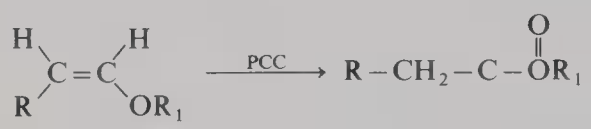


191 $Y = H_2$
194 $Y = O$



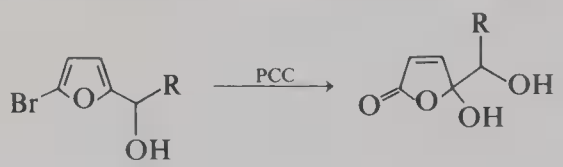
192 $R = CH_3$, $Y = H_2$
193 $R = H$, $Y = H_2$
195 $R = CH_3$, $Y = O$
196 $R = H$, $Y = O$

Pyridinium chlorochromate (PCC, **7**) oxidizes linear and cyclic enol ethers to esters and lactones with high efficiency.[202] This oxidation is the first example of the direct conversion of enol ethers to esters or lactones (Table XXXII).



(83)

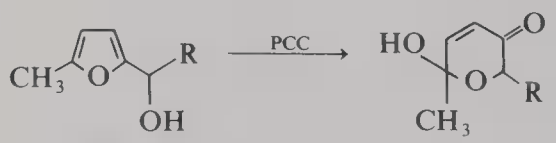
An unusual regiospecificity of PCC (**7**) is shown in its oxidation of 5-bromo-2-furylcarbinols (**197**) to γ-hydroxybutenolides (**198**)[429] or of 5-methyl-2-furylcarbinols (**199**) to the biologically important ring enlarged products **200** [cf. Eq. (10)].[195] The formation of **200**



(84)

197 **198**

with PCC (**7**) is preferable to the procedure using *m*-chloroperoxybenzoic acid as oxidant.[194,430] Oxidation occurs at the furan ring in spite of the presence of the secondary alcohol group. Table XXXIII summarizes some of the products from the PCC (**7**) oxidation of furans.



(85)

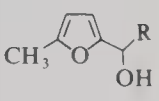
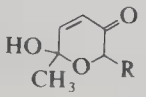
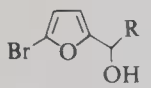
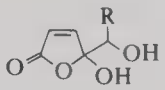
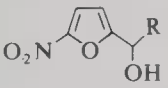
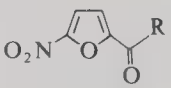
199 **200**

TABLE XXXII. PCC (**7**) Oxidation of Enol Ethers to Esters or Lactones[a]

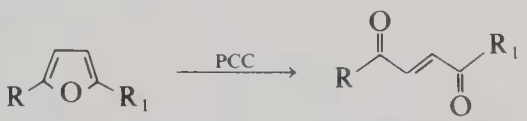
Enol ether	Product	Yield (%)
5-Cholesten-3β-vinyl ether	Cholesteryl-3β-acetate	95
5α-Pregnan-3β-acetate-20-vinyl ether	5α-Pregnan-3β, 20-diacetate	90
Ethyl vinyl ether	Ethyl acetate	75
2,3-Dihydro-4H-pyran	δ-Valerolactone	90
2,3-Dihydrofuran	γ-Butyrolactone	85

[a] Reference 202.

TABLE XXXIII. Oxidation of Furan Ring Systems by Pyridinium Chlorochromate (PCC, 7)

Substrate	Product	Yield (%)	Reference
			
$R=CH_3$		91	195
$R=n-C_6H_{13}$		94	195
$R=CH_2-CH=CH_2$		90	195
			
$R=n-C_5H_{11}$		60	429
$R=c-C_6H_{11}$		65	429
$R=n-C_{10}H_{21}$		75	429
			
$R=n-C_5H_{11}$		77	432
$R=n-C_8H_{17}$		75	432
$R=n-C_{10}H_{21}$		75	432
$R=n-C_{12}H_{25}$		85	432

Alkylfurans (**201**) undergo oxidative ring fission to α,β-unsaturated-γ-dicarbonyl compounds (**202–204**) in 60%, 90%, and 90% yield, respectively.[431] The initial product, which has the *cis* configuration, undergoes *cis–trans* isomerism due to heating or the acidic character of PCC.



(86)

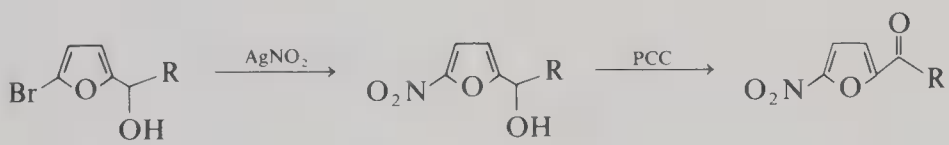
201

202, $R=H$, $R_1=n-C_{12}H_{25}$

203, $R=CH_3$, $R_1=n-C_{12}H_{25}$

204, $R=CH_3$, $R_1=n-C_8H_{17}$

If an electron attracting group deactivates the furan ring, oxidation occurs at the alcohol functional group [Eq. (86), Table XXXIII].[432]



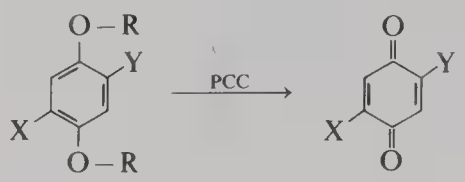
(87)

205 **206** **207**

3.10. Oxidation of Silyl Ethers

Silyl ethers of hydroquinones (**208**) are important intermediates for the preparation of naturally occurring quinones. The deprotection of the quinone is easily accomplished with

PCC (**7**).[433] The reaction is easily performed in dichloromethane at 23–25°C (Table XXXIV). This procedure is more advantageous than the previously used oxidants (nitric acid or silver(II) oxide and ceric ammonium nitrate).



208 **209** (88)

3.11. Oxidation of Carbonyl Compounds

3.11.1. Aldehydes

As indicated above, the chromium(VI) oxidation of aldehydes to carboxylic acids is not synthetically useful. Aldehydes are intermediates in the chromium(VI) oxidation of other functional groups.

TABLE XXXIV. Oxidation of Silyl Ethers (**208**) to Quinones by PCC (**7**)[a]

R	X	Y	Yield (%) of **209**
$(CH_3)_3Si$	H	H	99
$(CH_3)_3Si$	H	CH_3	62
$(CH_3)_3Si$	H	OCH_3	65
$(CH_3)_3Si$	CH_3	CH_3	93
$(CH_3)_3Si$	t-C_4H_9	t-C_4H_9	91
t-C_4H_9-Si(CH$_3$)$_2$	H	CH_3	90
t-C_4H_9-Si(CH$_3$)$_2$	H	OCH_3	50
t-C_4H_9-Si(CH$_3$)$_2$	CH_3	CH_3	80
t-C_4H_9-Si(CH$_3$)$_2$	t-C_4H_9	t-C_4H_9	99

[a] Reference 433.

3.11.2. Ketones

The chromic acid (**1**) oxidation of cyclobutanones to gamma lactones has been described above [Eqs. (63)–(65)].[385,386,434]

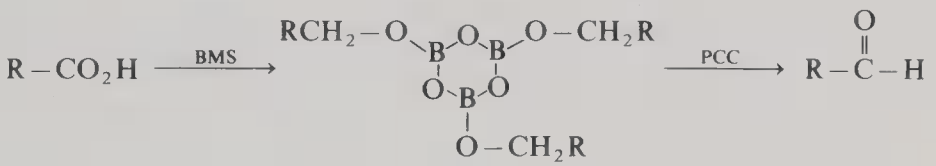
3.12. Oxidation of Carboxylic Acids and Their Derivatives

3.12.1. Carboxylic Acids

The results of the chromium(VI) oxidation of aliphatic carboxylic acids have been reported.[435–437]

Chromium(VI) oxidizes α-hydroxy acids to carbonyl compounds.[438–441]

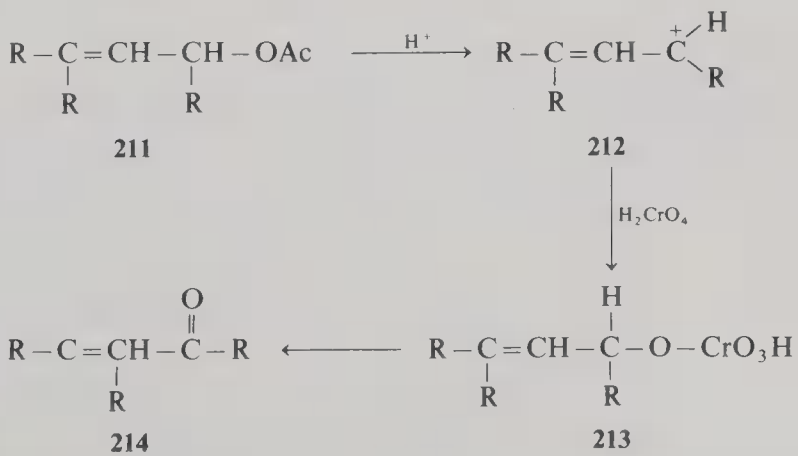
A convenient conversion of carboxylic acids into aldehydes has been described.[442] This method involves the rapid reduction of the carboxylic acid with borane–dimethyl sulfide (BMS), followed by oxidation of the resultant trialkoxyboroxine (**210**), without isolation, with PCC (**7**) in refluxing dichloromethane. This reaction is broadly applicable, tolerating many substituents, such as chloro, methoxy, nitro, cyano, and ester groups. It appears to be equally applicable to both aliphatic and aromatic carboxylic acids. The tolerance of borane–dimethyl sulfide (BMS) toward a wide variety of functional groups, combined with the mild nature of PCC as an oxidizing agent, makes this method simple, general, and, consequently, far superior to many of the procedures previously utilized.[443]



210 (89)

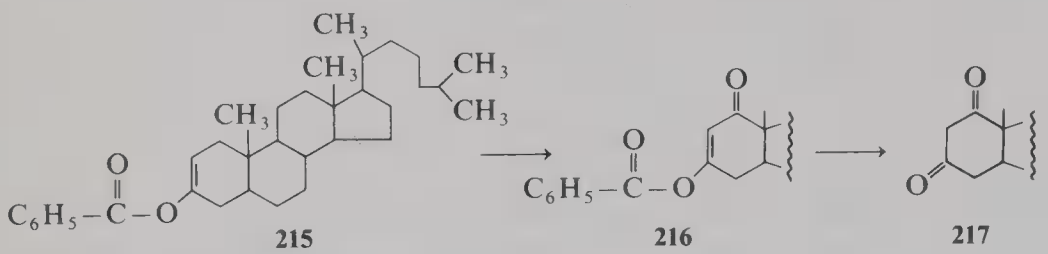
3.12.2. Esters

Steroidal allylic acetates (**211**), which can form strongly resonance stabilized allylic cations (**212**), are oxidized smoothly by chromic acid (**1**) in acidic medium to the corresponding α,β-unsaturated ketones (**214**).[444] Axial acetates are more reactive than the equatorial counterparts. The oxidation of **211** was also performed with Jones reagent, sodium chromate, chromium trioxide in acetic acid, chromium trioxide in acetic acid–sodium acetate, PCC (**7**), and chromium trioxide in pyridine.[444]



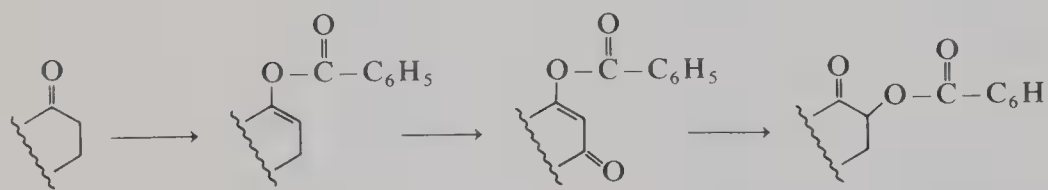
211 **212** **213** **214** (90)

The enol benzoate of 5α-cholestan-3-one (**215**) with sodium chromate in acetic acid and acetic anhydride gives 1-oxo-5α-cholest-2-en-3-yl benzoate (**216**), which can be hydrolyzed to 5α-cholestane-1,3-dione (**217**).[445,446] This oxidation follows a path different than that of most oxidation of enol esters which takes place on the double bond itself rather than at one of the allylic positions.[447–449]



215 **216** **217** (91)

Application of the above oxidation system to several types of cyclic enol benzoates gave, in addition to allylic oxidation [Eq. (91)], a rearrangement to an α-benzoyloxy-ketone [**218**, Eq. (92)].[446] Table XXXV shows that the yields and ratios of the allylic oxidation products and the rearranged ones vary greatly, and depend on electronic and steric factors.[446]



218 (92)

3.13. Oxidation of Nitrogen Compounds

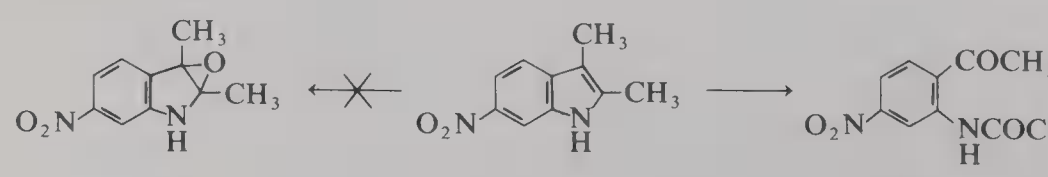
Chromium(VI) oxidants have also been useful for the analytical determination of hydrazine,[450] arylamines,[451] isonitroso groups,[452] catecholamines,[453] nitramines,[454] indazolinones,[455] triazenes,[456] pentaaza-1,4-dienes,[456] and azoxy groups.[457]

3.13.1. Amines

Benzoquinones have been obtained from the chromium(VI) oxidation of anilines.[458] The chromic acid (**1**) oxidation of *N*-alkylarylamines leads to aldehydes in yields up to 37%.[459,460]

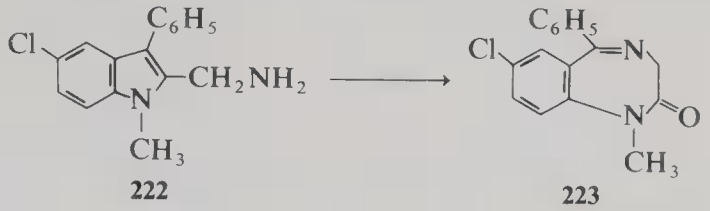
The effect of ozone on the oxidation of benzimidazole by hexavalent chromium compounds has been reported.[461,462]

The product previously identified as 2,3-dimethyl-6-nitroindole 2,3 epoxide (**220**)[463] from the aqueous formamide chromic acid oxidation of 2,3-dimethyl-6-nitroindole (**219**) has been shown to be a mixture of **219** and *N*-(2-acetyl-5-nitrophenyl)acetamide (**221**).[464,465]



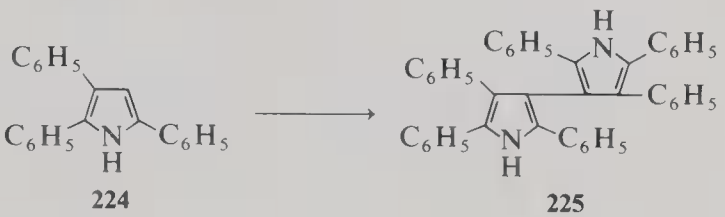
220 **219** **221** (93)

2-Aminomethyl-5-chloro-1-methyl-3-phenylindole (**222**) reacted rapidly with chromic acid (**1**) to give 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (**223**).[466]

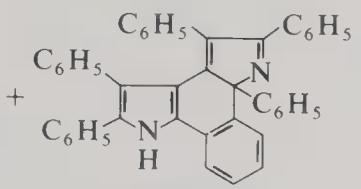


222 **223** (94)

Oxidation of 2,3,5-triphenylpyrrole (**224**) with potassium dichromate in benzene solution at 23–25°C gave several reaction products, including the 3,3′-pyrryl dimer (**225**) and the condensation product **226**.[467]

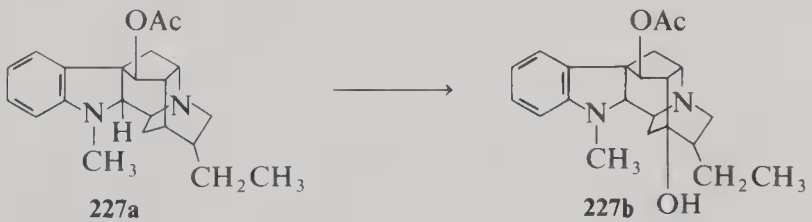


224 **225**



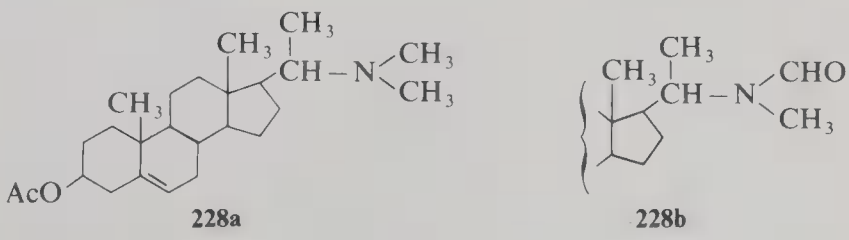
226 (95)

Oxidation occurs alpha to nitrogen in the reaction of 21-deoxyajmaline-17-epi-O-acetate (**227a**) to (**227b**) with chromium trioxide in pyridine.[468a]



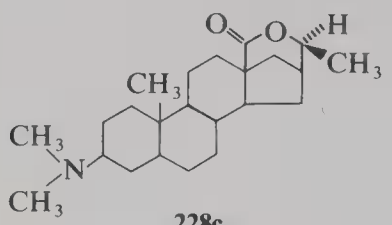
227a **227b** (96)

The oxidation of steroidal amines with chromium trioxide in pyridine occurs in excellent yields.[468b] For example, acetylrehine (**228a**) is oxidized to the *N*-formyl derivative (**228b**, 96%), and *N*-methylparavallarine (**228c**) gives the corresponding amide (**228d**, 97%). It is of interest to note that oxidation occurs at the primary carbon–hydrogen bond and the more

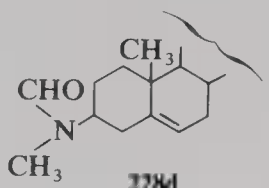


228a **228b**

reactive tertiary C–H bond is not attacked at all, which is explicable in terms of steric factors.[468]

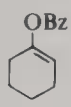
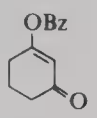
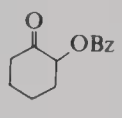
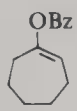
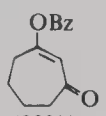
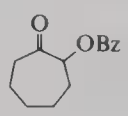
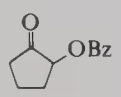
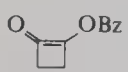
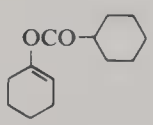
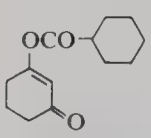
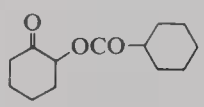
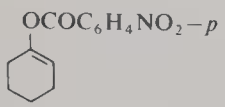
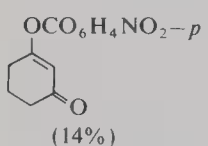
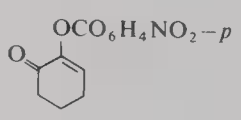
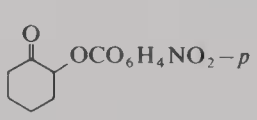
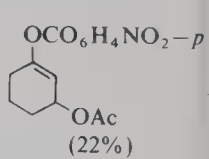
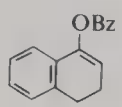
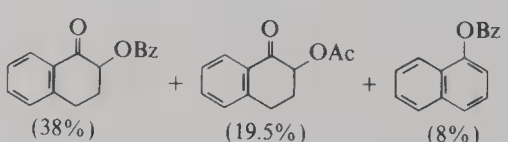
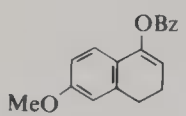
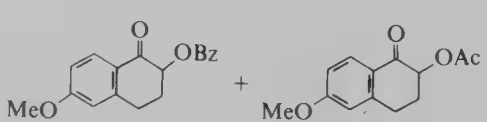


228c



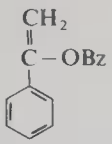
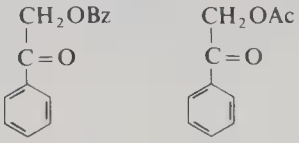
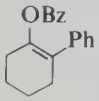
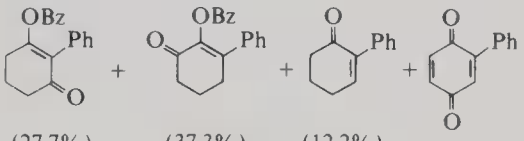
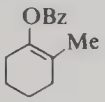
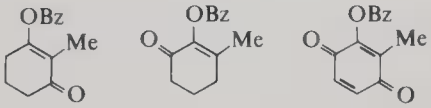
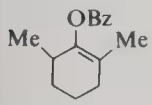
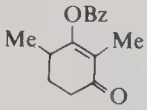
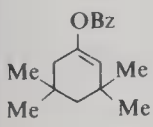
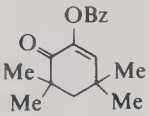
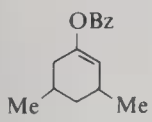
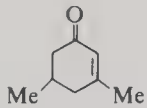
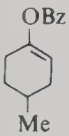
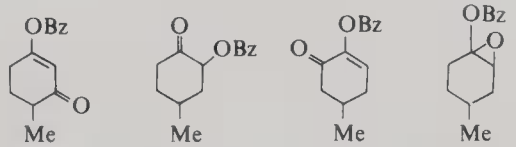
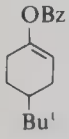
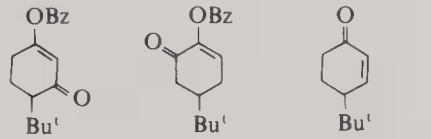
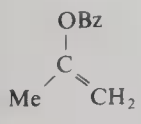
228d

TABLE XXXV. Oxidation of Enol Esters with Sodium Chromate[a]

Enol ester	Oxidation products, yield (%)
	 (50%)  (15%)
	 (20%)  (45%)
	 (10%)  (13%)
	 (10%)
	 (35%)  (24%)
	 (14%)  (12.4%)  (10.1%)  (22%)
	 (38%) + (19.5%) + (8%)
	 (40%) + (50%)

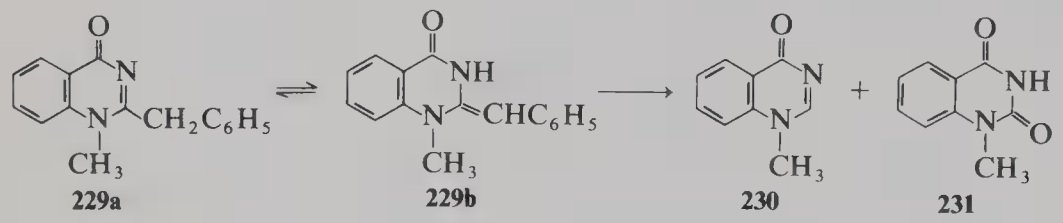
[a] Reference 446.

TABLE XXXV. (*Continued*)

Enol ester	Oxidation products, yield (%)
	 (45%) (47%)
	 (27.7%) (37.3%) (12.2%) (4.3%)
	 (30.1%) (17.5%) (12.3%)
	 (48%)
	 (56%)
	 (60.2%)
	 (44%) (10%) (14.5%) (2.2%)
	 (18.6%) (31%) (21%)
	No products identified

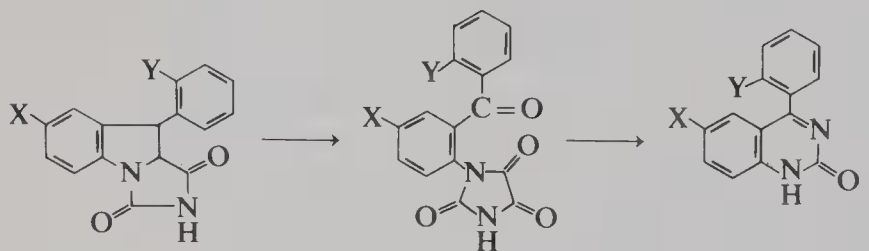
3.13.2. Amides

Arborine (**229**), the major quinazolinone alkaloid of *G. arborea* (Roxb.) DC. (Rutaceae), undergoes facile oxidation on brief heating with chromic acid (**1**) in glacial acetic acid to give glycorine (**230**, 78%) and glycosmicine (**231**, 14%).[469,470] The oxidation of a number of 1,2- and 2,3-disubstituted and 2-monosubstituted alkyl/aryl derivatives of 4-quinazolinone has also been studied.[470]



(97)

The chromic acid (**1**) oxidation of indole-1,2-dicarboxamides (**232**) led to imidazolidinetriones (**233**), which on hydrolysis with base gave the corresponding dihydroquinazolinones (**234**).[471]

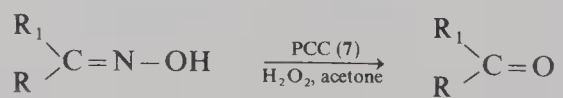


X = NO_2 Y = H
X = Cl Y = F

(98)

3.13.3. Oximes

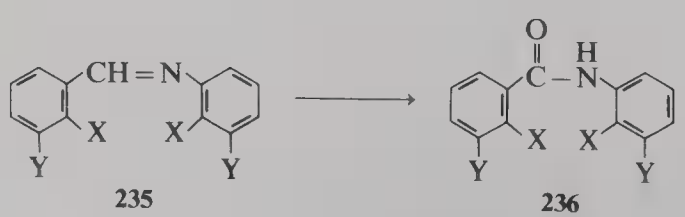
Cleavage of oximes to regenerate the carbonyl compound has been accomplished with PCC (**7**) alone[472] and with the PCC (**7**)–hydrogen peroxide system.[473] The latter novel system is more rapid than PCC (**7**) alone (Table XXXVI).



(99)

3.13.4. Imines

Benzylidene aniline (**235**) and various aromatic imines react with chromyl chloride (**3**) to give benzanilides (**203**).[474]



(100)

TABLE XXXVI. Deoximation with Pyridinium Chlorochromate/Hydrogen Peroxide System[a]

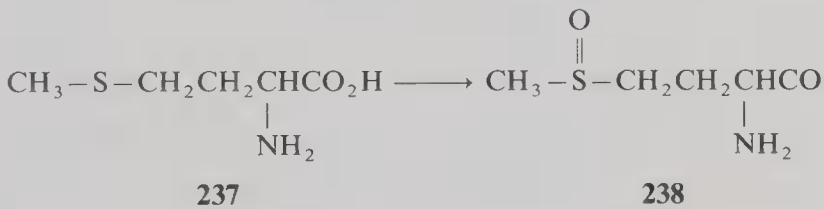
Carbonyl compound	Yield (%)
Cyclohexanone	75
4-*t*-Butylcyclohexanone	64
2-Methylcyclohexanone	67
Cycloheptanone	71
Acetophenone	80
4-Methoxyacetophenone	73
Benzophenone	55
Benzaldehyde	35
Camphor	78
Cholestan-3-one	85

[a] References 472, 473.

3.14. Oxidation of Sulfur Compounds

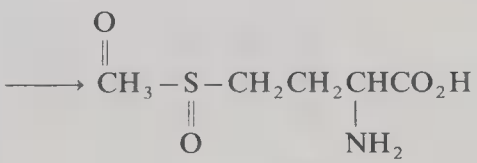
The rapid formation of the chromic acid ester of 2,2,6-trimethylnonane-6-thiol in acetic acid has been observed.[475]

Methionine (**237**) was determined by direct and indirect titration with potassium dichromate.[476] Dichromate oxidizes methionine to its sulfoxide at 20–25°C and to its sulfone at elevated temperature. The chromium(VI) oxidation of sulfides generally leads to sulfones in poor to quantitative yields.[476,477–480]



(101)

237 **238**



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3.15. Oxidation of Organic Halides

One of the most efficient procedures for the oxidation of halides to carbonyl compounds involves the use of chromic acid attached to an anion exchange resin.[481]

Aqueous chromate ion oxidizes allylic and halomethylated aromatics to allylic and aromatic aldehydes.[482] The oxidation is more efficient in the presence of quarternary ammonium and/or phosphonium chloride.

Bis(tetrabutylammonium) dichromate (**13**) is an excellent reagent for the oxidation of activated alkyl halides to the corresponding carbonyl compounds (Table XXXVII).[95]

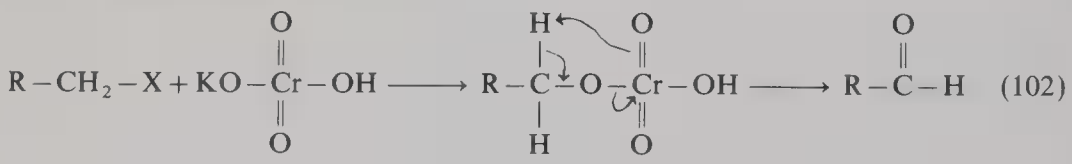
The reaction between activated alkyl halides and potassium dichromate in anhydrous

TABLE XXXVII. Aldehydes from the Chromium(VI) Oxidation of Organic Halides

Organic halide	Oxidant	Yield (%)	Reference
1-Bromooctane	A[a]	20	483
2-Bromooctane	B[b]	17	95
	B	72	95
Benzyl bromide	A	80	483
	B	95	95
Benzyl chloride	B	81	95
Farnesyl bromide	A	80	483
	B	92	95
Geranyl bromide	A	82	483
γ, γ-Dimethylallyl bromide	A	78	483

[a] Potassium dichromate in HMPT in the presence of crown ether (Ref. 483).
[b] Bis(tetrabutylammonium) dichromate (**13**) (Refs. 95, 482).

HMPT in the presence of crown ether provides an attractive synthetic route to aldehydes in fair to excellent yields (Table XXXVII).[483]

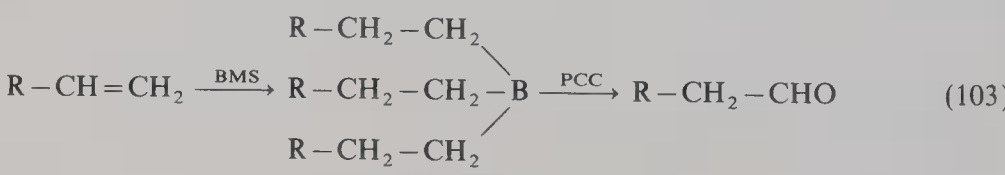


(102)

Chromyl chloride (**3**) oxidizes benzyl chloride to phenylmethanal.[105]

3.16. Oxidation of Organoboranes

The oxidation of organoboranes (**240**) with PCC (**7**) proceeds via the formation of borate esters as observed by the ^{11}B NMR spectrum of aliquots from the incomplete reaction. Representative examples of this high yield, highly convenient, easy workup procedure, one-pot method for the conversion of terminal olefins to aldehydes [Eq. (103)] are shown in Table XXXVII*,[335,336,385,491]



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240

Trialkyl borates (**241**), which are readily prepared either by esterification of boric acid or by the reaction of alcohols with borane–dimethyl sulfide (BMS), are oxidized to aldehydes

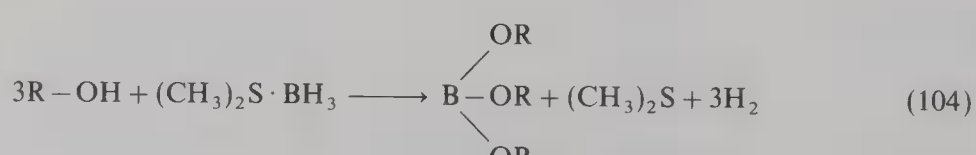

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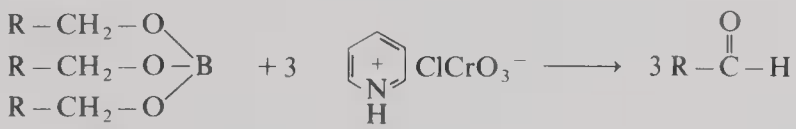
TABLE XXXVIII. Oxidation of Organoboranes in Pyridinium Chlorochromate (PCC, 7)

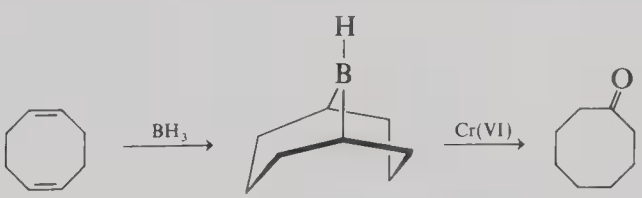
Alkene	Product(s)	Product distribution	Yield (%)	Reference
1-Hexene	Hexanal	95	73	335
	2-Hexanone	5		
1-Octene	Octanal	94	70	335
	2-Octanone	6		
1-Decene	Decanal	95	74	335
	2-Decanone	5		
1-Dodecene	Dodecanal	94	78	335
	2-Dodecanone	6		
3,3-Dimethyl-1-butene	3,3-Dimethylbutanal	98	64	335
	3,3-Dimethyl-2-butanone	2		
Methylenecyclohexane	Cyclohexylcarboxaldehyde	99	71	335
	1-Methylcyclohexanol	1		
(E)-4-Octene	Octan-4-one		88	336
Cyclohexene	Cyclohexanone		81	336
Cycloheptene	Cycloheptanone		83	336
(Z)-Cyclooctene	Cyclooctanone		88	336
(Z)-Cyclononene	Cyclononanone		92	336
(Z)-Cyclodecene	Cyclodecanone		92	336
(Z)-Cyclododecene	Cyclododecanone		92	336

and ketones with PCC (**7**).[491] In certain cases there can be advantages in going from borate esters (**241**) to the carbonyl compounds rather than directly from the alcohols (Table XXXIX).[491]



241 **7** (105)

Chromic acid oxidizes 9-borabicyclo[3.3.0]nonane (9-BBN, **242**), 10-borabicyclo[4.3.0]decane, and 11-boradicyclo[5.3.0]-undecane to the respective ketones cyclooctanone (60%), cyclononanone (65%), and cyclodecanone (62%).[490]



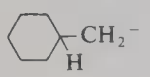
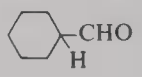
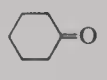
242 (106)

Boronic acids (**243**) are easily oxidized by chromic acid. Probable mechanisms have been discussed.[492,493]

$$(CH_3)_3CB(OH)_2 + CrO_3 \xrightarrow{H_2O} (CH_3)_3COH + H_3BO_3 + Cr(III) \qquad (107)$$

243

TABLE XXXIX. Oxidation of Trialkyl Borates with Pyridinium Chlorochromate (7) to Aldehydes and Ketones[a]

Alkyl group of trialkyl borate (241)	Product	Yield (%)
$n-C_6H_{13}-$	$n-C_5H_{11}-CHO$	64
$n-C_7H_{15}-$	$n-C_6H_{13}-CHO$	67
$n-C_8H_{17}-$	$n-C_7H_{15}-CHO$	76
$C_6H_5-CH(CH_3)-$	$C_6H_5-C(=O)-CH_3$	89
		78
		88

[a] Reference 491.

4. EXPERIMENTAL CONSIDERATIONS AND PROCEDURES

4.1. General Considerations

Care must be exercised in the handling of oxochromium(VI) compounds. Many chromium(VI) compounds are classified in OSHA Category I.[1]

CAUTION: Add chromium trioxide in small portions to HMPT with stirring at 20°C. A violent decomposition can result if crushed CrO_3 is added to HMPT[‡,84,85]

CAUTION: The chromium trioxide–pyridine complex can be prepared *in situ* in CH_2Cl_2.[†,28,88,91] This procedure appears to be safer than the method for preparing Sarett reagent.[23,25–28]

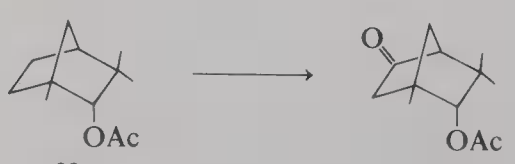
CAUTION: In order to avoid a fire, powdered CrO_3 must be added in small portions in a nitrogen atmosphere to ice-cooled DMF.[93]

CAUTION: In preparing a solution of chromyl acetate (**2**), it is necessary to add the CrO_3 to the acetic anhydride slowly with stirring and cooling. The addition of acetic anhydride to CrO_3 usually leads to a fire and often leads to an explosion.[3,62,267,268]

4.2. General Procedures and Typical Detailed Procedures

4.2.1. Carbon–Hydrogen Bonds

Oxidation of endo-Fenchyl Acetate (29) to 5-Oxo-endo-fenchyl Acetate (30) by Chromyl Acetate (2).[5] To an oxidant mixture containing 15.3 g of CrO_3 in 166 ml of AcOH–Ac_2O



29 **30** (108)

(50/50) were slowly added 9.9 g of **29**. The reaction mixture, which was protected with a $CaCl_2$ tube, was kept for 26 h at $41 \pm 2°C$ in a water bath. (No change in product composition was found if the drying tube was replaced by a loosely fitted stopcock.) Since the mixture was homogeneous for most of the reaction time no stirring was normally used. During the reaction the color of the mixture changed from brown-red to green. After the oxidation was complete, the chromium complexes and most of the Ac_2O were hydrolyzed by addition of saturated aqueous Na_2CO_3 until the mixture was slightly basic. The solution was then extracted six times with 80 ml of pentane–ether (50/50) mixture. In order to avoid emulsions and to optimize partition of the products, the extraction was first done very carefully, but shaking efficiency was increased with each step. If necessary, the emulsions were broken with the addition of 2 ml of ethanol. The combined ether phases were then washed three times with carbonate solution followed by water, 1 *M* H_2SO_4, and finally with water to neutral pH. Removing the solvent left 8.2 g of half crystalline crude product.

Prefractionation was done by high-vacuum distillation after an addition of 0.5 g NaOAc by first using a 10 cm Vigreux column. The first fraction was mainly unreacted **29**. Fraction II, which distilled at about 75°C (0.2 mm), contained the main product (**30**, 5.5 g). The distillation residue (2.7 g) still contained **30** as a main component but side products were markedly enriched. The distillation residue was fractionated by preparative GLC.

In order to prevent possible hydrolysis of acetates in the product by Na_2CO_3, some reaction mixtures were isolated by distillation of solvent in vacuum followed by addition of water instead of Na_2CO_3, and then extracted with ether. No change in product distribution was observed. Some preparative GLC fractionations were made directly from the initial oxidation product.

4.2.2. Allylic Carbon–Hydrogen Bonds

*Oxidation of Cholesteryl Acetate (**42**) to 5-Cholesten-7-one-3β-ol Acetate (**43**) by Chromium Trioxide · Pyridine [Ratcliffe's Reagent, Eq.(16)].*[111] Prior to a typical oxidation, chromium trioxide (Alfa-Ventron 99%) was stored in a desiccator under vacuum over P_2O_5 for 24 h before use. Pyridine (Baker Analyzed Reagent) was dried over 4-Å molecular sieves for two days. Dichloromethane (Mallinckrodt Analytical Reagent) was dried over anhydrous $CaCl_2$ overnight at 20–25°C and then fractionally distilled. The 39.5–40.5°C fraction was stored over 4-Å molecular sieves.

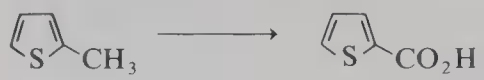
In a typical oxidation, to an ice-bath cooled, rapidly stirred solution of pyridine (2.5 g, 30 mmol) in 30 ml of dichloromethane under nitrogen was added 1.5 g (15 mmol) of CrO_3. The deep burgundy solution was stirred for 5 min, and the ice-bath was removed. After 10 min additional stirring, a solution of 429 mg (1 mmol) of cholesteryl acetate (**42**) in 1 ml of dichloromethane was added in one portion. A tarry precipitate immediately began forming on the sides and bottom of the flask, soon slowing the magnetic stirring bar. After stirring 24 h at 20–25°C, the reaction solution was decanted and the tarry deposit in the flask was washed with dichloromethane. The solvent was removed *in vacuo* at 20–25°C, and the residual oil was dissolved in 200 ml of ether and filtered. The ether filtrate was washed twice with 25 ml of 5% HCl, once with 25 ml of saturated NaCl, and then dried ($MgSO_4$). Evaporation of the ether gave a white solid which was recrystallized from methanol to give 332 mg (72%) of 5-cholesten-7-one 3β-ol acetate (**43**), mp 157–158°C; ir (KBr) 1675, 1740 cm^{-1}; uv λ_{max}^{EtOH} 237 nm ($\varepsilon = 12{,}500$).

*Oxidation of Cholesteryl Benzoate to 7-Ketocholestryl Benzoate by Chromic Anhydride-3,5-dimethylpyrazole [DMP, **11**, cf. Eq. (16)].*[81] It is important to prepare the oxidant at low temperature (usually −25 to −20°C) by adding the 3,5-dimethylpyrazole (DMP, **11**) as quickly as possible to the CrO_3 suspended in dry dichloromethane. It is equally important that the CrO_3 be dried over P_2O_5 before use for most efficient oxidation. When the molar ratio of CrO_3 to steroid is ca. 20, the reaction is complete in ~30 min; when it is *ca.* 10, the reaction takes as long as 5 h for completion. A typical reaction is conducted thus: Chromium trioxide (6.0 g, 60.0 mmol) is suspended in dry dichloromethane (50 ml) at −20°C and the

DMP (5.76 g, 60 mmol) is added in one portion. After stirring at −20°C for 15 min, cholesteryl benzoate (2.44 g, 5 mmol) is added and the mixture is stirred for 4 h while maintaining the temperature between −10 and −20°C. Sodium hydroxide solution (25 ml, 5 *M*) is then added and the mixture is stirred for 1 h at 0°C. The phases are then separated. The organic layer is washed with dilute HCl to remove the DMP, which can be recovered by subsequent basification of this acidic wash. The dichloromethane phase is now washed with water, saturated NaCl solution, and evaporated to yield a residue, which is crystallized from cyclohexane to give 7-ketochloresteryl benzoate, 1.86 g, 74%.

4.2.3. Alkylaromatics

*Oxidation of 2-Methylthiophene (**244**) to Thiophene-2-carboxylic Acid (**245**) by Sodium Dichromate.*[57] 2-Methylthiophene (**244**, 30.0 g, 0.306 mol), sodium dichromate (110 g, 0.37 mol, 21% excess), and water were heated at 250°C for 16 h. No starting material could be recovered. Acidification of the strongly alkaline filtrates (pH 13) gave carbon dioxide, hydrogen sulfide, and thiophene-2-carboxylic acid (**245**, 25 g), mp 137–138°C. The ether



244 **245** (109)

extracts of the acidified filtrates gave additional **245** (7 g), mp 137–138°C, for a total yield of 82% (32 g, 0.25 mol). The oxidation results were independent of the excess sodium dichromate employed (0%–64% excess).[57]

*Oxidation of 2-Methylnaphthalene (**246**) to 2-Naphthoic Acid (**247**) by Sodium Dichromate.*[57] 2-Methylnaphthalene (**246**, 320 g, 2.25 mol), sodium dichromate (1050 g,

246 **247** (110)

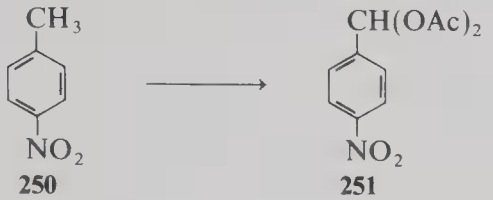
3.50 mol, 50% excess), and water (1.8 liters) were shaken in an autoclave (3.25 liters) for 18 h at 250°C. The reactor was emptied at 60°C and the content was filtered to remove chromic oxide. The filter residue was washed with warm water (7 liters) until all of the sodium 2-naphthoate was removed. The aqueous solution was acidified with HCl (1:1). After the mixture had cooled overnight, the precipitate which had formed was filtered, washed well with water, and air dried. White product (**247**, 360 g, 2.09 mol) was obtained in 93% yield, mp 184–185°C. When larger excesses of sodium dichromate (55%–64%) were employed, the yields were 90%–92%, and more carbon dioxide was formed.[57]

*Oxidation of Fluorene (**248**) to Fluorenone (**249**) by Sodium Dichromate.*[57] Fluorene (**248**, 50 g, 0.30 mol), sodium dichromate (100 g, 0.34 mol; 70% excess), and water (250 ml) were heated in a shaking autoclave (500 ml) for 18 h at 250°C. The mixture of fluorenone (**249**) and chromic oxide (green) was filtered with suction and washed well with water (pH of

248 **249** (111)

filtrate ~13). The dried filter cake was extracted with hot 2-propanol. The bright yellow extracts were filtered to remove suspended particles, concentrated, and diluted while hot with water to incipient turbidity. On cooling, fluorenone (**249**, 50 g, 91% yield) was obtained, mp 82–83°C. Dilution of the mother liquors with water gave additional **249** (4.4 g, 8%, mp 82–83°C); the total yield was 99%.

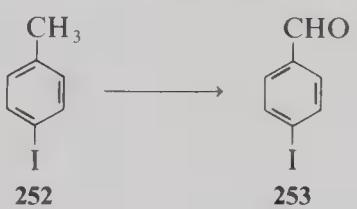
*Oxidation of 4-Nitrotoluene (**250**) to 4-Nitrobenzaldehyde Diacetate (**251**) by Chromyl Acetate (**2**).*[62,267,268] CAUTION: In preparing a solution of chromyl acetate (**2**), it is necessary to add the CrO_3 to the acetic anhydride slowly with stirring and cooling. The addition of acetic anhydride to chromium trioxide usually leads to a fire and often leads to an explosion.



250 **251** (112)

To a stirred solution of 50 g (0.36 mol) of 4-nitrotoluene (**250**) in 400 ml of acetic anhydride, which is cooled in an ice–salt bath, is slowly added 80 ml of concentrated sulfuric acid. When the mixture has cooled to 0°C, a solution of 100 g (1.0 mol) of CrO_3 in 450 ml of acetic anhydride is added slowly, with stirring so that the temperature does not exceed 10°C, and stirring is continued for 2 h at 5–10°C after the addition is completed. The reaction mixture is poured into two 3-liter beakers one-third filled with crushed ice, and water is added to make the total volume 5–6 liters. The solid is separated by filtration and washed with water until the washings are colorless. The product is suspended in 300 ml of 2% aqueous Na_2CO_3 solution and stirred. After thorough mixing the solid is filtered, washed with water, and finally with 20 ml of ethanol. After drying in a vacuum desiccator, there is obtained 60–61 g (65%–66%) of 4-nitrobenzaldehyde diacetate (**251**).

*Oxidation of 4-Iodotoluene (**252**) to 4-(Iodophenyl)methanal (**253**) by Chromyl Chloride (**3**).*[106] A solution of 4-iodotoluene (**252**, 43.6 g, 0.2 mol) in carbon tetrachloride (150 ml) was placed in a three-necked flask, immersed in ice-cold water. Chromyl chloride (**3**, 65.2 g,



252 **253** (113)

0.42 mol) in carbon tetrachloride (150 ml) was allowed to run in dropwise, with vigorous stirring, during 1 h. The mixture was stirred at 20–25°C for a further 1 h, and then heated slowly to reflux during another 1 h. The mixture was stirred while refluxing for a further 20 h. The cooled reaction mixture was poured slowly with vigorous stirring by hand onto sodium sulfite (60 g) dissolved in water (300 ml) containing ice (300 g). Dilute (1:1) hydrochloric acid (100 ml) was added to dissolve the basic chromium salts, the organic layer was separated, and the aqueous layer was extracted three times with portions of carbon tetrachloride. The combined organic solution was washed with water and dried. The residue left when the solvent was removed was distilled, giving the product (**253**), bp 145–150°C at (25 mm), mp 55–65°C, 27.0–30.0 g (58%–64%). A forerun, bp 125–130°C (25 mm) (3.5–5.0 g) was largely unchanged **252**. The 4-iodobenzaldehyde (**253**) can be recrystallized from aqueous ethanol to mp 75°C.

4.2.4. Indans and Tetralins

*Oxidation of 1,1-Dimethylindan (**63**) to 3,3-Dimethyl-1-indanone (**64**) by Chromium Trioxide in Acetic Acid [Eq.(26)].*[281] To a stirred mixture of 5.85 g (0.04 mmol) of **63** dissolved in 1 liter of AcOH was added 107 ml of 10% CrO_3 in AcOH over a 30-min period. The reaction temperature remained below 30°C. The solution was stirred overnight, diluted with 5 liters of water, and extracted with 1-liter portions of ether. The combined ether extract was washed with 10% NaOH, dried ($MgSO_4$), and concentrated by distillation. This

procedure gave 6.0 g of orange-colored oil, which on distillation (70°C; 0.2 mm) gave 5.6 g (88%) of colorless **64**.

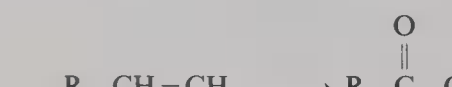
General Procedure for the Oxidation of Tetralins to Tetralones by Chromic Acid (1).[282] To a magnetically stirred solution of 0.04 mol of hydrocarbon in 1 liter of acetic acid was added dropwise 170 ml of 10% aqueous CrO_3 acetic acid solution (the chromic acid solution

(114)

was prepared by dissolving 21 g (0.21 mol) of CrO_3 in 190 ml of AcOH and 10 ml of water) over a period of 30 min. The reaction temperature was maintained between 17 and 21°C with an ice bath. The reaction was allowed to proceed to completion (ca. 2 h) as evidenced by GLC. The reaction was then diluted with 6 liters of distilled water and extracted with ether (2 × 1.5 liters). The combined ether extract was washed with water and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The resulting crude products were distilled.

4.2.5. Alkenes

General Procedure for the Mercury(II) Catalyzed Oxidation of Terminal Olefins to Methyl Ketones by Jones Reagent (Table XIV). Method A.[322] To a 500-ml Erlenmeyer flask was added 200 ml of acetone, 5 ml of water, and 6.8 g (20 mmol) of mercuric propionate. The flask was placed in a water bath and, with stirring, 100 mmol of olefin was added to the



(115)

bright yellow solution. Jones reagent (2 *M*, 75 ml) was added dropwise during 4 h. Ice was added as necessary to maintain the temperature at 25 ± 5°C. The dark greenish-brown solution was stirred for an additional 4 h and then poured into water (200 ml) and extracted with diethyl ether (3 × 75 ml). The combined extracts were washed with water (3 × 50 ml), saturated NaCl solution (1 × 50 ml), and water (1 × 50 ml), and dried ($MgSO_4$).

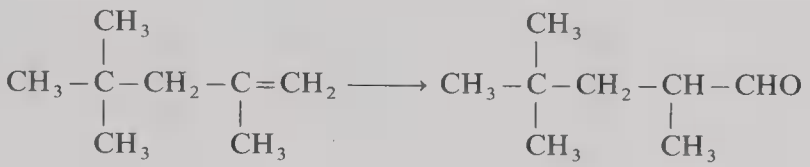
General Procedure for the Mercury(II) Catalyzed Oxidation of Terminal Olefins to Methyl Ketones by Jones Reagent (Table XIV). Method B.[322] To a 500-ml Erlenmeyer flask was added 22.0 g (74 mmol) of sodium dichromate dihydrate, 50 ml of water, and 300 ml of dioxane. With stirring, 6.8 g (20 mmol) of mercuric propionate and 35 ml of trifluoroethanoic acid were added. The dark orange-rad solution was stirred until the salts had dissolved (ca. 10 min), and the flask was placed in a water bath. With continued stirring, 100 mmol of olefin was added. The solution became dark and warm; ice was added as necessary to maintain the temperature at 25 ± 5°C. The solution was stirred for 18 h, poured into water (300 ml), and extracted with hexane (3 × 75 ml). The combined extracts were washed with water (3 × 50 ml), saturated NaCl solution (1 × 50 ml), and water (1 × 50 ml), and dried ($MgSO_4$).

*Oxidation of Phenylethene to 1-Phenyl-2-iodoethanone (**254**) by Silver Chromate-Iodine (Table XV).*[323] To a suspension of silver chromate (1.10 g, 3.3 mmol) and 4 Å molecular sieves (1.5 g) in 15 ml of dichloromethane was added iodine (1.14 g, 4.5 mmol) and a

(116)

solution of pyridine (118 mg, 1.5 mmol) in 0.75 ml of dichloromethane at 0°C and stirred for 5 min. A solution of phenylethene (312 mg, 3.0 mmol) in 5 ml of dichloromethane was added dropwise during 5 min to the ice-cooled suspension, which was stirred for 20 min at 0°C. Then, the cooling bath was removed and the reaction mixture was stirred for an additional hour at 20–25°C. The dark brown mixture was filtered through a pad of Celite. The filtrate was washed with 5% aqueous $Na_2S_2O_3$ and saturated aqueous NaCl, and dried ($MgSO_4$). The crude product (668 mg) obtained after concentration was purified on column chromatography (ca. 20 g of silica gel; eluant, hexane/ether 90/10) to give 1-phenyl-2-iodoethanone (**254**, 636 mg, 86%) as a slightly yellow oil, which on cooling crystallized: mp (hexane) 34.0–34.5°C, ir (neat) 1685 cm^{-1} (vs, C=O); NMR (CCl_4) 4.25 (s, 2H, CH_2ICO-), 7.28-7.65 (m, 3H, aromatic), 7.87–8.10 ppm (m, 2H aromatic); MS *m/z* (rel intensity) 246 (M_+, 18), 119 (M^+-I, 13), 105 (M^+-CH_2I, 20), 77 (Ph^+, 100), 51 ($M_+-C_2H_2COH_2I$, 40).

*Oxidation of 2,4,4-Trimethyl-1-pentene (**255**) to 2,4,4-Trimethylpentanal (**256**) by Chromyl Chloride (**3**, Table XVI).*[142,148] In a 5-liter three-necked flask fitted with a mechanical stirrer, a thermometer, and a dropping funnel equipped with a calcium chloride drying tube are placed 112.2 g (1.00 mol) of freshly distilled 2,4,4-trimethyl-1-pentene (**255**)



(117)

255 **256**

and 1 liter of dichloromethane. The flask is immersed in an ice–salt bath, and the stirred solution is cooled to 0–5°C. A solution of 158 g (1.02 mol) of freshly distilled chromyl chloride in 200 ml of dichloromethane is added dropwise with stirring from the dropping funnel while the temperature is maintained at 0–5°C. The reaction mixture is stirred for 15 min, and 184 g of 90%–95% technical grade zinc dust is added. The mixture is stirred for 5 min, 1 liter of ice water and 400 g of ice are added as rapidly as possible, and the mixture is stirred for an additional 15 min. The ice–salt bath is replaced by a heating mantle, and the flask is fitted for steam distillation. After distillation of the dichloromethane the residue is steam distilled. The distillate is transferred to a separatory funnel, the organic layer is separated, and the aqueous layer is washed with three 50-ml portions of dichloromethane. The combined organic phases are distilled through a 56-cm vacuum-jacketed Vigreux column to remove the solvent. The product is transferred to a 250-ml round-bottomed flask and distilled. After removal of a small amount of dichloromethane, the fraction boiling at 45–52°C (15 mm) is collected to give 90–100 g (70%–78%) of 2,4,4-trimethylpentanal (**256**).

*Oxidation of Cyclododecene to α-Chlorocyclododecanone by Chromyl Chloride (**3**, Table XVII).* Two general procedures (A and B), differing only in the temperature during chromyl chloride addition, have been employed.[324]

Procedure A. A solution of 16.6 g (0.10 mol) of cyclododecene (Chemical Samples Co.; GLC analysis revealed 91% E, 7% Z, and 2% diene) in 500 ml of reagent acetone was cooled in a dry ice–acetone bath to −70°C and then treated with 33.0 g (0.21 mol) of chromyl chloride (Alfa Ventron Co.), which was added via a dropping funnel with vigorous stirring of the solution. Addition was controlled so that a temperature of −65°C was not exceeded. After addition was complete (~30 min), the mixture was stirred at −75°C for 1 h, then allowed to warm to 20–25°C, and stirred for 1 h. The homogeneous, dark red-brown mixture was quenched by slowly pouring it into an ice-cold aqueous solution of $NaHSO_3$ (30 g, 0.3 mol of $NaHSO_3$ in 1000 ml of H_2O). The green mixture was stirred for 30 min in an ice bath and then extracted with 2 × 500 ml of ethyl acetate–hexane (1:1). The organic phases were washed with 500 ml of H_2O and 500 ml of NaCl (saturated, aqueous), then

combined, dried ($NaSO_4$), filtered, and concentrated to yield a greenish yellow oil weighing 24.0 g (100%). The crude product was distilled to afford 17.1 g (79%) of α-chlorocyclododecanone bp 100–102°C (0.075 mm) as a yellow liquid which solidified on standing to yield white prisms (from hexane), mp 56–57°C.

Procedure B. The reaction was run identically to *Procedure A* except that the chromyl chloride was added to the solution cooled in an ice–salt bath such that a temperature of 3°C was not exceeded. After addition, the mixture was stirred at −5°C for a h, then allowed to warm to 20–25°C, and stirred at 20–25°C for 1 h. The quench and workup were carried out as before to yield 69% α-chlorocyclododecanone.

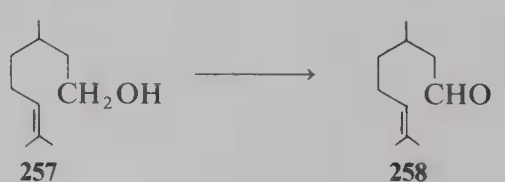
*Preparation of 3-Methyl-1-oxo-1,4,4a,5,6,7,8,8a-octahydronaphthalene (**119**) by the Pyridinium Chlorochromate (PCC, 7) Oxidation of **113** [Eq. (47), Table XXI].*[343] PCC (4.0 mmol) was added to a stirred solution of **113** (1.34 mmol) in dry dichloromethane (9 ml). After 4.5 h at 20°C the solution was diluted with dry diethyl ether (15 ml) and the supernatant liquid was passed through a short pad of Florisil using fresh ether to wash the insoluble black residue and the Florisil pad. The solvent was evaporated under reduced pressure and the crude product was dissolved in dry benzene (7 ml). *p*-Toluenesulfonic acid (20 mg) was added and the resulting solution was heated under reflux for 1.5 h. After workup, the mixture gave crude 3-methyl-1-oxo-1,4,4a,5,6,7,8,8a-octahydronaphthalene (**119**, 78%), which was purified by chromatography on silica gel, eluting with 1:4 ether petroleum ether. The mp of the 2,4-dinitrophenylhydrazone is 198.5–200°C.

4.2.6. Alcohols

Preparation of Pyridinium Chlorochromate (PCC,7).[32] To 184 ml of 6 *M* HCl (1.1 mmol) was added 100 g (1 mol) of CrO_3 rapidly with stirring. After 5 min the homogeneous solution was cooled to 0°C and 79.1 g (1 mol) of pyridine was carefully added over 10 min. Recooling to 0°C gave a yellow-orange solid which was collected on a sintered glass funnel and dried for 1 h *in vacuo* (yield 180.8 g, 84%). The solid is not appreciably hydroscopic and can be stored for extended periods at 20–25°C without change.

Oxidation of 1-Heptanol to Heptanal by PCC (7).[32] In a 500-ml round-bottom flask fitted with a reflux condenser was suspended 32.3 g (150 mmol) of pyridinium chlorochromate (**7**) in 200 ml of anhydrous CH_2Cl_2. 1-Heptanol (11.6 g, 100 mmol) in 20 ml of CH_2Cl_2 was added in one portion to the magnetically stirred solution. After 1.5 h, 200 ml of dry ether was added and the supernatant decanted from the black gum. The insoluble residue was washed thoroughly (3 × 50 ml) with anhydrous ether, where upon it became a black granular solid. The combined organic solution was passed through a short pad of Florisil, and the solvent was removed by distillation. Distillation of the residual oil through a short Vigreux column gave 8.87 g (78%) of heptanal, bp 59–61°C (30 mm).

*Oxidation of Citronellol (**257**) to Citronellal (**258**) by PCC (7).*[32] This example is given in order to illustrate the procedure used with the acetate-buffered reagent. Pyridinium chlorochromate (**7**) (1.23 g, 5.7 mmol) and NaOAc (0.093 g, 1.14 mmol) were suspended in 5 ml of anhydrous CH_2Cl_2 and citronellol (**257**, 0.59 g, 3.8 mmol) in 5 ml of CH_2Cl_2 was added in one portion to the magnetically stirred solution. After 2 h the reaction was worked up as described above to yield 0.52 g of crude citronellal (**258**). Column chromatography on silica gel gave 0.48 g (82%) of **258**.



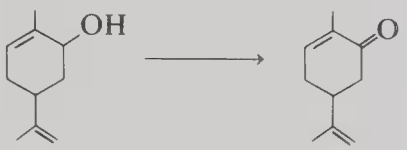
257 **258** (118)

*Oxidation of 5α-Cholest-8(14)-ene-3β,7α,15α-triol (**153**) to 5α-Cholest-8(14)-ene-3β,7α-diol-15-one (**154**) by PCC (7).*[392] PCC (**7**, 3.5 g) was added to a solution of **153** (1 g,

2.4 mmol) in a mixture of dichlorochromate containing 2% pyridine (200 ml) at 2°C. The mixture was stirred for 0.5 h under an atmosphere of nitrogen, saturated NaCl solution was added, and the mixture was thoroughly extracted with chloroform. The extract was dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure. The brown residue was purified on a silica gel column using 1:1 ethyl acetate–methylbenzene. The product (**154**) was recrystallized from aqueous acetone. The yield was 819 mg (82%); mp 167.5–168.5°C.

Preparation of Pyridinium Chlorochromate Absorbed on Alumina.[401] To a solution of CrO_3 (6 g) in 6 *M* hydrochloric acid (11 ml) is added pyridine (4.75 g) within 10 min at 40°C. The mixture is kept at 10°C until a yellow-orange solid forms. Reheating to 40°C gives a solution. Alumina (50 g) is then added to the solution with stirring at 40°C. After evaporation in a rotary evaporator, the orange solid is dried in vacuum for 2 h at 20–25°C. The reagent can be kept for several weeks under vacuum in the dark without losing its activity.

*Oxidation of Carveol (**259**) to Carvone (**260**) by PCC (**7**) on Alumina.*[397] The above reagent (7.5 g, 6.1 mmol) is added to a flask containing a solution of carveol (**259**, 0.60 g, 3.8 mmol) in *n*-hexane (10 ml). After stirring for 2 h, the solid is filtered and washed with three 10-ml portions of ether. The combined filtrates were evaporated and vacuum distilled to afford carvone [**260**, 0.54 g (93% 0; bp 104°C (11 Torr)].



259 **260** (119)

Preparation of Cross-linked Poly(vinylpyridine) Resin (PVP).[97] Poly(vinyl alcohol) (2.4 g) was dissolved in 550 ml of boiling distilled water and the solution was placed in a 2-liter resin kettle equipped with Teflon seals, a reflux condenser, a nitrogen inlet, and a mechanical stirrer. The solution was stirred under nitrogen at 80°C and a solution of 25 g of 4-vinylpyridine and 1.5 g of divinylbenzene in 50 ml of toluene was added rapidly. After addition of 1 g of azobisisobutyronitrile (AIBN) the polymerization was allowed to proceed under constant vigorous stirring. Polymer beads started to appear very rapidly, but the mixture was left at 80°C overnight. The resin beads were collected by filtration through cloth and washed extensively with water, acetone, ether, dichloromethane, and finally methanol. After drying under vacuum, 25.1 g of almost white PVP resin beads were obtained. A suitable 2% cross-linked vinylpyridinedivinylbenzene resin is also available commerically from Polysciences, Inc.

*Preparation of PVPCC (**14**).*[97] To 10 g of cross-linked PVP resin (50–100 mesh) suspended in 20 ml of water was added 9 g of chromic anhydride and 10 ml of concentrated hydrochloric acid. The mixture was stirred at 23–25°C for 1 h and filtered and the resin was washed with distilled water until the filtrate was clear. Freshly prepared PVPCC has a bright orange color which turns to brown upon drying *in vacuo* (60°C, 5 h). The resin can be used directly without drying or can be stored in dry form. Titration of the chlorochromate resin was done in two ways: indirectly by titration of the filtrate and wash liquid collected during the preparation of PVPCC (**14**), or directly by titration of the chromate displaced from the resin by reaction with aqueous 2 *M* potassium hydroxide overnight. In a typical titration, a freshly prepared solution of ferrous ammonium sulfate was used to reduce the chromate after acidification with phosphoric acid and using diphenylamine sulfonate as indicator. Both methods gave comparable results; however, the results reported in this discussion are those which were obtained in the direct titrations. Thus, the PVPCC (**14**, 19.3 g) resin obtained above from 10 g of PVP contained 3.6 mmol of chlorochromate per gram of dry reagent. The PVPCC resins (**14**) obtained in similar preparations contained up to 3.95 mmol of chlorochromate per gram. In most cases the PVPCC resins (**14**) were not dried thoroughly before use, but were simply air dried after washing with water. Typically, a PVPCC resin

(**14**) prepared from 1 g of PVP, 0.92 g of CrO_3, and 1 ml of concentrated HCl contained 7.5–7.9 mmol of chlorochromate after thorough washing with water and air drying.

*Oxidation of Cinnamyl Alcohol to Cinnamaldehyde using PVPCC (**14**).*[97] Best results in the oxidation reactions were obtained using wet PVPCC resins (**14**). Thus, in instances where the dry resin was used, it had to be soaked briefly (5–10 min) in water prior to filtration to remove the excess water and before use in oxidation reactions. Alternately, the PVPCC, (**14**) would be prepared immediately before use by reaction of the required amounts of PVP, CrO_3, and HCl, followed by thorough washing with water and filtration. The second procedure was often preferred over the first as it eliminated the lengthy drying step. In a typical oxidation, the PVPCC (**14**) obtained by reaction of 1 g of PVP with CrO_3 and HCl as described above (or 1.9–2 g of dry reagent soaked in water and filtered) was used in 4–10 ml of cyclohexane at 75–80°C. After addition of 1.7 mmol of the alcohol, the mixture was stirred at 75–80°C and small aliquots were withdrawn at regular time intervals for chromatographic analysis. The percent conversion was calculated directly from the chromatograms after calibration. Some reactions were also carried out using less PVPCC for the same amount of alcohol. Reactions were also carried out on a larger scale using, for example, the PVPCC (**14**) prepared above from 10 g of PVP to oxidize 2.4 g of cinnamyl alcohol in 50 ml of cyclohexane at 60°C. The reaction was monitored by GLC and had essentially reached completion in 60 min. After 105 min, the reaction mixture was filtered and the resin washed with ether and dichloromethane to extract the cinnamaldehyde. After evaporation of the solvent, 2.0 g of pure cinnamaldehyde (84%) was obtained.

*Preparation of PDC (**8**).*[33] Pyridine (80.6 ml) was gradually added to a cooled solution of 100 g (1 mol) of CrO_3 in 100 ml of water at <30°C. The solution was diluted with 400 ml of acetone and cooled to -20°C. After 3 h the orange crystals were collected, washed with acetone, and dried *in vacuo*; yield: 127.2 g (68%).

*Oxidation of Alcohols to Carbonyl Compounds by PDC (**8**)*[33]*: General Procedure.* All oxidations were conducted in dry apparatus with good stirring. As little as 2 ml of DMF or 2.5 ml of CH_2Cl_2 per g of PDC may be used. Reactions involving CH_2Cl_2 solvent were diluted with ether or ether–pentane, filtered and evaporated to afford product. Last traces of chromium species can easily be removed by filtering an ethereal solution through a small amount of anhydrous magnesium sulfate or silica gel. Reactions involving DMF as solvent were worked up by pouring into 7–10 vols of water and extracting with ether or ether–pentane.

*Preparation of 2,2′-Bipyridinium Chlorochromate (BiPy · $HCrO_3Cl$, **9**).*[37] Chromium(VI) oxide (10.0 g, 0.11 mol) is added, rapidly with stirring, to 6 M hydrochloric acid (18.4 ml, 0.11 mol). After dissolution of chromium(VI) oxide is complete, 2,2′-bipyridine (15.6 g, 0.1 mol) is added in portions with vigorous stirring. The resultant yellow slurry is stirred for 1 h at 20–25°C. The product is collected by suction on a sintered glass funnel and washed with cold distilled water (2×15 ml). The resultant solid yellow filter cake is dried *in vacuo* for 3 h at 20–25°C; yield: 26.8 g (92%). Recrystallization of impure **9** from hexanes leads to a cleaner complex.[36] The material is best stored for extended periods protected from light and over calcium chloride.

*Oxidation of Cinnamyl Alcohol to Cinnamaldehyde by 2,2′-Bipyridinium Chlorochromate (**9**).*[37] A solution of cinnamyl alcohol (0.5 g, 3.73 mmol) in dichloromethane (10 mol) is added to a stirred suspension of 2,2′-bipyridinium chlorochromate (3.37 g, 11.5 mmol) in dichloromethane (15 ml). The mixture is stirred for 4 h while dark brown granular chromium reduction products are formed. It is then diluted with anhydrous ether (15 ml) and filtered through a small Hirsch funnel packed 1–2 cm deep with Celite using ether as a wash solvent. The clear filtrate is then washed with 5% hydrochloric acid (2×25 ml) and 10% sodium carbonate solution (2×25 ml), and dried (Na_2SO_4). Removal of the drying agent and evaporation of the solvent gives a slightly yellow oil which is distilled via Kugelrohr to give pure cinnamaldehyde; yield: 0.32 g (86%); bp 136°C (20 Torr). Typically the purity of the crude carbonyl compound is greater than 99% as determined by GLC analysis.

Preparation of Tetra-n-Butylammonium Chromate (12).[38] To an aqueous solution (25 ml) of CrO_3 (1.0 g, 10 mmol), an aqueous solution (50 ml) of tetrabutylammonium chloride (2.92 g, 10.5 mmol) is rapidly added at 20–25°C with stirring. Immediately a yellow-orange solid precipitates. The reaction mixture is cooled to 0°C, then the solid is collected on a sintered glass funnel, carefully washed with cold water, dried under vacuum over P_2O_5, and stored over $CaCl_2$; yield: 2.76 g (77%).

Oxidation of 3,4,5-Trimethoxybenzyl Alcohol to 3,4,5-Trimethoxybenzaldehyde with Solid Tetra-n-Butylammonium Chromate (12).[38] To a chloroform solution (10 ml) of 3,4,5-trimethoxybenzyl alcohol (0.5 g, 2.52 mmol), tetra-*n*-butylammonium chromate (2.17 g, 6.04 mmol) is added at 23–25°C with stirring. The reaction mixture is heated at 60°C for 3 h, then diluted with ether, poured into 1 *M* sodium hydroxide solution, washed with a saturated sodium chloride solution, and dried (Na_2SO_4). The solvent is removed under reduced pressure to leave a white solid from which pure 2,4,5-trimethoxybenzaldehyde is obtained by chromatography on silica gel, eluting with a 60/40 cyclohexane/ethyl acetate mixture; yield: 0.385 g (78%).

Oxidation of Diphenylmethanol to Benzophenone by Tetra-n-Butylammonium Chromate 12 in Chloroform Solution.[38] An aqueous solution (28 ml) of tetra-*n*-butylammonium chloride (1.58 g, 5.68 mmol) is rapidly added to an aqueous solution (14 ml) of CrO_3 (0.54 g, 5.4 mmol) with stirring at 20–25°C. Chloroform (200 ml) is added and the chromate salt is carefully extracted. Then the chloroform solution is concentrated to 6 ml and diphenylmethanol (0.5 g, 2.71 mmol) in chloroform (4 ml) is added with stirring. After 3 h at 60°C the reaction is worked up as reported for 3,4,5-trimethoxybenzyl alcohol; pure benzophenone is obtained; yield: 0.450 g (91%).

Preparation of Bis-Tetra-n-Butylammonium Dichromate (TBADC, 13).[96] The reagent is easily prepared by addition of a concentrated aqueous solution (300 ml) of potassium dichromate (29.4 g, 0.1 mol) to a saturated aqueous solution (300 ml) of tetra-*n*-butylammonium bromide (64.4 g, 0.2 mol). TBADC (**13**) precipitates and can be recovered by filtration (62.8 g, 90%); mp 79–80°C (from hexane); uv λ_{max} 275 nm ($\varepsilon = 4620$), 345 nm ($\varepsilon = 3180$), 360 nm ($\varepsilon = 3500$).

Oxidation of 4-Methoxybenzyl Alcohol to 4-Methoxybenzaldehyde by Bis-Tetra-n-Butylammonium Dichromate (TBADC, 13).[96] To a solution of **151** (1.38 g, 0.01 mol) in CH_2Cl_2 (40 ml), TBADC (7 g, 0.01 mol) was added and the solution was refluxed (1 h). The workup consists either in a filtration on a silica gel column (10 g silica/mmol of substrate) or concentrating *in vacuo* the solution and adding at 0°C an excess of 99% formic acid to the residue. As an alternative to the last procedure, after concentrating the solution *in vacuo*, celite and diethyl ether (3×50 ml) were added. The mixture was filtered and the filtrate concentrated *in vacuo*. 4-Methoxybenzaldehyde was obtained in 80% yield (1.1 g); bp 80–82°C (2 mm); ir $\nu_{max} = 1680\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 10.0$ (s, 1H, CHO), 7.85 (d, 2H, $J = 7$ Hz, Ar), 7.05 (d, 2H, $J = 7$ Hz), 3.95 (s, 3H, OCH_3).

Oxidation of Geraniol to Gerianial by TBADC (13).[96] Pure geraniol (1.54 g, 0.01 mol) was oxidized under the conditions described above. Usual workup gave the crude product; yield 90%, 1.38 g. GLC analysis showed that this consisted of 90% geraniol and 10% nerol. Pure geraniol was obtained by silica gel chromatography; bp 117°C (20 mm); ir $\nu_{max} = 1695\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 9.85$ (d, 1H, $J = 7$ Hz, CHO), 5.85 (d, 1H, $J = 7$ Hz, $=CH-CHO$), 5.1 (s, 1H, $-CH=$), 2.18 (s, 3H, CH_3), 2.1 (m, 4H, CH_2) 1.7 (s, 3H, CH_3), 1.6 ppm (s, 3H, CH_3).

Molecular Sieve Assisted Oxidation of Nucleosides.[413] In typical experiments the alcohols were added to a suspension of the oxidative reagent (1.5–5 equiv) with molecular sieve powder (0.5–4 g per mmol of starting material) in dichloromethane (2.5–5 ml per mmol of alcohol). The mixture was well stirred for 10–120 min and the reaction followed by TLC. When the oxidation was complete the reaction mixture was diluted with diethyl ether and filtered through a glass filter filled with silica gel containing $CaSO_4$ (10%) (silica gel G, Merck Darmstadt). Removal of the solvent gave the pure carbonyl compound.

Comparative studies of the molecular sieves have shown that the oxidation rate

increases in the order 5 Å < 10 Å < 4 Å < 3 Å. Furthermore with the 3Å type the reaction can be performed with a lower weight of sieve and smaller volume of solvent.

4.2.7. Benzyl Ethers

General Procedure for the Oxidation of Benzyl Ethers to Acids, Esters, and/or Ketones by the Jones Reagent.[421] The benzyl ether (5.0 mmol) was dissolved in 100 ml of dry acetone and cooled in an ice bath. The Jones reagent (4 equiv) was added dropwise over the appropriate period of time and the reaction was allowed to stir mechanically. The reaction mixture was quenched with ether and water and then extracted with four 50-ml portions of ether. The combined ether layers were washed with three 30-ml portions of saturated aqueous $NaHCO_3$, dried, and concentrated to give the benzoate ester, ketone, and benzyl ether if the reaction had not gone to completion. This mixture was analyzed by GLC and NMR comparison with authentic samples. The combined $NaHCO_3$ extracts were acidified and cooled to 0°C, and the benzoic acid was obtained by filtration.

Oxidation of 5-Dodecyl-2-methylfuran to 2,5-Dioxo-3-heptadecene by PCC (7).[432] 5-Dodecyl-2-methylfuran (1.1 g) diluted with anhydrous dichloromethane (10 ml) was added to a suspension of pyridinium chlorochromate (PCC, **7**, 4 g) in anhydrous dichloromethane (50 ml). The mixture was heated under reflux for 24 h and then filtered through Florisil. The solvent was evaporated and the crude product purified by chromatography on silica gel, eluting with 9:1 benzene/ether. The yield of 2,5-dioxo-3-heptadecene was 90% (1.05 g); mp 75–76°C.

4.2.8. Silyl Ethers

*General Procedure for the Oxidation of Silyl Ethers (**208**) to Hydroquinones (**209**) by PCC (7).*[433] To a solution of the bis-silyl ether (**208**, 1 mmol dissolved in 8 ml of dichloromethane) at 25°C was added PCC (**7**, 2 mmol). The mixture was stirred for 2 h and then evaporated to dryness. The residue was extracted with anhydrous diethyl ether (10 ml) and the extract passed through a column of Florisil (8–10 g) eluting with diethyl ether. In the case of the trimethylsilyl ethers, evaporation of the ether eluent gave the pure quinones. With the *t*-butyldimethylsilyl ethers evaporation of the eluent gave a mixture of quinone and *t*-butyldimethylsilanol. The pure quinone was obtained by washing the semisolid residue with ice-cold heptane or by recrystallization from heptane.

4.2.9. Trialkyloxyboroxines

*Preparation of Trioctyloxyboroxine (**210**, $R = n-C_7H_{15}$): Typical Procedure.*[442] In a dry, 250-ml round-bottom flask provided with a septum inlet, magnetic stirring bar, and a reflux condenser attached to a connecting tube leading to a mercury bubbler, are placed octanoic acid (9.51 ml, 60 mmol) and diethyl ether (75 ml) under nitrogen. (In certain cases, the carboxylic acid is dissolved in tetrahydrofuran instead of diethyl ether.) The mixture is stirred vigorously and borane-dimethyl sulfide (BMS, Aldrich: 6.12 ml, 60 mmol) is added dropwise from a syringe. Following the addition of initial 2–3 ml of BMS, when the gas evolution has ceased, the mixture is heated under gentle reflux to complete the evolution of gas (hydrogen). The remainder of the BMS is added at such a rate as to maintain a gentle reflux. Following completion of the addition, the mixture is heated under reflux for 1 h. The solvent and dimethyl sulfide are removed under vacuum and dichloromethane (20 ml) is introduced to dissolve the product. ^{11}B NMR ($CDCl_3/BF_3$ etherate: $\delta = -19.1$ ppm.

*Preparation of Octanal via Trioctyloxyboroxine (**210**, $R = n-C_7H_{15}$); Typical Procedure.*[442] To a well-stirred suspension of pyridinium chlorochromate (14.3 g, 66 mmol) in dichloromethane (100 ml) taken in a 5000-ml flask equipped as described above, is added dropwise to the above solution of trioctyloxyboroxine in dichloromethane. The stirred mixture is heated under reflux for 1 h and then diluted with diethyl ether (150 ml). The

supernatant liquid is filtered through Florisil (100 g) contained in a 300-ml sintered glass funnel; the solid residue is triturated with diethyl ether (3 × 50 ml) and passed through the same Florisil column. The colorless filtrate is concentrated and distilled under reduced pressure to give octanal; yield: 5.9 g (77%); bp 64–65°C (15 mm). The product may also be recovered by steam distillation from the dichloromethane reaction mixture.

Analogous procedures are used for the synthesis of the other aldehydes. In the case of solid aldehydes, the products are purified by recrystallization from suitable solvents, in the case of liquid aldehydes the products are distilled.

4.2.10. Esters

Oxidation of 3,3,5,5-Tetramethylcyclohex-1-enyl Benzoate to 3,3,5,5-Tetramethyl-6-oxocyclohex-1-enyl Benzoate by Sodium Chromate.[446] 3,3,5,5-Tetramethylcyclohex-1-enyl benzoate (1.29 g, 5.0 mmol) was dissolved in 1:1:1 acetic acid–acetic anhydride–carbon tetrachloride (48.6 ml). The solution was maintained at 25°C, sodium chromate (1.62 g, 0.01 mol; vacuum dried over P_2O_5 at 100°C for 24 h) was added at once, and the reaction flask was closed and shaken until all the oxidant had dissolved. The reaction was followed by TLC. The starting material disappeared after 60 h, and the mixture was poured into ether (100 ml)–ice (100 g), and stirred for 1 h. After two more extractions of the aqueous solution with ether (2 × 50 ml) the combined organic phase was washed successively with saturate aqueous $NaHCO_3$ (3 × 100 ml), water, and saturated sodium chloride solution, dried, and evaporated. Recrystallization of the resulting solid mixture gave 3,3,5,5-tetramethyl-6-oxocyclohex-1-enyl benzoate (760 mg, 56%) mp (from ethyl acetate-light petroleum) 126°C, λ_{max} 236 nm ($\varepsilon = 10{,}470$).

4.2.11. Oximes

Deoximation with Pyridinium Chlorochromate/Hydrogen Peroxide System: General Procedure.[473] To a well-stirred solution of pyridinium chlorochromate (6.37 g, 30 mmol) and oxime (15 mmol) in acetone, a 30% solution of hydrogen peroxide (6.5 ml) is slowly added at 0–10°C. After 10 min, acetone is removed in vacuo, water (50 ml) is added, and the residue is extracted with ether (3 × 30 ml). The combined extracts are washed with 5% sodium thiosulfate solution (20 ml), 1 *M* hydrochloric acid (15 ml), water, and dried ($MgSO_4$). Evaporation of the solvent gives the crude carbonyl derivatives which are purified by distillation or by column chromatography [silica gel, 70-230 mesh; ether/dichloromethane (1:1) as eluent].

4.2.12. Organoboranes

Preparation of Octanal from Octene via Hydroboration and Oxidation with PCC (7).[335] *Procedure A.* In an oven-dried, nitrogen-flushed, 100-ml round-bottom flask fitted with a septum inlet, magnetic stirring bar and a connecting tube leading to a mercury bubbler, were placed 2.04 ml of borane/dimethyl sulfide (BMS) (20 mmol, neat reagent was 9.8 *M* in BH_3) and 20 ml of dichloromethane. To this solution was added (9.4 ml, 60 mmol) 1-octene dropwise with vigorous stirring. The reaction mixture was stirred for 1 h at 20–25°C, and then the solvent and methyl sulfide were removed using a water aspirator. The resulting trialkylborane was added dropwise to a well-stirred suspension of 38.3 g of pyridinium chlorochromate (PCC) (180 mmol) in 150 ml of dichloromethane, taken in a 500 ml round-bottom flask fitted with a septum inlet, a magnetic stirring bar and a reflux condenser with a connecting tube leading to a mercury bubbler. After the initial vigorous reaction subsided, the mixture was refluxed for 4 h with stirring. It was then cooled to 20–25°C, diluted with 200 ml of dry ethyl ether and filtered through 100 g of 100–200 mesh Florisil contained in a 350 ml sintered glass funnel. The residue in the flask was triturated with ether (3 × 50 ml) and the solvents removed on a rotary evaporator. The resulting liquid,

on distillation under reduced pressure, gave 5.4 g (70% yield) on octanal (containing ~5% of 2-octanone), bp 65–66°C (15 mm); η_D^{20} 1.4185.

Procedure B. The oxidation reaction was carried out in the same manner as described in Procedure A. To the reaction mixture, after refluxing for 4 h, was added 50 ml of water. Steam distillation provided a condensate consisting of dichloromethane, aldehyde, and water. The organic layer was separated, dried ($MgSO_4$), and solvent removed. Distillation under reduced pressure afforded 5.3 g (69% yield) of octanal (containing ~5% of 2-octanone) bp 65–66°C (15 mm), η_D^{20} 1.4185.

*Preparation of Trioctyl Borate (**241**, $R = n-C_7H_{15}$): Typical Procedure.*[491] To an oven-dried, nitrogen-flushed 100 ml round-bottom flask, fitted with a septum inlet, a magnetic stirring bar, and a reflux condenser topped with a connecting tube leading to a mercury bubbler, borane-dimethyl sulfide (BMS, Aldrich; 2.04 ml; 20 mmol) is added with the help of a syringe. The mixture is stirred at 20–25°C and 1-octanol (9.43 ml, 60 mmol) is added dropwise with a syringe. Stirring is continued at 20–25°C until the evolution of hydrogen ceases. The mixture is then heated at 100°C in an oil bath for 1 h. The flask is cooled and dimethyl sulfide is pumped off at reduced pressure to give the pure ester; yield: 7.5 g (94%). ^{11}B NMR (neat/BF_3etherate): $\delta = -18.5$ ppm.

*Preparation of Octanal from Trioctyl Borate (**241**): Typical Procedure.*[491] In an oven-dried, nitrogen-flushed, 250-ml round-bottom flask, fitted with a septum inlet, a magnetic stirring bar, and a reflux condenser topped with a connecting tube leading to a mercury bubbler, are placed powdered pyridinium chlorochromate (PCC) (14.3 g, 66 mmol) and dichloromethane (100 ml). To the well-stirred suspension, a solution of trioctyl borate (7.96 g, 20 mmol) in dichloromethane (20 ml) is added with the help of a double-ended needle. The mixture is stirred under reflux for 1 h. Then, ether (150 ml) is added and the mixture is filtered through a column containing Florisil (100 g). The solid residue in the flask is triturated with ether (3 × 50 ml) and filtered through the same Florisil column. The combined colorless filtrate is concentrated and distilled under reduced pressure to give pure octanal: yield: 5.89 g (76%); bp 66–67°C (15 Torr); η_D^{20}: 1.4182.

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3

The Oxidation of Organic Compounds by Active Manganese Dioxide

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1. INTRODUCTION

In the series of reagents used in heterogeneous oxidation reactions, active manganese dioxide has acquired a prominent place among such oxidants as copper oxide, mercury(II) oxide, silver oxide, lead dioxide, sodium bismuthate,[1–3] nickel peroxide,[4,5] manganese(III) acetate,[6,7] silver carbonate on Celite,[8] seloxcette[9] (chromic anhydride intercalated in graphite), and the recently introduced potassium permanganate on molecular sieves[10] and barium manganate ($BaMnO_4$).[11,12] The last two reagents[10,11] may be efficient oxidants for the conversion of alcohols into carbonyl compounds (under mild conditions).

The discovery by Ball, Goodwin, and Morton[13] over 30 years ago of almost quantitative conversion of vitamin A_1 into retinal by precipitated manganese dioxide was quickly followed by the realization that this new type of reaction involves a special or "active" form of the oxidant. Today, active manganese dioxide is an established reagent for many useful oxidative transformations. Thus, the reagent in neutral media has been extensively applied for the selective oxidation of α,β-unsaturated alcohols (ethylenic, acetylenic, and benzylic); also of saturated alcohols, phenols, and polyhydroxy compounds. Subsequent studies have shown that, besides alcohols, many other classes of organic compounds are oxidized by this reagent, including amines, hydrazines, hydrocarbons, heterocyclic compounds, and various natural products. The literature on the subject is substantial, and includes several reviews.[14–19] The manganese dioxide oxidation of organic nitrogen compounds[20] or steroids[21] under neutral conditions has also been reviewed; Chinn[22] discussed some synthetic and mechanistic aspects of manganese dioxide oxidations as compared to other oxidants.

The aim of this chapter is to discuss important synthetic applications of active manganese dioxide, and to show its selectively and specificity as an oxidant, as a

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dehydrogenation reagent, as a coupling reagent, and as a selective, analytical tool in the determination of the structure of complex, organic molecules derived from natural products. The review also includes a discussion of the mechanism of action, and of the complexity of the heterogenous reactions. The literature cited covers the period ending June 1984.

1.1. Types and Methods of Preparation of Active Manganese Dioxide

Active manganese dioxide has been prepared by several methods,[15,18,23,24] giving products of various activities.[15,18] The present commercial sources of active manganese dioxide (e.g., Aldrich Chemical Co., Madison, Wisconsin, U.S.A.; E. Merck, Darmstadt, West Germany; or BHD Lab, London, England) offer a reagent that gives reproducible results (e.g., in the oxidation of α,β-unsaturated alcohols). The general procedure for the preparation of the active form of manganese dioxide involves precipitation of the reagent by mixing warm, aqueous solutions of manganese sulfate and potassium permanganate at various pH values. The method of Attenburrow, Cameron, and Chapman (ACC method)[25] requires alkaline conditions (to afford a very active and widely used reagent), whereas the procedure of Mancera, Rosenkranz, and Sondheimer (MRS)[26] employs acid conditions (to give a second, widely used reagent). The preparation of a special type of active manganese dioxide (acid conditions), either by mixing of aqueous solutions of manganese dichloride and potassium permanganate at 70°C,[19] or by mixing hot or cold (0–10°C) solutions of manganese sulfate and potassium permanganate,[24] has been reported. The original method[13] employs a neutral medium, to give a somewhat less active product. After thorough washing with water, the precipitated material is usually activated by drying at 110–120°C for 12–24 h; however, drying of the oxide for a longer time at 125°C gives more active material.[27] Another widely accepted method for the preparation of active manganese dioxide involves pyrolysis of manganese salts such as the carbonate,[28] oxalate,[28] or nitrate[29] at 250–300°C; the product may be used directly, although the activity of these oxides is increased by washing with dilute, aqueous nitric acid and drying[28] at 230°C, but drying of this material at 150°C for 18 h gives a more active form.[30] Active manganese dioxide has also been prepared by wet oxidation of manganous carbonate ($MnCO_3 + HNO_3/NaClO_3 \rightarrow MnO_2$).[31] Still another procedure for preparing active manganese dioxide involves passing ozone through an acadic solution of a manganese salt.[32]

Goldman[33] reported that the wet filter-cake of manganese dioxide prepared by Attenburrow's procedure can conveniently be activated by azeotropic removal of water through distillation of the suspension with benzene. This procedure removes the occluded water and, presumably, also the water adsorbed to the oxidatively active sites on the surface of the oxidant. By this procedure, an activated manganese dioxide can be consistently produced, and it may be stored under benzene until used. This reagent is an efficient oxidant giving reproducible results.

Carpino[34] has employed a new preparation of active manganese dioxide. A suspension of activated carbon in aqueous potassium permanganate is refluxed until the pink color has completely disappeared. The precipitated oxide, adsorbed on carbon, is filtered off, and activated by drying at 105–110°C for 8–24 h. The reagent was found satisfactory for the oxidation of amines, hydrazines, hydrazones,[34] and α,β-unsaturated alcohols.[35] Active manganese dioxide supported on silica gel has been successfully used for cyclization reactions of certain alkaloids.[36]

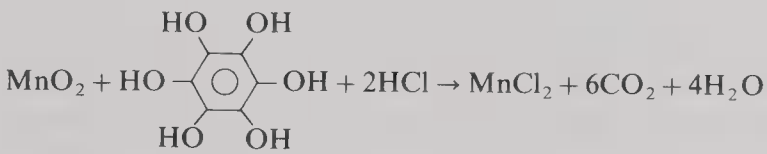
Vereshchagin and co-workers[15,37] compared the reactivity of various manganese oxides, including active manganese dioxide, towards some organic substrates. The authors found[37] that the efficiency of oxidation of benzyl alcohol proceeds in the order of γ-MnO_2 > active manganese dioxide > α-MnO_2; they also concluded that the oxidizing power of active manganese dioxide depends on the content of the active, γ-MnO_2 form in the oxidant, and, because of this, the γ-form of manganese dioxide is a more efficient oxidant[37] than Attenburrow's MnO_2 (ACC).[25] Thus, the γ-modification of manganese dioxide can be recommen-

ded as a selective oxidizing agent for activated hydroxyl groups of organic compounds. Active γ-MnO_2,[37] as described in Ref. 19, has recently been found[38] to be the only oxidant examined that is suitable for quantitative conversion of 4,5-dihydro-1,2-oxazoles into 1,2-oxazoles.

The mechanism of formation of various modifications of manganese dioxide having high electrochemical, electrocatalytic, and catalytic reactivity (e.g., β-MnO_2 and γ-MnO_2) has been studied.[39,40]

1.1.1. Standardization of Active Manganese Dioxide[19]

The procedure is based on the time needed to reduce a known weight of active manganese dioxide. Usually, the oxidant (250–300 mg) is added at room temperature to a magneticalli stirred solution of hexahydroxybenzene (200 mg in 50 ml of *M* hydrochloric acid) [(Eq. (1)]. The time needed for complete disappearance of the solid, as observed visually, or by monitoring of the intensity of the benzenoid adsorption at 260–270 nm, is usually 4–8 min for very active material (activity gradient A), 8–12 min for active form (activity gradient B), and 12–20 min for medium activity (gradient C). This grading is in good agreement with findings involving the conventional oxidation of cinnamyl alcohol to the aldehyde in neutral medium.[15,29] The standard potential, E^0, for the redox reaction $MnO_2 + 4H^+ + 2e \rightarrow Mn^{2+} + 2H_2O$ in strong acid solution is +1.57 V; $E^0 = 1.239$ V (solid); $MnO_2 + 4H^+ + 2e \rightarrow Mn^{2+} + 2H_2O$ at pH = 6.8 is +0.47 V; in alkaline solution, $MnO_2 + 2H_2O + 2e \rightarrow Mn(OH)_2 + 2OH^-$, the value is zero ($E^0 = -0.05$ V).[18]



(1)

1.1.2. Preparation of Very Active Manganese Dioxide[19]

A solution of manganese dichloride tetrahydrate (220 g) in water (2 liters) at 70°C is gradually added during 10 min, with stirring, to a solution of potassium permanganate (160 g) in water (2 liters) at 60°C in a hood. A vigorous reaction ensues with evolution of chlorine; the suspension is stirred for 2 h and is kept overnight at room temperature. The precipitate is filtered off, washed thoroughly with water (4 liters) until pH is 6.5–7 and the washing gives a negligible chloride test, and dried at 120–130°C for 18 h; this gives a chocolate-brown, amorphous powder; yield: 195–200 g (activity gradient A, 4–6 min). Alternatively, the wet cake is mixed with benzene (1.2 liters) and water is removed by azeotropic distillation[33] giving a chocolate-brown, amorphous powder; yield: 195 g (activity gradient A, 6–8 min).

1.1.3. Preparation of Active Manganese Dioxide[24]

Method A. Active manganese dioxide was made by mixing hot solutions of manganese sulfate and potassium permanganate, maintaining a slight excess of the latter for several hours, washing the product thoroughly with water, and drying it at 110–120°C. Its activity was unchanged after keeping it for many months, but is was deactivated by water, methanol, thiols, or excessive heat (500°C). Manganese dioxide was less active when prepared in the presence of alkali,[25] and ineffective when precipitated from hot solutions containing a large excess of manganese sulfate.

Method B. Cold (0–10°C) solutions of potassium permanganate and an excess (1.2 equiv) of manganese sulfate were mixed and the product was collected after 5 min, washed once only with cold water, and dried at 110–120°C. The manganese dioxide thus

obtained was acidic, and was used for the specific oxidation of retronecine (tetrahydropyrrolizine allyl alcohol) to an aldehyde; if the oxide was washed free of acid, dehydrogenation of the ring was observed.

1.1.4. Preparation of Active γ-Manganese Dioxide[37]

To a solution of manganese sulfate (151 g) in water (2.87 liters) at 60°C is added, with stirring, a solution of potassium permanganate (105 g) in water (2 liters), and the suspension is stirred at 60°C for 1 h, filtered and the presipitate washed with water until free of sulfate ions. The precipitate is dried to a constant weight at 60°C; yield: 120 g (dark-brown, amorphous powder).

1.2. Effects of Solvent on Oxidation

The choice of a solvent in the oxidation of organic compounds with manganese dioxide appears to be important; the effect of various organic solvents (either nucleophilic or electrophilic) on chemical reactivity is known.[41,42] In general, the polarity of the solvent influences the degree of self adsorption, the rate of adsorption of the reactants (substrates), and the rate of desorption of the products. The media most widely used for oxidations with active manganese dioxide at room temperature are saturated hydrocarbons (e.g., petroleum ether, pentane, cyclohexane), chlorinated hydrocarbons (e.g., chloroform, dichloromethane, tetrachloromethane), benzene, toluene, chlorobenzene, diethyl ether, tetrahydrofuran, 1,4-dioxan, ethyl acetate, acetone, acetonitrile, glacial acetic acid, dimethyl sulfoxide, dimethyl formamide, and pyridine.

Solvents that compete with a substrate for being adsorbed on the oxide surface, thus deactivating the oxidant, are unsatisfactory (e.g., primary and secondary alcohols, methyl, ethyl, and isopropyl alcohols); partial deactivation of the oxidant has also been observed in acetone, ethyl acetate, and dimethyl sulfoxide. A similar range of solvents has been used for oxidations at higher temperature; this may include water, acetic acid, or pyridine, or mixtures of them. Although an aprotic solvent, acetonitrile, proved to be an excellent reaction medium for a series of unique manganese dioxide oxidations, it is unstable on prolonged treatment (e.g., reflux) with the reagent, undergoing a slow hydrolysis to an amide.

When using highly active oxide preparations, chlorinated solvents are recommended, because ignition of the vapors of inflammable solvents has been reported.[28] As already mentioned, the nucleophilic or electrophilic nature of the solvent may determine the course of the reaction. Thus, Ball, Goodwin, and Morton[13] observed that vitamin A in petroleum ether is converted into retinene, whereas, in diethyl ether, it forms anhydrovitamin A. Hydroquinone (quinol) in acetone,[43] benzene, or chloroform[44] is oxidized by manganese dioxide to *p*-benzoquinone, whereas in tetrahydrofuran, quinhydrone is formed.[44] The nonallylic hydroxy group in gibberellin A_4 (a natural hormone that promotes the growth of cucumber seedlings) is oxidized by manganese dioxide in dichloromethane, but not in *p*-dioxan.[45] Similar oxidations of steroid 5-en-3β-ols in refluxing benzene produce 4,6-dienones,[46] whereas, in dimethylformamide or pyridine at room temperature, the products are 4-en-3-ones.[47]

Gritter and Wallace[29] investigated the effect of solvents on the yiels of acrolein from allyl alcohol and found that best yields were obtained using light petroleum or ethyl ether. The use of benzene decreased the yield by about 20%–30% and the use of chloroform or tetrachloromethane decreased it by 50%. It has been suggested that the solvent effect is related to its affinity for manganese dioxide. Thus lower yields may be expected with benzene as compared to petroleum ether because the former solvent competes more with the reductant for a position on the surface of the oxidant.[26]

The proportion of solvent is not critical; usually, five to ten times the volume of the substrate being oxidized is used.

1.3. Time and Temperature Effects on Oxidation

The time and temperature required for manganese dioxide oxidations depend on the activity of the oxidant, the nature of the substrate, and, because the reaction is heterogeneoous, the proportions of the reactants. The commercial availability of a highly active reagent allows the reaction time to be lessened considerably.

The duration of oxidation at room temperature varies over wide ranges; whereas oxidation of α,β-unsaturated alcohols is usually complete in a few minutes[48] or a few hours,[25] formation of steroid dienones[46] and oxidation of alkylanilines may require 16–24 h.[49,50] In order to shorten the reaction time, oxidation is frequently conducted above room temperature (refluxing solvent), and the water formed is sometimes removed by azeotropic distillation. Unfortunately, the elevated temperature can bring about undesired side effects; for example, oxidation of a carbon atom bearing a hydroxy group may be accompanied by dehydrogenation of an olefinic bond to a diene system, or by migration of a double bond,[51] or even rupture of a carbon–carbon bond.[52] As the reaction is heterogenous and takes place on the surface of the dioxide, the amount of manganese dioxide needed for efficient reaction depends on its particle size. The particle size normally employed is 100–200 mesh; that is 0.06–0.2 mm and the average BET surface area of active manganese dioxide powder is 14.2–15 $m^2\,g^{-1}$. Consequently, a considerable excess of the oxidant is always necessary; the ratio of substrate to dioxide can range from 1:5 to 1:20 (w/w) (for α,β-unsaturated alcohols), and 1:50 (w/w) has been used for oxidation of dialkylanilines and saturated alcohols. The observed increase in the rate of oxidation with manganese dioxide with increasing available surface supports the postulated importance of the adsorption on the outcome of the oxidation. The decrease in the rate sometimes observed after the maximum value was reached could be simply a dilution effect.

1.4. Structure of Active Manganese Dioxide

Composition analysis[44] of various active manganese dioxide preparations showed hydrogen 0.04%–0.5%, active oxygen (iodometric) 12.8%–14.1%, and total oxygen (vacuum-fusion analysis) 23.5%–25.8%. Recent examinations (flame photometry and atomic adsorption) of manganese dioxide samples showed some adsorbed (e.g., coprecipitated) impurities, mainly potassium or sodium sulfate or chloride (0.5%–1.2%) and traces of alkaline earths and transition metals, all depending on the purity of the starting reagents; the magnetic measurements of samples indicated that, in addition to preponderant Mn(IV) species, they contained a small proportion of lower manganese components [possibly oxides and hydroxides of Mn(III) and Mn(II), in addition to the coprecipitated Mn^{2+} ions from the strating material].

Several studies have appeared on the structural features of various modifications of active manganese dioxide.[23,37,40,44,53] As shown by x-ray diffraction studies, most of the active forms of manganese dioxide prepared by the precipitation method are either amorphous or of low to moderate crystallinity, containing various proportions of β- or γ-MnO_2 forms. However, the oxidant prepared in deuterium oxide instead of water has been found[44] to be a dark-colored, crystalline material having a structure resembling that of γ-MnO_2 [(Eq. (2)].

$$MnSO_4 + KMnO_4 + D_2O \xrightarrow{\text{acidic, } 80^\circ C} 2\,MnO_2 \qquad (2)$$

Thermogravimetric analysis of active manganese samples from 20 to 600°C[19] revealed the presence of nonbonded and bonded water molecules (e.g., hydroxyl ligands) and the presence of labile oxygen atoms (e.g., surface oxygen ligands). The presence of some hydrated manganese dioxide species[39,54a] is thus necessary for activity of the oxidant. On the basis of spectroscopic and ESR studies, and thermogravimetric analysis,[19] it was proposed[44] that the precipitated form of manganese dioxide may contain a locked, water-associated chain; this

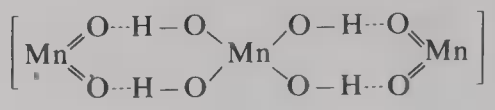


FIGURE 1. Proposed locked, water associated chain structure for precipitated (active) manganese dioxide.

structure provides important active sites of low electron density on the surface of the oxidant, and potentially labile, surface oxygen atoms and labile hydroxyl groups (Fig. 1).

It is known that strictly crystalline manganese dioxide (β-MnO_2 or γ-MnO_2 forms > 98% crystalline), or species containing an excess of water of hydration (e.g., pyrolusite) are poor oxidants.

2. MECHANISM

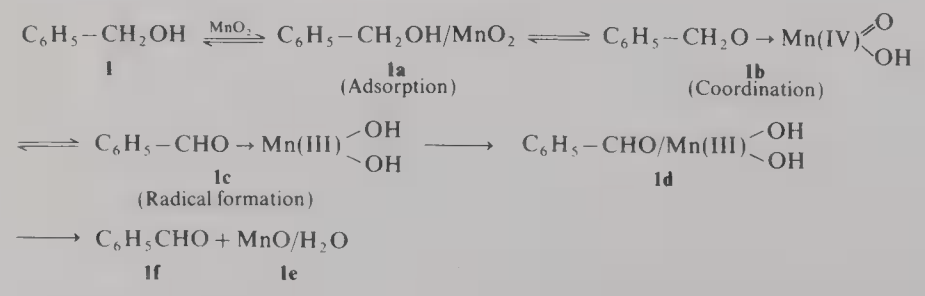
2.1. Free-Radical Mechanism

The precise elucidation of the mechanism of oxidation by manganese dioxide is difficult, because of the nature of the heterogeneous reaction involved.[3] The difficulties encountered in the study of these reactions may involve the structure of the oxidant, particularly the relationship of its surface-active sites towards a substrate (quadrupole/dipole, electrostatic interactions),[39,54b] in addition to the stereoelectronic factors of the organic substrate.

Despite recent progress in this direction,[19,33,44,55,56] the mechanism of oxidation by active manganese dioxide, particularly the details of the solid surface/substrate interaction (e.g., the identification of the active adsorbed species), or the elementary steps on the solid surface,[56] still needs clarification. Previous studies on the mechanism of manganese dioxide oxidation suggested the presence of an adsorptive process. The triphasic reaction pathway postulated *a priori*[13] consisted in adsorption of the substrate onthe surface of the oxide, followed by oxidation, and desorption of the product; this has some validity. The evidence of adsorption (e.g., chemisorption) has been provided in the oxidation of hexahydroxybenzene with active manganese dioxide via x-ray powder diffraction measurement of the rate of adsorption of the substrate, and the exclusive surface reaction via electron-diffraction measurement of the manganese dioxide complex formed.[44] However, strong evidence has been educed that, alternatively, the oxidation involves a free-radical intermediate[33,44,55–70,75,139,193,439,448,449] and, in certain cases, formation of a complex,[44] or, even, involvement of all of the ionic pathway, either via a cyclic transition-intermediate[71] or via a manganic ester intermediate.[72,73]

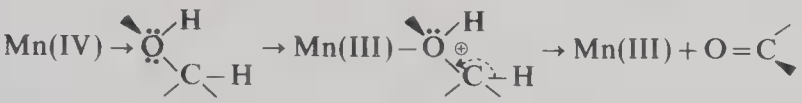
On the basis of kinetic studies, Goldman[33] proposed a radical mechanism for the oxidation of benzyl alcohol (**1**) by manganese dioxide. The suggested steps are (a) adsorption to give **1a**, (b) formation of a coordinated complex **1b**, (c) transfer of a hydrogen atom to give the stable radical **1c**, and (d) intramolecular electron transfer to give products **1d**–**1f** (Scheme 1).

SCHEME 1



By using manganese dioxide labeled with ^{18}O, it has been shown[74] that, during oxidation of uranium(IV) ions, the oxygen in the uranyl ion is derived from the solid oxidant; this indicates that an oxygen atom can be directly transferred from the oxidant; it also confirms that adsorption on the surface is an integral part of the oxidation process. The participation of the surface oxygen in the heterogeneous, liquid-phase oxidation of hydrocarbons, e.g., cyclohexene, cumene, and tetralin (R), catalyzed by manganese dioxide (M) (and other transition-metal oxides) has been established; the mechanism involve[75] the hydroperoxide intermediate (ROOH), hydroxyl radicals (HO·), and the resonance-stabilized, radical species (R·) (Scheme 2, Steps 1–9).

On adsorption, there may be total or partial transfer of electrons, resulting in the formation of free radicals. Knowing that chemisorption (via allylic or an aromatic π bond, or via manganese ions and alcohol oxygen electron coordination) [(Eq. (3)] is involved during



(3)

the oxide–substrate interaction,[44] the detection of free electrons of the adsorbent is difficult, because of the reaction between the lattice defects and the chemisorbed particles.[54b,76,77] However, the formation of a neutral, semiquinone radical ($\cdot OC_6H_4OH$) (SQ, step 1) and the formation of a radical anion (SA, pH = 9, step 2) has been observed by ESR spectroscopy in the oxidation of hydroquinone (HQ) in water with manganese dioxide.[56b] A modified mechanism for this reaction has been proposed, such that Mn(IV) on the surface of manganese dioxide is reduced to Mn(II), e.g., $Mn(OH)_2$*, via participation of a surface species, MnO_2* (steps 3 and 4, Scheme 3).[56a] A striking example of the participation of a free-radical intermediate has been reported[44] in the oxidation of pyrene in chloroform with manganese dioxide, to give 1,6- and 1,8-pyrenediones. The formation of these products can be rationalized in terms of an attack of the surface oxygen (e.g., ligands) or hydroxyl radicals on the hydrocarbon, to give either a hydroperoxide (ROOH) or a phenolic (diol) intermediate (ROH). The author[44] suggested that consumption of one equivalent of active oxygen

SCHEME 2

Initiation:

(1) $ROOH + M \overset{k_1}{\rightleftharpoons} ROOH...M$

(2) $ROOH...M \xrightarrow{k_2} RO^{\cdot} + {}^{\cdot}OH...M$

(3) $ROOH + {}^{\cdot}OH...M \xrightarrow{k_3} RO^{\cdot}{}_2 + H_2O + M$

(4) $RO^{\cdot} + RH \xrightarrow{k_4} ROH + R^{\cdot}$

Propagation:

(5) $R^{\cdot} + O_2 \xrightarrow{k_5} ROO^{\cdot}$

(6) $ROO^{\cdot} + RH \xrightarrow{k_6} ROOH + R^{\cdot}$

Termination:

(7) $ROO^{\cdot} + ROO^{\cdot} \xrightarrow{k_7}$ inactive products $+ O_2$

(8) $ROO^{\cdot} + M \overset{k_8}{\rightleftharpoons} ROO^{\cdot}...M$

(9) $ROO^{\cdot}...M + ROO^{\cdot} \xrightarrow{k_9}$ inactive products

SCHEME 3

(1) $HQ \underset{k_2}{\overset{k_1}{\rightleftharpoons}} SQ$ on MnO_2 surface

(2) $SQ \underset{k_4}{\overset{k_2}{\rightleftharpoons}} SA + H^+$ in liquid phase

(3) $HQ + MnO_2^* \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} SQ + MnO(OH)^*$

(4) $HQ + MnO(OH)^* \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} SQ + Mn(OH)_2^*$

present in manganese dioxide corresponds to two hydroxyl radicals, as shown for certain hydrated forms of it [(Eq. (4)]. Such a pathway would provide reactive species that could

$$\left[O=Mn\begin{matrix}OH\\OH\end{matrix} \right] \rightarrow 2\,\dot{O}H \rightarrow 2\,O^* + H_2O + Mn^{2\oplus} \tag{4}$$

either abstract hydrogen atoms or donate hydroxyl radicals. This mechanistic approach is analogous to that proposed for the oxidation of alcohols by nickel peroxide.[4]

2.2. Ionic Mechanism

2.2.1. Cyclic Transition Intermediate

Recently, Kwart and George[71] studied the mechanism of a heterogeneous oxidation of alcohols, e.g., benzyl alcohol, by manganese dioxide (and by nickel peroxide). In the concerted mechanism, the authors[71] proposed a cyclic transition-state (e.g., coordination sphere) involving couped-hydrogen and electron-transfer processes on the surface of the manganese dioxide (via tunneling in a reaction of linear H-transfer) (Fig. 2). Mechanistic preferences appear to be determined by factors that control the distance of separation between the reaction centers involved in the H-transfer step.

2.2.2. Manganic Ester Intermediate

A novel, oxidative rearrangement of a bicyclic alcohol has been reported by Hall and Story,[73] who found that quadricyclanol (**2**) in chloroform is rapidly rearranged by active manganese dioxide (MRS)[26] to norbornadienol (**3**), which is then oxidized at 45°C to the tricyclic oxide (**4**) and benzaldehyde (**5**) in yields of 5%–70%; other forms of active manganese dioxide were ineffective. The authors[73] suggested a mechanism in which the first step is formation of a manganic ester, followed by isomerization via carbonium ions to give

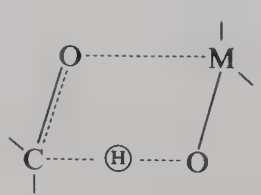
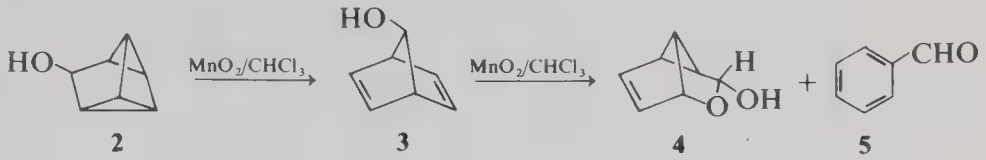


FIGURE 2. Linear H transfer in transition element oxidation of alcohols, where M is a transition element with tetragonal, tetrahedral, or octahedral coordination sphere.

an oxygen-insertion product **4**. A rearrangement involving a loss of a proton by the carbonium ion will then give rise to the aromatic product **5**. In view of our present knowledge,[33,44,56] all the ionic pathways suggested[73] could be partially operable; some of the rearrangements mentioned can be explained by the free-radical mechanism.



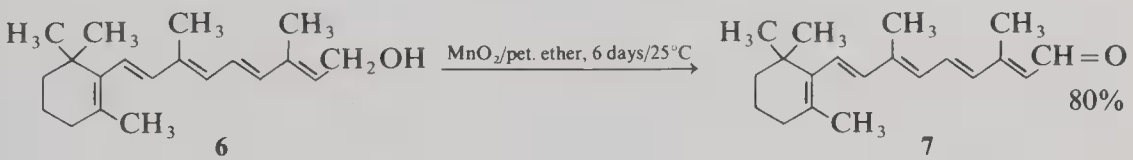
2 **3** **4** **5**

3. OXIDATION OF ALCOHOLS AND HYDROXY COMPOUNDS

3.1. α,β-Unsaturated Alcohols (α,β-Ethylenic, Primary and Secondary Alcohols)

3.1.1. Vitamin A_1 and Analogs

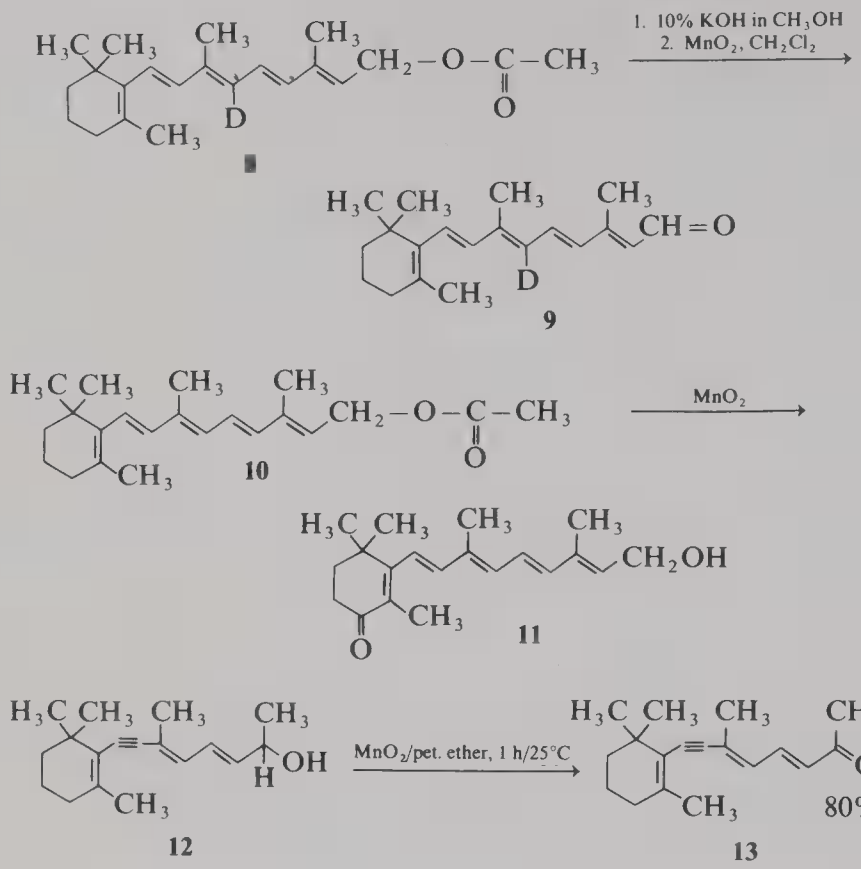
Only a few of the oxidation methods for converting primary and secondary, α,β-unsaturated, polyene alcohols into the corresponding α,β-unsaturated carbonyl compounds are mild enough to be applicable to sensitive compounds. In one of these, active manganese dioxide is utilized as the oxidant. The first organic compound to be oxidized in nonaqueous, inert, organic media (BGM reagent)[13] was vitamin A_1 (retinol) **6**, which is derived from an oxidative hydrolysis of β-carotene and is a C_{20} pentaene allylic alcohol; **6** was thus converted for the first time into isometrically pure A_1 aldehyde (retinal) **7** in high yield.[13] Active manganese dioxide in inert, organic solvents was the reagent of choice in the recent oxidation of a series of sensitive retinols to retinals[94,95]; also, in a recent conversion of 9-*cis*-11-*cis*-13-*cis*-retinol (highly twisted about the Δ^{12} single bond) with MnO_2 (30-fold excess, low-boiling petroleum ether, 1 h, 4°C) into the corresponding retinal (82% yield),[96] and conversion of *all-trans*-10-monodeuterioretinol **8** into 10-monodeuterioretinal **9**, following saponification of the acetate group.[97]



6 **7**

The direct attack on the conjugated methylene group in the vitamin A_1 ring by manganese dioxide is exemplified in the oxidation of vitamin A_1 acetate **10** to 3-oxovitamin A_1 **11**.[98,99] By application of Attenburrow's manganese dioxide, it was possible to oxidize, in 1 h, the mixed-polyene, secondary alcohol **12** to the ketone **13** in 80% yield.[25] The mild nature of the reaction with manganese dioxide is well illustrated by conversion of the four geometrical isomers of vitamin A_1 (*all-trans*, *neo*, 6-*cis*, and 2,6-di-*cis*) into the corresponding retinenes (retinals) (61%–80% yield) without any isomerization.[100] This mildness is also shown in the oxidations of vitamin A_1,[101] vitamin A_2,[102] 8,9-dihydrovitamin A,[25] vitamin A isomers,[103] vitamin A analogs,[104,105] carotenes, and carotenoids.[106,107]

The stereoselective synthesis of 7-*cis*, 9-*cis*-β-ionylideneacetyldehyde involved oxidation of the corresponding alcohol with freshly prepared active manganese dioxide (room temperature, 1 h, CH_2Cl_2 74% yield); similarly, a mixture of 7-*cis*, 9-*cis* and 7-*cis*, 9-*cis*; 13-*cis*-retinal was obtained following oxidation of the corresponding mixture of the retinol isomers (MnO_2, CH_2Cl_2, 0.75 h, r.t.).[108] In all cases, manganese dioxide proved to be superior to other reagents, such as 5,6-dichloro-2,3-dicyano-1,4-benzoquinone (DDQ) or the Oppenauer oxidant; the latter, for example, failed with acetylenic alcohols.[109]

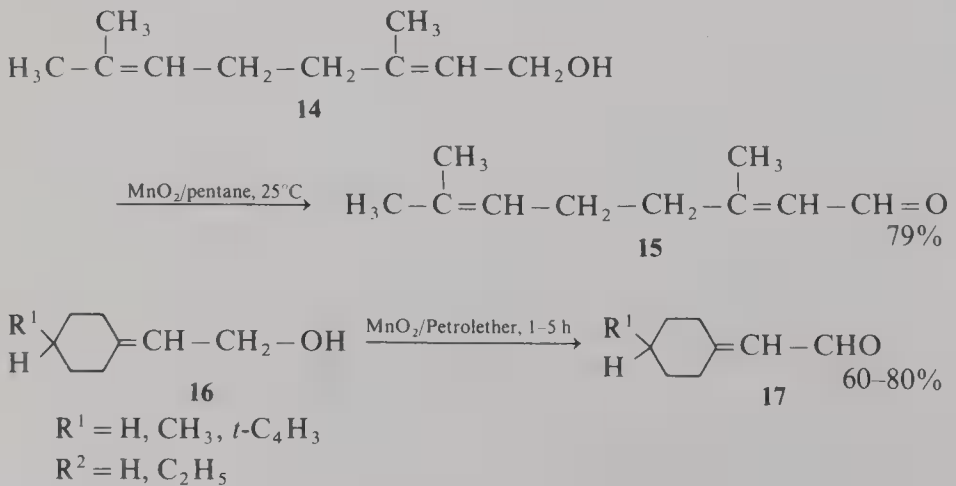


9 10 11 12 13

Recently, the oxidation of a series of α,β-unsaturated[727–740, 756] and benzylic[757–761] alcohols with active manganese dioxide has been reported and some of these are summarized in Tables I and II, respectively.

3.1.2. α,β-Ethylenic, Primary and Secondary Alcohols

A high-yield conversion of the simplest, ethylenic primary alcohols into aldehydes, e.g., allyl alcohol[25,29] or crotyl alcohol,[28] or conversion of **14** into **15** in 79% yield,[28] indicated that a single, alkenic bond in the α-position to the hydroxyl group provides sufficient activation to bring about the reaction. The oxidation has been observed where the unsaturation is a part of an alkenic, alkynic, aromatic, alicyclic, or carbonyl system. Thus, 2-cyclohexylideneethanols **16** ($R^1 = H, CH_3, t\text{-}C_4H_9$) were oxidized by manganese dioxide, to give the corresponding cyclohexylideneacetaldehydes **17** (60%–80% yield)[110]; similarly,



14 **15** **16** **17**

$R^1 = H, CH_3, t\text{-}C_4H_3$

$R^2 = H, C_2H_5$

TABLE I. Selective Oxidations of α,β-Unsaturated Alcohols with MnO_2

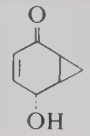
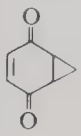
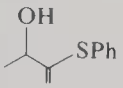
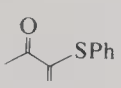
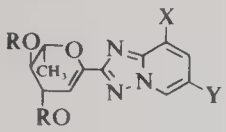
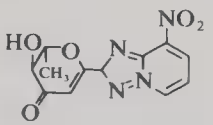
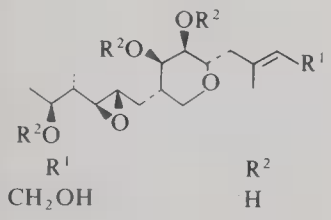
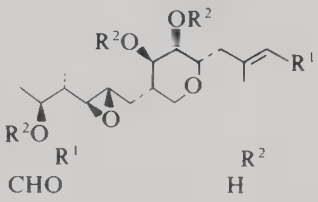
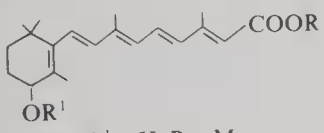
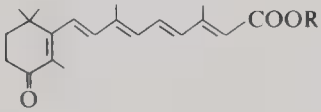
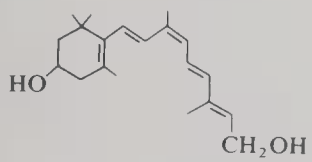
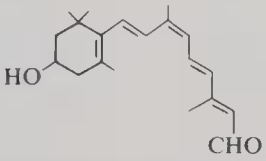
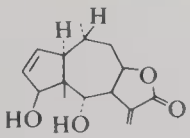
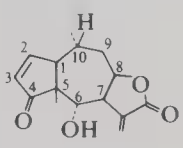
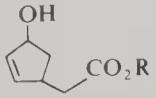
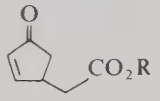
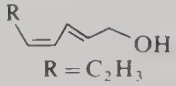
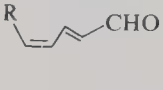
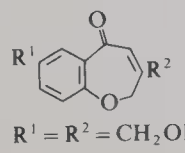
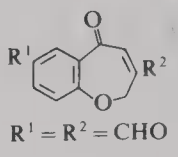
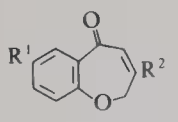
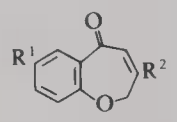
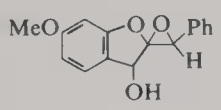
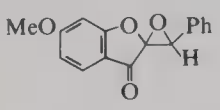
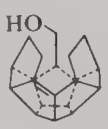
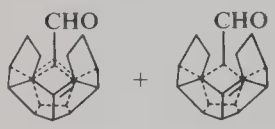
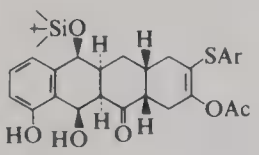
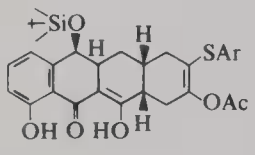
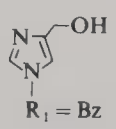
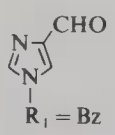
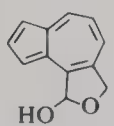
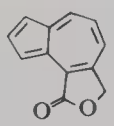
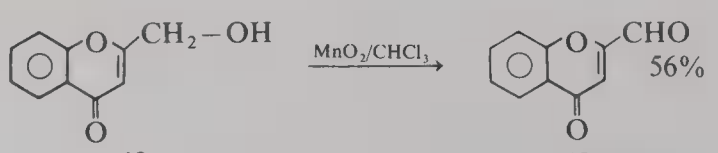
Substrate	Product	Reaction conditions	Yield (%)	Reference
		MnO_2/CH_2Cl_2 25°C, 4 h	92	727
		$MnO_2/CHCl_3$ 25°C, 20 h	32	729
 ■ = H; X = NO_2; Y = H		$MnO_2/CHCl_3$	40	730
 R^1 = CH_2OH, R^2 = H	 R^1 = CHO, R^2 = H	$MnO_2/CHCl_3$	63	732
 R^1 = H, R = Me		MnO_2/CH_2Cl_2 5°C–25°C, 1 h	84	733
		MnO_2/CH_2Cl_2 25°C	55	735
		MnO_2/CH_2Cl_2 25°C	65	736
		$MnO_2/CHCl_3$	70	738
 R = C_2H_3		MnO_2/petroleum ether	71	739

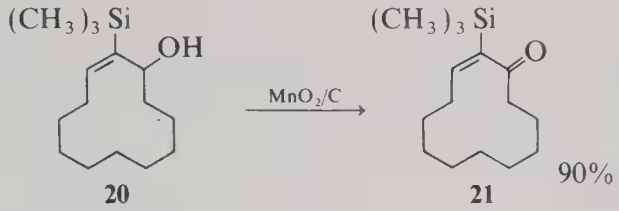
TABLE II. Selective Oxidation of Unsaturated and Benzyl Alcohols with Active MnO_2

Substrate	Product	Reaction conditions	Yield (%)	Reference
 $R^1 = R^2 = CH_2OH$	 $R^1 = R^2 = CHO$	MnO_2/CH_2Cl_2 8:1 ratio 25°C	67	756
 $R^1 = R^2 = CH_2OH$	 $R^1 = CH_2OH$, $R^2 = CHO$	MnO_2/CH_2Cl_2 4.5:1 ratio 25°C	73	756
		MnO_2/ether	60	757
		MnO_2/CH_2Cl_2	42 + 45	758
		MnO_2/acetone	76	759
 $R_1 = Bz$	 $R_1 = Bz$	MnO_2/dioxane	73	760
		$MnO_2/CHCl_2$	90	761

2-hydroxymethylchromone **18** was converted into 2-formylchromone **19** (56% yield),[111] and, in the presence of the activated manganese dioxide on charcoal, the alcohol **20** underwent slow oxidation (12 days) to give the ketone **21** (90% yield).[112] α-Hydroxy ethers are also oxidized by manganese dioxide, suggesting that the reaction may be initiated by any structure that provides an electron-rich source in the position adjacent to the hydroxyl group. Confirmation of the structure in methyl-4-hydroxy-4-phenyl-2-butenoate **22** came from the manganese dioxide oxidation of the allylic group, to give the known methyl 4-oxo-4-phenyl-2-butenoate **23** in 74% yield.[113]

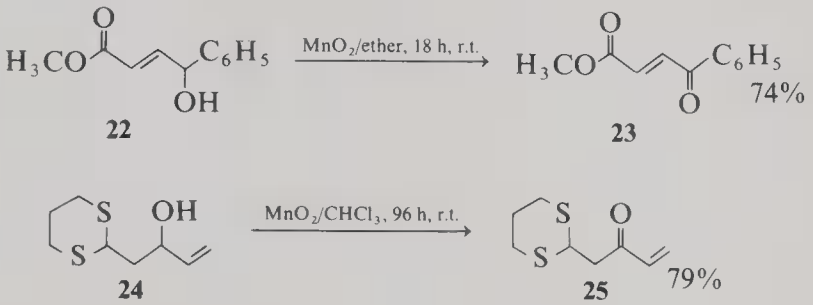


18 **19**



20 21

Oxidation of 1,1-trimethylenedithio-4-penten-3-ol **24** with manganese dioxide afforded the Michael acceptor 1,1-trimethylenedithio-4-penten-3-one **25** (79% yield), a useful intermediate in the synthesis of alkaloids.[114]

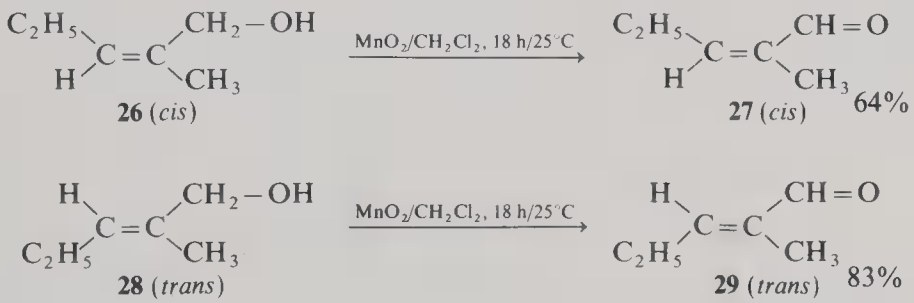


22 23

24 25

3.1.3. Oxidation of cis- and trans-Unsaturated Alcohols

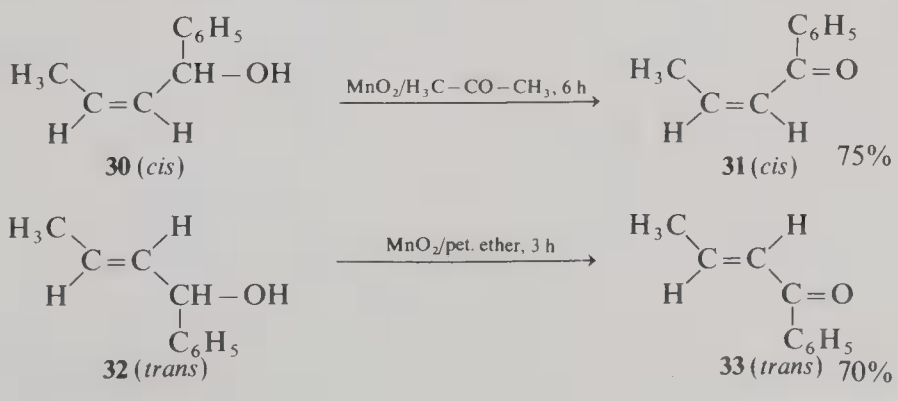
As mentioned earlier, the *cis*- and *trans*-α,β-unsaturated chain alcohols show approximately the same rate of oxidation with active manganese dioxide, generally giving products without isomerization across the double bond, thus demonstrating the mildness of the reagent. For example, *cis*-2-methyl-2-penten-1-ol **26** was converted into *cis*-2-methyl-2-pentenal **27** in 64% yield, and the *trans*-isomer **28** afforded the *trans*-aldehyde **29** in 83%



26 (*cis*) **27** (*cis*)

28 (*trans*) **29** (*trans*)

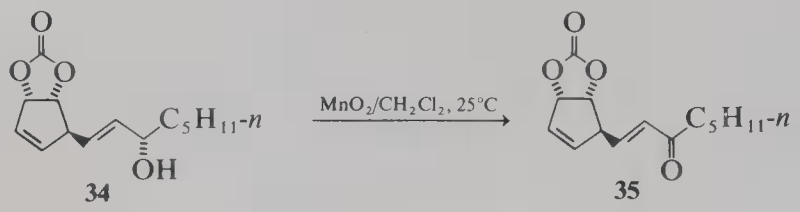
yield.[115] Analogous oxidation of the geometrical isomers *cis*-1-phenyl-2-buten-1-ol **30** and the *trans* alcohol **32** gave *cis*- and *trans*-ketones, **31** and **33**, in 75% yields, respectively.[43] Similarly, *cis*-2-penten-1-ol was oxidized to *cis*-2-pentenal in 42% yield, and the *trans* isomer gave the *trans* aldehyde in 38% for a 1 g batch and a 90 % yield for an 8 g batch.[116]



30 (*cis*) **31** (*cis*)

32 (*trans*) **33** (*trans*)

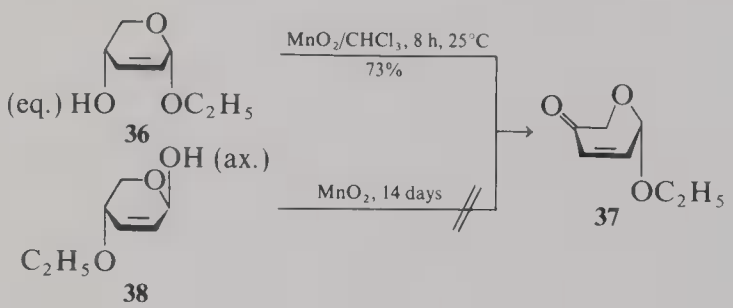
The *cis* and *trans* isomers of 2-ionylidene-ethanols (C_{14} alcohols) were converted into C_{14} aldehydes without isomerization.[117] No isomerization has been observed in oxidation of similar *cis* and *trans* α,β-unsaturated alcohols[43,116–119] or in conversion of the unsaturated hydroxylactone **34** into the prostaglandine intermediate enone **35**.[120]



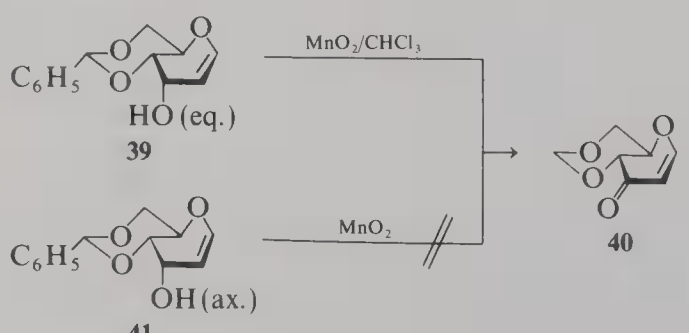
Stereoelectronic Effects in the Oxidation of Alcohols. In addition to such physical factors as the solvent, the type and quantity of the reagent, the temperature, and the elapsed time, important in manganese dioxide oxidation of alcohols, steric factors (particularly arrangement about a hydroxyl group) appear to have a pronounced effect on the rate of oxidation. Although *cis* and *trans* unsaturated alcohols (ethylenic and acetylenic) show roughly the same rate of oxidation by manganese dioxide at room temperature, Boehm and co-workers[78,79] observed some *cis–trans* isomerization in the transformation of pentadienols and pentenynols into carbonyl derivatives. Some optically active alcohols [e.g., (+)-*cis*- or *trans*-5-methylcyclohex-2-enols] showed a change in the sign of optical rotation on oxidation with manganese dioxide.[80]

However, there are reports[81–83] that, on oxidation with manganese dioxide, many cyclic, allylic alcohols definitely favor a particular orientation of their hydroxyl groups.

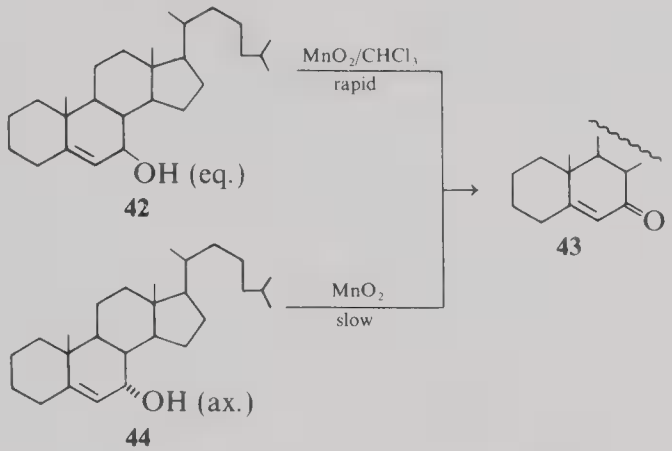
An apparent stereochemical effect in manganese dioxide oxidation of some allylic carbohydrates has been observed by Fraser-Reid and co-workers.[81,82] Whereas the α-D anomer of "*cis*-dihydropyran-2-ol" (**36**; ethyl 2,3-dideoxy-α-D-glycero-2-enopyranoside) having an *equatorial* hydroxyl group is readily oxidized by manganese dioxide (MRS)[26] to give the α,β-unsaturated ketone **37**, the β-D anomer **38**, having an *axial* hydroxyl group, is inert.



Similarly, the D-glucal derivative **39** having an *equatorial* hydroxyl group at C-3 is oxidized to give the 3-ulose derivative **40**, but the D-glucal derivative **41** (axial OH) is not affected.[82] However, the authors[81,82] pointed out that there must be other factors than stereochemical (e.g., half-chair conformations, or an anomeric effect) responsible for failure of **38** or **41** to be oxidized. Finally, the authors[81,82] proposed that the difference in facile oxidation of **36** and



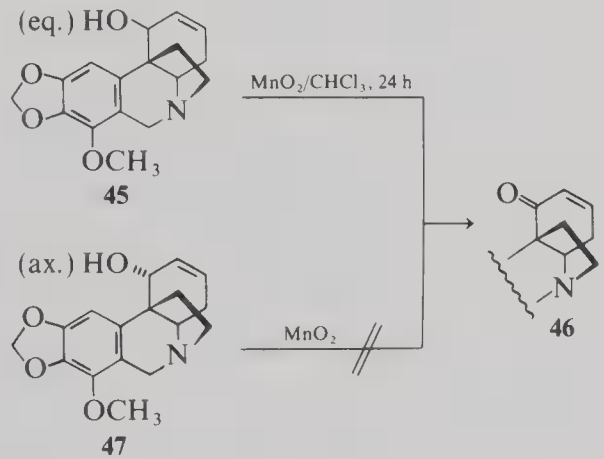
39 as compared to **38** and **41** somehow related to the fact that the anomers adopt H1 and 1H conformations, respectively. In a study of the rate of oxidation of epimeric, steroid, allylic alcohols by manganese dioxide, Nickon and Bagli[84] found that 7β-hydroxycholest-5-ene **42** (*equatorial* OH) is oxidized faster (to give the α,β-unsaturated ketone **43**) than 7α-hydroxycholest-5-ene **44** (axial OH). Similarly, cholest-4-en-3β-ol is oxidized by manganese dioxide in half to one-third the time needed for cholest-4-en-3α-ol.[83] Favored oxidation of *cis*-alcohols by manganese dioxide has also been found[85] for a mixture of *cis*- and *trans*-5.7(20)-pregnadien-3β, 16α-diols, and for similar steroid *cis*-alcohols.[86]

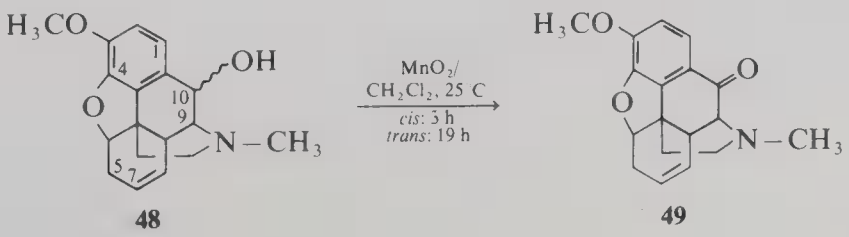


A stereochemical tendency in manganese dioxide oxidation has also been observed in the alkaloid series. Thus, 1-epibuphanamine (**45**; *equatorial* OH) is oxidized to the corresponding oxo-derivative **46**, whereas buphanamine (**47**; *axial* OH) is not affected.[87,88] Similarly, the 10-*cis*-hydroxycodeine **48** (*equatorial* OH) is oxidized faster (to give the keto derivative **49**) than the *trans* isomer (*axial* OH).[89]

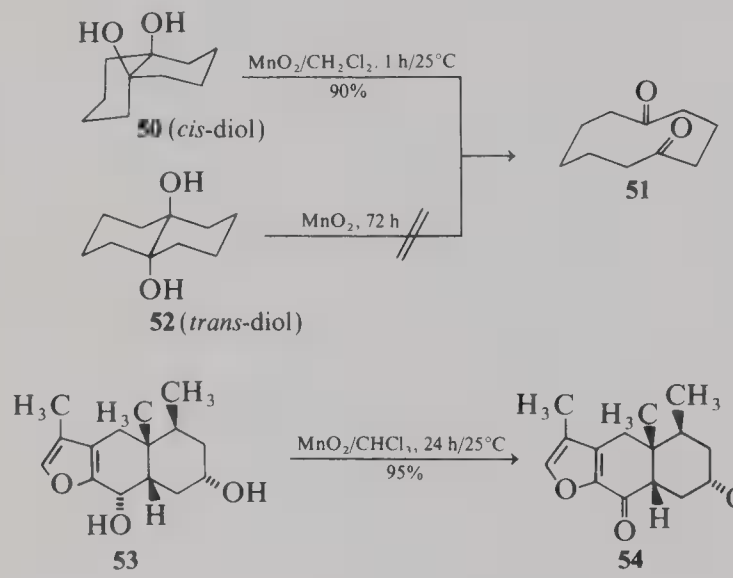
Owing to the steric factors, an allylic alcohol having a $\Delta^{2,3}$-structure (isocaranine) was not oxidized by manganese dioxide.[90]

However, in contrast, Djerassi and co-workers[91] oxidized both *cis*- and *trans*-alcohols of steroids to the corresponding keto derivative with manganese dioxide, and steroid allylic alcohols of both orientations have also been oxidized.[46]





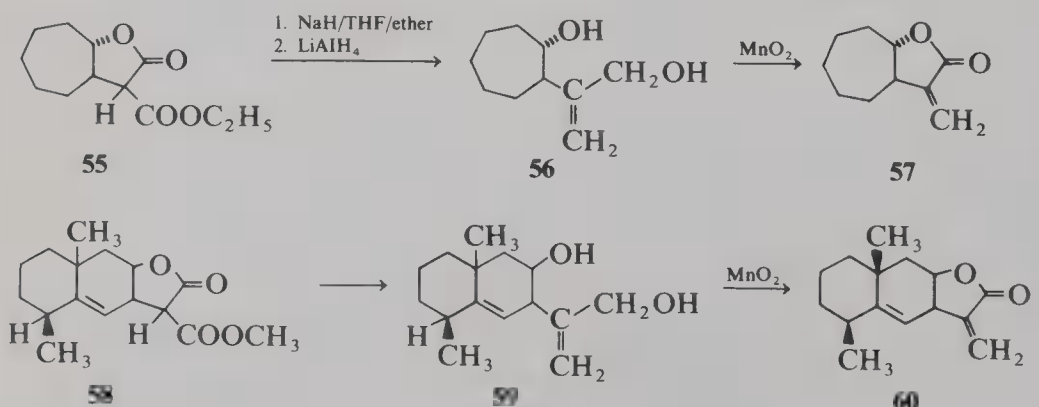
A striking example of a stereochemical preference in active manganese dioxide oxidation of the saturated alcohols (under mild conditions) has been reported by Ohloff and Giersch.[92] Thus, 9, 10-*cis*-decalindiol (**50**; and other *vic*-diols) is easily oxidized to diketone **51** in 90% yield, whereas the 9, 10-*trans* isomer **52** (and other conformationally rigid diols with a dihedral angle of 180° subtended by the hydroxy groups) remains unaffected even on prolonged treatment with the reagent.[92] A stereochemical dependence was also observed in the terpene series. Thus, treatment of a sesquiterpenoid furanopentasol (a *cis*-fused-ring diol **53**) with manganese dioxide in chloroform gave *cis*-fused ketoalcohol **54** in 95% yield[93]; oxidation of a second hydroxy group was apparently prevented by the steric arrangement of two of the rings.



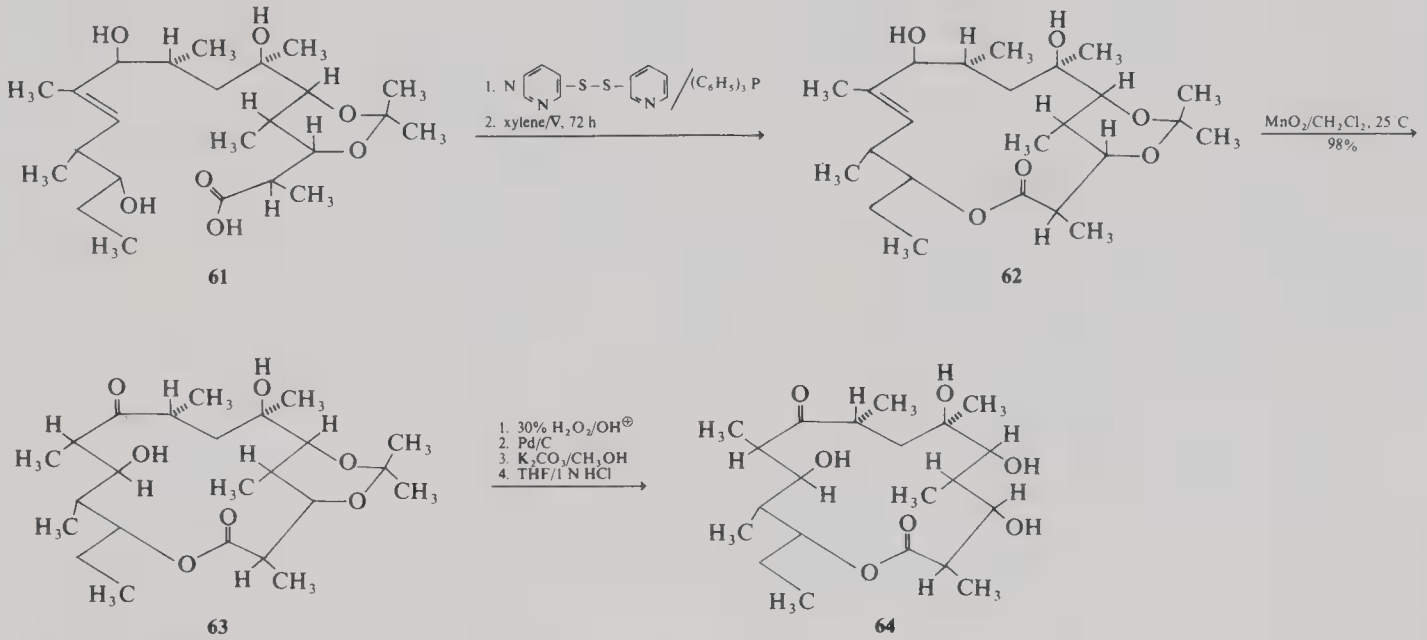
3.1.4. α,β-Unsaturated Lactones

The unsaturated lactone moiety (e.g., α-methylene lactone) constitutes a major structural feature of many natural products, e.g., sesquiterpenes; methods for the synthesis of α-methylene lactones have been reviewed.[121] Marshall[122–124] reported a new approach to the synthesis of α-methylene lactones; for example, starting with malonic ester lactone, the sequence involves a reductive elimination, to give an allylic alcohol, followed by an oxidative cyclization (MnO_2), to give a lactone. This is demonstrated in the conversion of the cycloheptane lactone ester (**55**) into α-methylene lactone (**57**) via intermediate **56**, and in a similar synthesis of the *dl*-alantolactone (**60**) via intermediates **58** and **59**.[123,124]

Corey and co-workers[125,126] developed a new effective method for the synthesis of macrocyclic lactones that required a manganese dioxide oxidation; the procedure involved a

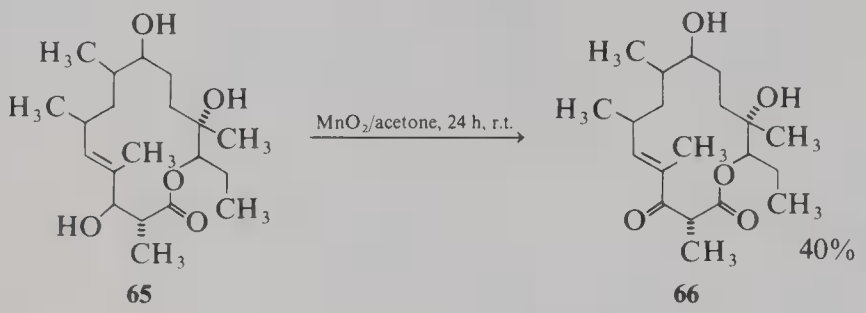


SCHEME 4



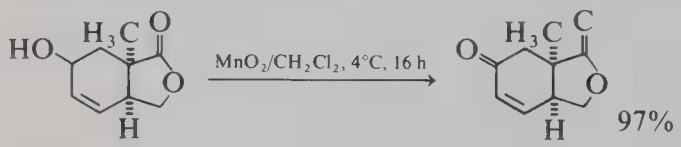
61 62 63 64

simultaneous activation of both hydroxy and carboxy groups toward lactonization. For example, synthesis of erythronolide B (**64**), the aglycone of the antibiotic erythromycin, was effected by the following sequence, via the acyclic hydroxy acid **61**, the diol **62** and the keto intermediate **63**[125] (Scheme 4). The favored allylic hydroxy oxidation in the triol **65** (dihydrokromycin, a macrolide antibiotic aglycon) with manganese dioxide in acetone yielded the α,β-unsaturated ketone **66** in 40% yield.[127] Dihydroactinodiolid (**70**;



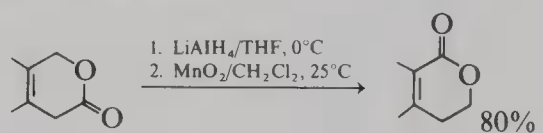
65 **66**

1,6,6-trimethyl-2-oxa-3-oxobicyclo-[4.3.0]non-4-ene) can be prepared in a simple way by oxidation of either *cis*-β-ionol **67**, of the *trans*-alcohol **69**, or of 1,3,7,7-tetramethyl-2-oxabicyclo[4.4.0]-3,5-decadiene (**68**) with activated manganese dioxide in benzene at reflux temperature for 36 h (method A). The cyclic ether **68** is easily obtained in 89% yield from **67** by reaction with chromic trioxide in pyridine/dichloromethane at 20°C (method B)[128] (Scheme 5). Manganese dioxide in dichloromethane was the reagent of choice for the preparation of a sensitive keto lactone **72** in hight yield (97°) from the hydroxy lactone **71**.[129]



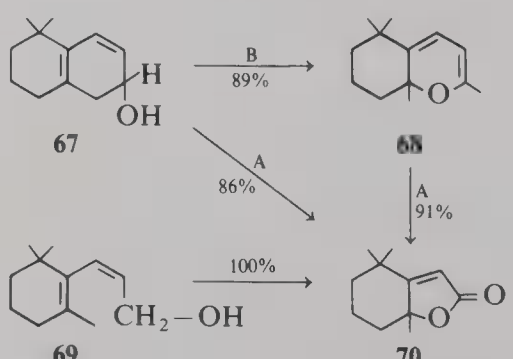
71 **72**

A useful synthetic method for the transformation of lactones has recently been described; the procedure involves, at first, the reduction of the original lactone **73** with lithium aluminum hydride, followed by oxidation of the resulting diol with manganese dioxide, to give a new lactone **74** in 80% yield.[130]



73 **74**

SCHEME 5

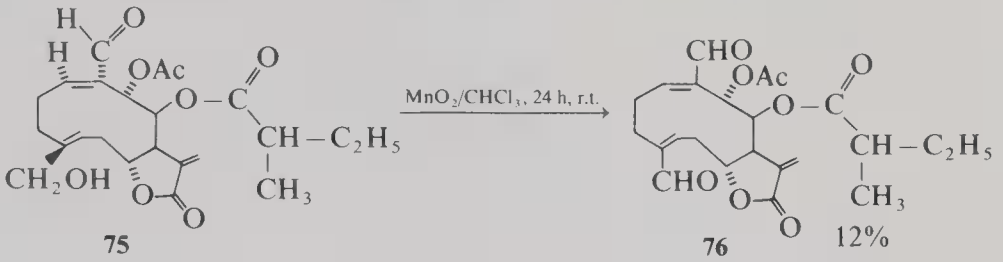


67 **68**

69 **70**

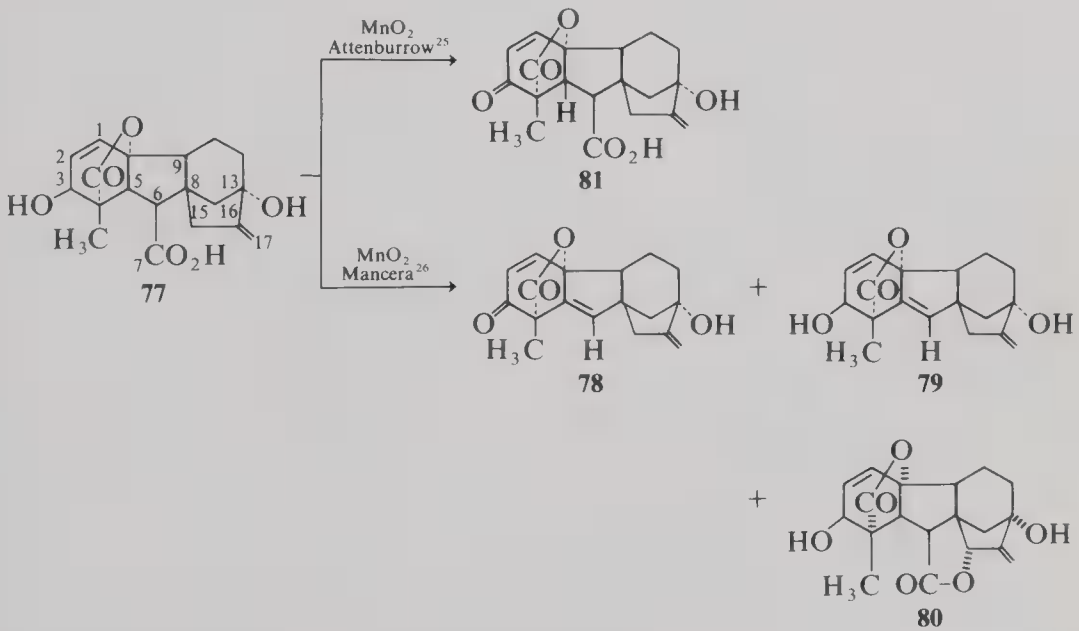
Method A: Activated MnO_2/C_6H_6; 80°C/36 h
Method B: CrO_3/pyridine/CH_2Cl_2; 20°C/$\frac{1}{2}$ h

To determine the geometry of the 4,5-double bond, acanthespermal B (a natural sesquiterpene lactone **75**) was oxidized with manganese dioxide in chloroform to give the dialdehyde **76** whose ^{1}H-NMR spectrum exhibited a signal for the new aldehyde proton at $\delta = 10.22$ ppm indicating that the 4,5-bond was *trans*.[131]



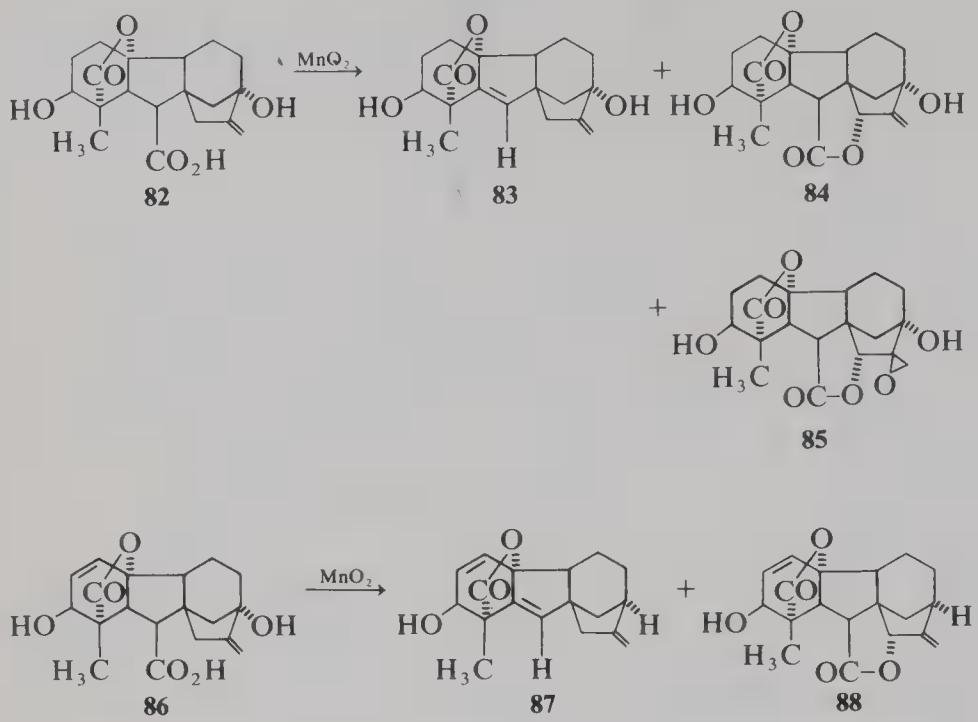
75 **76**

Oxidation of Gibberellins. Gibberellins, cell-elongating plant hormones, definitely play a role in the downward-growth behavior (geotropism) of roots. Oxidation of gibberillic acid (**77**), containing allylic and nonallylic hydroxyl groups, with manganese dioxide has been studied.[45,132–134] However, "anomalous" behavior of **77** toward various types of manganese dioxide has been observed. As reported by Serebryakov and co-workers,[135] treatment of **77** in acetone with acidic MnO_2 (MRS)[26]* gives rise to the products of oxidative decarboxylation (**78** and **79**) and oxidative lactonization **80**, with the formation of the enone (**78**) (~10% yield). However, oxidation of **77** in acetone using the Attenburrow oxide (alkaline MnO_2)[25] yields the keto acid **81** in 56% yield. The general nature of these transformations in the series of gibberellins has been demonstrated[136] by using gibberellin A_1 (**82**), containing saturated hydroxyl groups and gibberellin A_7 **86**, containing an allylic hydroxyl group. Here, the reaction with acidic MnO_2 in acetone brings about oxidative decarboxylation, and lactonization also; thus, **82** gave a diene **83** (3%–4%), a dilactone **84** (11%–15%), and an epoxydilactone **85** (~2% yield). The gibberellin **86**, on similar oxidation, produced a triene **87** and a dilactone **88**. It appears that oxidative decarboxylation and lactonization induced by acidic MnO_2[26] may be fairly general for all gibberellins. Thus, the presence of a Δ^{16}-double bond in **77**, **82**, or **86** is necessary for the occurrence of oxidative lactonization at C-15.



77 **81** **78** **79** **80**

* The authors[135] defined the reagent as neutral MnO_2, although it was prepared[26] under acidic conditions.

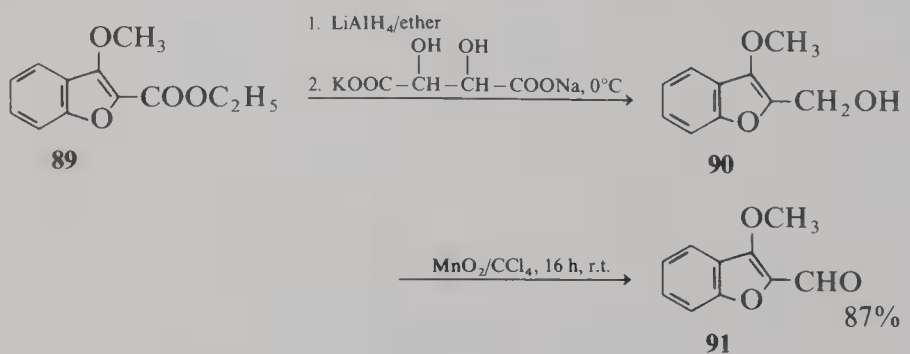


3.1.5. Additional Pertinent Oxidations

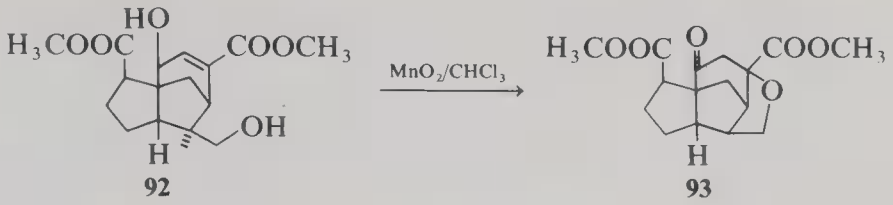
Manganese dioxide oxidation was succesfully applied in a structure elucidation of *germacranolide trifrucitin* (a natural sesquiterpene lactone).[137] A survey of the synthetic procedures for lactonization describes an application of the manganese dioxide reagent (e.g., oxidation of a diol followed by cyclization).[138]

A novel one-step synthesis of γ-lactones involved the reaction of manganic or other higher valent metal carboxylates with olefins and carboxylic acid. For example, treatment of 1-octene with active manganese dioxide in the presence of acetic acid yielded the corresponding γ-lactone in 46%–67% yield. A free-radical mechanism involving the selective generation and oxidation via organic free-radicals was presented.[139]

Aldehydes can be conveniently prepared from their carboxylic acid esters via alcohols. Beginning, for example, from the ester **89** (ethyl 3-methoxybenzofuran-3-carboxylate), the aldehyde **91** (3-methoxybenzofuran-2-carbaldehyde) was obtained in 87% yield by manganese dioxide oxidation of the intermediate primary alcohol **90** as shown.[140]

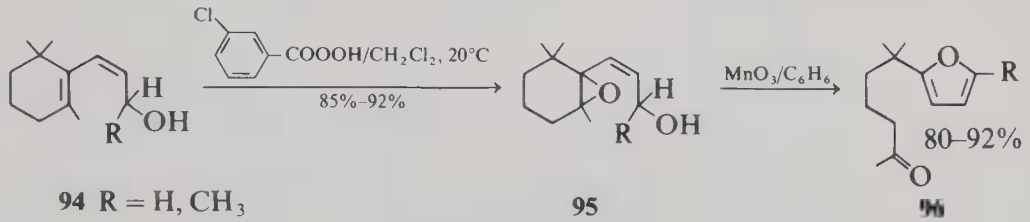


In certain cases an α,β-unsaturated alcohol on oxidation with active manganese dioxide has afforded a saturated cyclic keto-ether. For example, treatment of the sesquiterpene dimethyl shellolate (**92**) with the reagent produced a keto-ether (**93**); the reaction apparently proceeded by initial oxidation of **92** to an α,β-unsaturated ketone, followed by ring closure via a Michael-type addition of the tertiary hydroxy group to the conjugated system.[141]



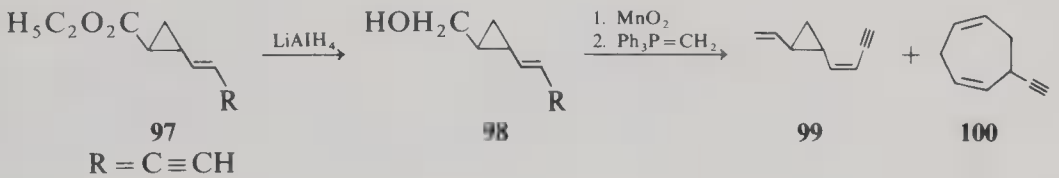
92 93

In contrast to the reactivity of their *trans*-analogs, the *cis*-epoxyalcohols **95** undergo formation of a α-substituted furan ring on treatment with activated manganese dioxide in refluxing benzene for 18–36 h, to give the furyl ketones **96** in high yields. The starting compounds **95** can be prepared from the allylic alcohols **94** by oxidation with *m*-chloroperoxybenzoic acid in dichloromethane at 20°C.[128] The synthesis of homologs of the seaweed pheromone ectocarpene has been described; starting from *trans*-isomer of the



94 R = H, CH_3 95 96

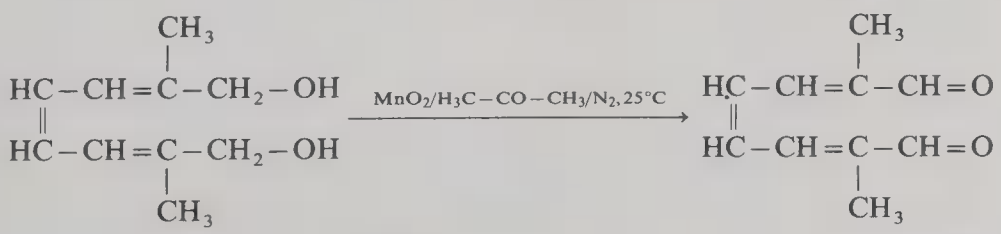
cyclopropane ester **97**, the sequence involves reduction, to give the alcohol **98**; oxidation of **98** with manganese dioxide, followed by the Wittig reaction, produces the natural products, e.g., dictyoterpene (**99**) having a cyclopropane structure, and ectocarpene (**100**) having a 1,4-cycloheptadiene structure.[142]



97 R = C≡CH 98 99 100

3.1.6. α,β-Unsaturated Diols and Polyols

In oxidation of α,β-unsaturated diols or polyols with active manganese dioxide, several reactions are possible, involving one or more hydroxyl groups (depending on their degree of activation by multiple bonds); in general, the rate of oxidation is in the order primary > secondary > tertiary hydroxy groups. For example, manganese dioxide oxidation of 2,7-dimethyl-2,4,6-octatriene-1,8-diol (**101**) gave dialdehyde (**102**) in 94% yield[143]; similar oxidation of the analog of **101**, e.g., conversion of **103** into **104** (95% yield),[144,145] or conversion of acetylenic diol, e.g., annulenediol **105** into the corresponding dialdehyde **106** (74% yield)[147]; similar oxidations of other conjugated diols or glycols[143,144,148,149] gave the dicarbonyl products in good yield. Preferential oxidation of the most activated (by conjugation)



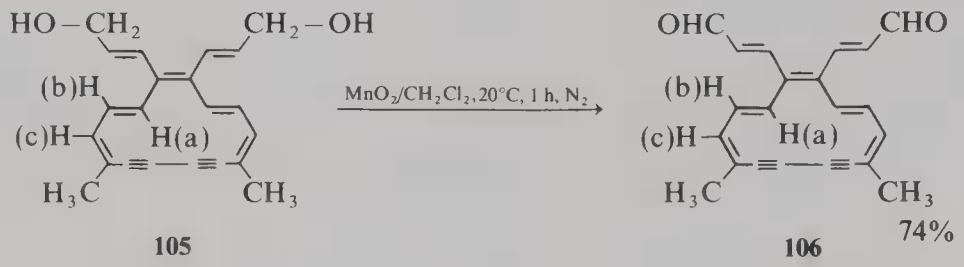
101 102 94%

$$HO-CH_2-CH=CH-O-CH=CH-CH_2-OH$$

103

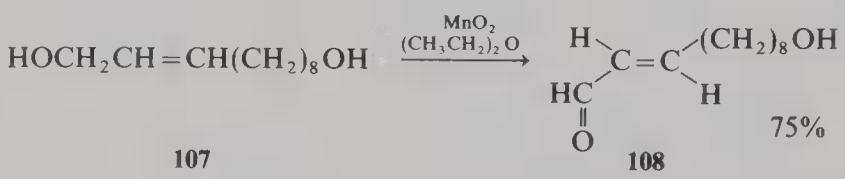
$$\xrightarrow{MnO_2/H_3C-CO-CH_3,\,12\,h} O=CH-CH=CH-O-CH=CH-CH=O$$

104 80%



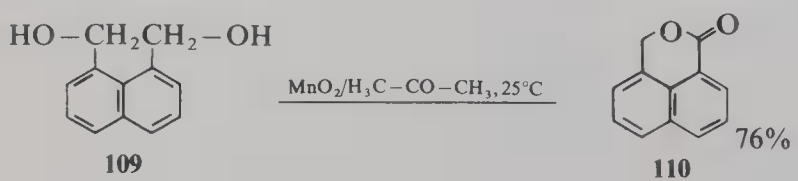
105 **106**

α-hydroxyl group in an α,β-unsaturated diol has been reported; thus, treatment of 2-undecen-1,11-diol (**107**) with manganese dioxide in diethyl ether gave *trans*-11-hydroxy-2-undecenal (**108**) (75% yield).[150] Preferential oxidation of pyridoxine [3-hydroxy-4,5-bis(hydroxymethyl)-2-methylpyridine] (a homolog of vitamin B_6) with ordinary[151] and active manganese dioxide[152,153] has been reported.



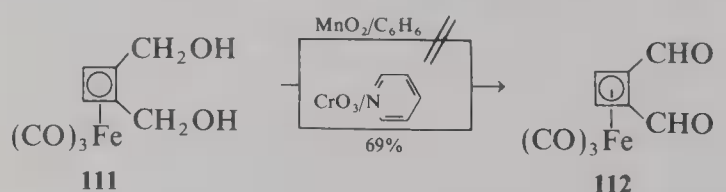
107 **108**

Oxidation of 1,8-bis(hydroxymethyl)naphthalene (**109**) with manganese dioxide gave, instead of the expected naphthalene-1,8-dialdehyde, 1-oxo-1H, 3H-naphtho[1,8-*cd*]pyran (**110**) in 76% yield.[154] Similarly, phthalide and new γ-lactones from 9-(hydroxymethyl)-phenanthrene-10-carboxylic acid and 4-(hydroxymethyl)-pyrene-5-carboxylic acid have been



109 **110**

prepared via a suggested[154] cyclic half-acetal intermediate, in 65%, 73%, and 58% yields, respectively. An attempt to oxidize iron tricarbonyl-1,2,3,4-μ-1,2-bis[hydroxymethyl]-1,3-cyclobutadiene (**111**) with active manganese dioxide in benzene has failed; the diol, however, was oxidized to dialdehyde (**112**) with the Collins reagent in 69% yield.[155]

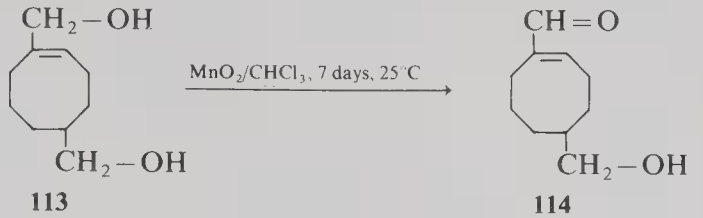


111 **112**

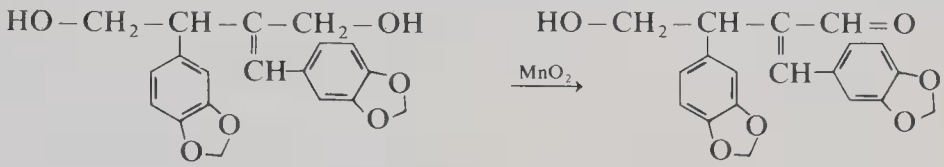
3.1.7. Conjugative Activation of α-Hydroxyl Groups in Unsaturated Alcohols

A break in the chain of conjugation in an unsaturated-bond system, even by one carbon atom, markedly decreases the rate of oxidation, and this partially constitutes the

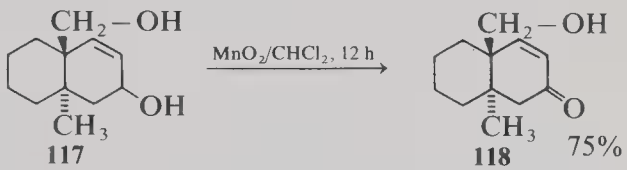
regiospecificity and selectivity of manganese dioxide oxidation, particularly noted with polyhydroxy terpenes, steroids, alkaloids, and other natural products. Thus, oxidation of 1,5-bis[hydroxymethyl]cyclooctene (**113**) with manganese dioxide gave 1-formyl-5-(hydroxymethyl)-cyclooctene (**114**) in 80% yield[156]; similar oxidation of **115** gave **116**[157] and, because of steric and conjugation effects, **117** was converted into **118** [10-(hydroxymethyl)-$\Delta^{3,4}$-*trans*-decalin-2-one][157] only; however, both hydroxy groups in α-santonin **119** were affected by the reagent (to give **120** in 50% yield, and a monoketo derivative in 25% yield).[159]



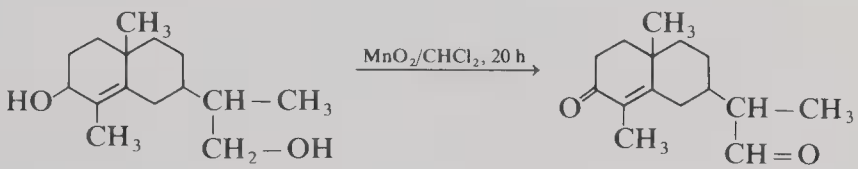
113 **114**



115 **116**



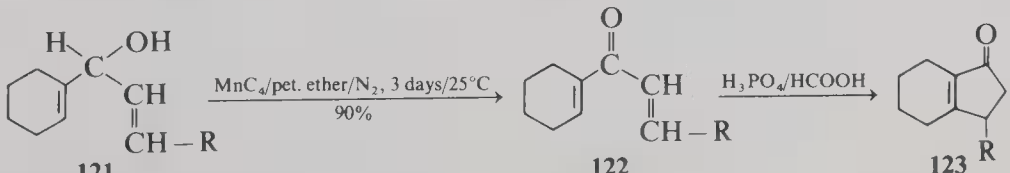
117 **118**



119 **120**

Other hydroxy compounds[160–163] in which the hydroxyl groups are activated to a different extent behave similarly. In one example,[160] treatment of (4-*trans*-2,4-dihydroxy-2,6,6-trimethylcyclohexylidene)-but-3-en-2-ol with manganese in acetone gave (3R)-4-[(2R, 4S)2,4-dihydroxy-2,6,6-trimethylcyclohexylidene]-but-3-en-2-one in 80% yield; the x-ray analysis has established its absolute configuration as 3S, 5R, 6R.[160] Side-chain allylic and other unsaturated alcohols in which double bonds are in conjugation with various saturated, unsaturated, or aromatic ring units, such as cyclopentene,[164] cyclohexane,[165] cyclohexene,[160,162,166–168] cyclohexadiene,[25,104,175] azulene,[172] derivatives of azulene,[173] furan and derivatives,[174,175] or ferrocene[176] have been efficiently oxidized with manganese dioxide to the corresponding carbonyl compounds.

A convenient method for the synthesis of an indanone derivative, e.g., **123**, involves oxidation, with manganese dioxide, of an unsaturated side-chain alcohol (e.g., **121**, a 1-cyclohex-1-en-1-ylalkan-1-ol), to give the cyclohexyl ketone **122** (R = H, 90% yield) which

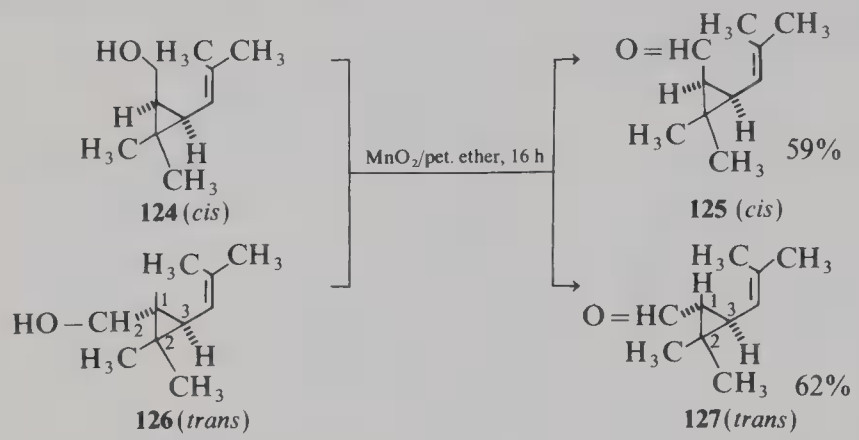


121 **122** **123**

R = H, CH_3, C_2H_5, C_3H_7, etc.

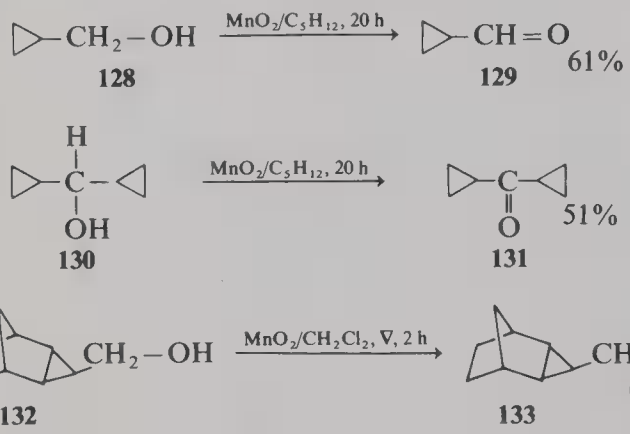
was then cyclized with phosphoric acid/formic acid to give the 4,5,6,7-tetrahydroindan-1-one (**123**) (R = H, 50% yield from **121**.[177]

Activation by a Cyclopropane Group. Activation of the α-hydroxyl group by a cyclopropane ring has been found[178] useful in the preparation of the sensitive, not isomerized, *cis*- and *trans*-chrysanthemyl aldehydes **125** and **127** from the corresponding alcohols **124** and **126** following treatment with active manganese dioxide.



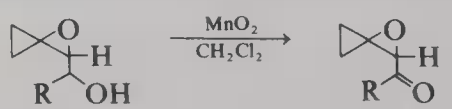
124 (*cis*) **125** (*cis*) **126** (*trans*) **127** (*trans*)

Facile oxidation of nonconjugated cyclopropane alcohols with manganese dioxide {e.g., conversions of **128** into **129**,[178] of **130** into **131**,[178] or of the bridged alcohol **132** (*exo* tricyclo[3.2.1.$0^{2,4}$]octan-3-ylmethanol) into **133**,[179] or of a mixture of the bridged



128 **129** **130** **131** **132** **133**

cyclopropane *exo* epimers, *exo*, *endo*-, and *exo-exo*-tricyclo[3.2.2.$0^{2,4}$]nonan-6-ol into a single ketone, *exo*-tricyclo[3.2.2.$0^{2,4}$]nonan-6-one (81% yield[180])} clearly demonstrated that activation of the hydroxyl groups by the three-carbon ring is equivalent to activation by conjugation. Alcohols in which the hydroxyl group is activated by two multiple bonds,[164,177,181,182,287] or other unsaturated, bicyclic,[156,161,166,183–187] or bridged[173,174] alcohols, are readily oxidized. Selectivity in oxidation of unsaturated, epoxy alcohols (where the epoxy ring is unaffected) has been observed[183,188]; an acetal group also remains intact on treatment with the reagent.[144] A new preparation of the cyclopropyl ketones **135** involves the oxidation of oxaspiropentyl alcohols **134** with active MnO_2 (30%–56% yield); note that the epoxide ring is not affected.[745]

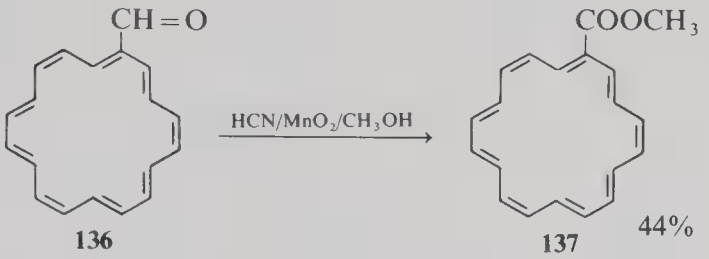


134 **135**

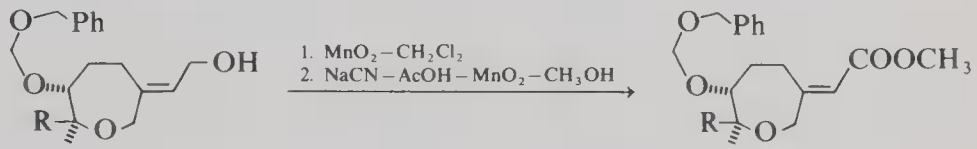
R = Me, Ph, H

3.1.8. Oxidation of α,β-Unsaturated Aldehydes

Active manganese dioxide was the reagent of choice in the oxidation of the highly unsaturated [18] annulenecarboxaldehyde (**136**) in tetrahydrofuran in the presence of methanol and hydrogen cyanide, to give methyl [18] annulenecarboxylate (**137**) in 44% yield.[189] Oxidation of **136** by other oxidants (e.g., Jones reagent) failed owing to complete destruction of the annulene system. The procedure is similar to the known method of Corey, Gilman, and Ganem[190] for the conversion of an α,β-unsaturated alcohol into the corresponding, unsaturated methyl ester via oxidative esterification, as exemplified in a recent conversion of the alcohol **138** into the ester **139**.[191]



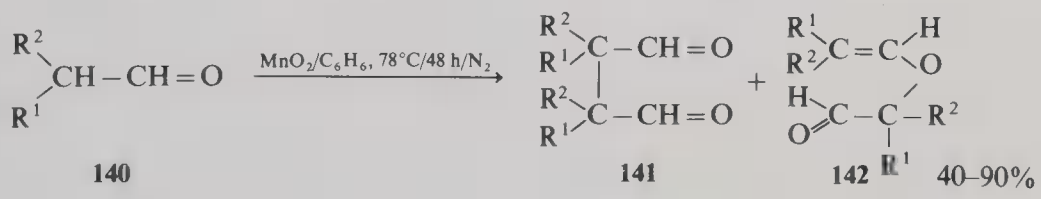
136 **137**



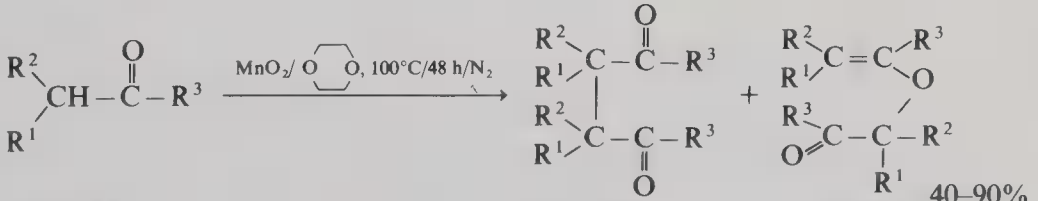
138 **139**

A novel reaction for the preparation of unsaturated aldehydes has been described,[192] by this procedure, saturated aldehydes of type **140** ($R^1=R^2=$ mixed alkyl, aryl, or other groups) in the presence of manganese dioxide undergo dimerization (presumably via a free radical intermediate) to give a mixture of products, e.g., alkenyloxy-aldehyde (**142**) and -dialdehyde **141**. Similarly saturated ketones (type **143** having also one hydrogen atom in the alpha position to the carbonyl group) have been converted by the reagent to the coupling products, e.g. diketones (type **144**) and keto-ethers (type **145**)[193] in 40%–90% yield.[192]

Almost identical oxidative coupling of aliphatic aldehydes and ketones in the presence of manganese dioxide has been reported in a French patent. Thus, treatment of isobutyraldehyde (**140** $R^1=R^2=CH_3$) or isopropyl methyl ketone (**143** $R^1=R^2=R^3=CH_3$) with the reagent in refluxing *p*-dioxan (24 h) gave a mixture of both the C–C coupling and C–O coupling products (e.g., dialdehyde **141** $R^1=R^2=CH_3$ or diketone **144** $R^1=R^2=R^3=CH_3$ or aldehyde-ether **142** $R^1=R^2=CH_3$ or keto-ether **145** $R^1=R^2R^3=CH_3$, respectively) in good yield; a free radical was proposed as the reaction intermediate.[193]



140 **141** **142**



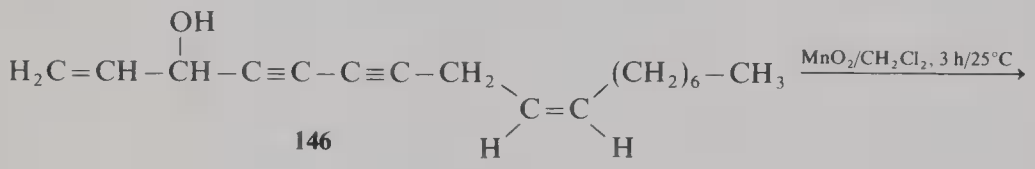
143 **144** **145**

R^1, R^2, R^3 = alkyl, cycloalkyl, alkenyl, aryl, alkaryl, aralkyl, heteroaryl

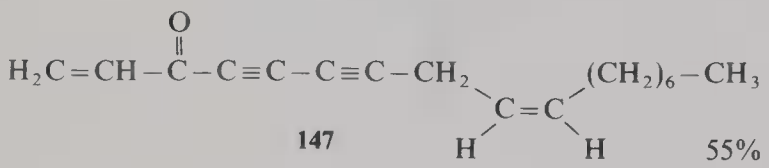
3.2. Acetylenic Alcohols

3.2.1. α,β-Unsaturated Acetylenic Alcohols

Manganese dioxide occupies an important place in the organic chemist's store of oxidants because of its mildness and selectivity, properties that are so important in the oxidation of sensitive, acetylenic alcohols. Acetylenic alcohols behave like α,β-unsaturated olefinic alcohols toward manganese dioxide oxidation; the presence of one (or two) triple bond(s) is sufficient to bring about rapid oxidation of the conjugated hydroxy groups. The mildness of the reagent is exemplified by the oxidation of **146** (*cis*-heptadeca-1,9-diene-4,6-diyn-3-ol) with manganese dioxide to give the *cis*-3-ketone **147** in 55% yield without isomerization.[194–195]

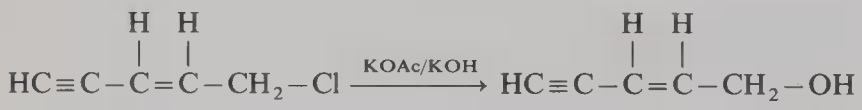


146

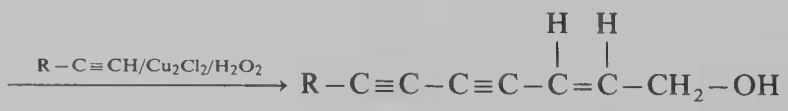


147 55%

No isomerization or rearrangement has been observed during the synthesis of three naturally occurring polyacetylenic esters **153** (R = $CH_3CH_2CH_2-$, *cis*-$CH_3CH=CH-$, and H_3C-, and $H_3C-C\equiv C-$) from the corresponding alcohols **150** (R = $CH_3CH_2CH_2-$, *cis*-$CH_3CH=CH-$, and $H_3C-C\equiv C-$) via intermediates **148**, **149**, **151**, and **152**,[196] or in conversion of highly unsaturated alcohol **154** into the corresponding acid **156** via aldehyde **155**.[197]



148 **149**



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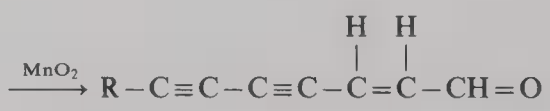

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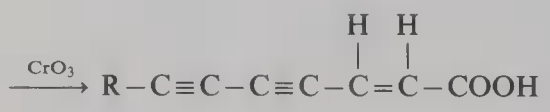

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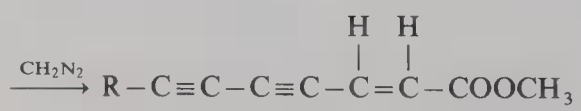

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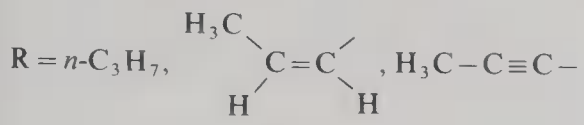


$$n\text{-}C_3H_7-C\equiv C-C\equiv C-\underset{H}{\overset{H}{C}}=\underset{H}{\overset{H}{C}}-CH_2-OH$$

154

$$\xrightarrow{MnO_2} n\text{-}C_3H_7-C\equiv C-C\equiv C-\underset{H}{\overset{H}{C}}=\underset{H}{\overset{H}{C}}-CH=O$$

155 90%

$$\xrightarrow{CrO_3/H_2SO_4} n\text{-}C_3H_7-C\equiv C-C\equiv C-\underset{H}{\overset{H}{C}}=\underset{H}{\overset{H}{C}}-COOH$$

156

$$C_2H_5-O-C\equiv C-Li + H_3C-\underset{H}{\overset{}{C}}=\underset{}{\overset{H}{C}}-CH=O$$

157 **158**

$$\xrightarrow{\text{ether, } N_2, -20^\circ C} C_2H_5-O-C\equiv C-\underset{}{\overset{OH}{CH}}-\underset{H}{\overset{H}{C}}=\underset{}{\overset{}{C}}-CH_3$$

159

$$\xrightarrow{MnO_2/CH_2Cl_2,\,4\,h/25^\circ C} C_2H_5-O-C\equiv C-\underset{}{\overset{O}{C}}-\underset{H}{\overset{H}{C}}=\underset{}{\overset{}{C}}-CH_3$$

160 40%

Using manganese dioxide (carefully washed to neutrality) in dichloromethane, Stork and Tomasz[198] were able to oxidize the highly unstable 1-ethoxy-3-hydroxyhex-4-en-1-yne (**159**) [prepared from the condensation of ethoxyacetylenelithium (**157**) with crotonaldehyde (**158**)] to give the alkali- and acid-sensitive ketone **160** in 40% yield, the first known ethynyl vinyl ketone. On oxidation with manganese dioxide, unsymmetrical acetylenic diols, unlike symmetrical olefinic[143] or acetylenic[144,145] diols, produce, instead of dicarbonyl products, aldols or ketols, e.g., conversion of **161** into aldol **162**, (R)-4,6,8-decatriyne-1,3-diol **163** into the oxo alcohol **164**,[195] or **165** into the ketol **166**.[199] However, multiple conjugation can activate both hydroxyl groups and, for example, the asymmetrical diols **167** and **169** have been oxidized to give dialdehyde **168**[199] and diketone **170**,[195] respectively.

$$HO-CH_2-CH_2-C\equiv C-C\equiv C-CH_2-OH$$

161

$$\xrightarrow{MnO_2/CHCl_3} HO-CH_2-CH_2-C\equiv C-C\equiv C-CH=O$$

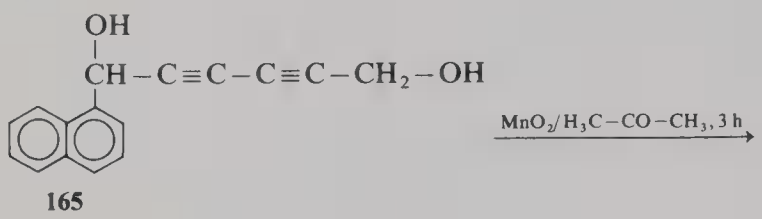
162

$$H_3C-C\equiv C-C\equiv C-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-CH_2-OH$$

163

$$\xrightarrow{MnO_2/CHCl_3,\,25°C} H_3C-C\equiv C-C\equiv C-\overset{\displaystyle O}{\overset{\|}{C}}-CH_2-CH_2-OH$$

164



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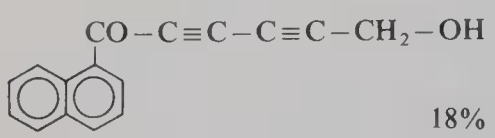


166

$$HO-CH_2-C\equiv C-C\equiv C-C\equiv C-CH=CH-CH_2-OH$$

167

$$\xrightarrow{MnO_2} O=CH-C\equiv C-C\equiv C-C\equiv C-CH=CH-CH=O$$

168

$$n\text{-}C_7H_{15}-CH=CH-\underset{\displaystyle OH}{\underset{|}{CH}}-C\equiv C-C\equiv C-\underset{\displaystyle OH}{\underset{|}{CH}}-CH=CH_2$$

169

$$\xrightarrow{MnO_2/CH_2Cl_2,\,17\,h} n\text{-}C_7H_{15}-CH=CH-\overset{\displaystyle O}{\overset{\|}{C}}-C\equiv C-C\equiv C-\overset{\displaystyle O}{\overset{\|}{C}}-CH=CH_2$$

170

3.2.2. Oxidation of Alkynic Alcohols of Type $R-CHOH-C\equiv CH$

Treatment of secondary alkynic alcohols **167a** with manganese dioxide gave ketones **168a** in 10%–70% yield.[200,201] The effect of the polarity of the solvent should be noted, e.g.,

of alcohol **167a** ($R = C_6H_5$), where the yield of ketone **168a** ($R = C_6H_5$) decreases from 65% to 20% to 10% when the reaction is performed in chloroform, acetone, or ether, respectively. A series of analogous acetylenic alcohols $R^1-\underset{\displaystyle OH}{\underset{|}{CH}}-C\equiv C-R^2$ [where R^1 = alkyl;

$$R-\underset{\displaystyle OH}{\underset{|}{CH}}-C\equiv CH \xrightarrow{MnO_2} R-CO-C\equiv CH$$

167a **168a**

$R = C_2H_5$, n-C_3H_7, 

$R^2 = H$[199,200]; $R^1 = R^2$ = alkyl[194]; R^1 = phenyl, $R^2 = H$[199]; R^1 = phenyl, R^2 = alkyl[199]; $R^1 = R^2$ = phenyl[199,202]; R^1 = furyl, $R^2 = H$[203]; R^1 = furyl, R^2 = alkyl[202,204]; or R^1 = thianyl, R^2 = alkyl[202,204]] have been successfully oxidized with manganese dioxide to the corresponding carbonyl compounds. Similarly polyacetylenic alcohols containing two consecutive, or alternate, triple bonds,[144,199,202] or three consecutive triple bonds,[144,195,205] or other acetylenic alcohols[198,201,206–208] have also been converted into the corresponding aldehydes and ketones.

In a recent example, a secondary alkynic alcohol **171** (prepared by condensation of the acetylene **169a** with propaldehyde (**170a**)) was oxidized with manganese dioxide, to give the ynone **172**.[209]

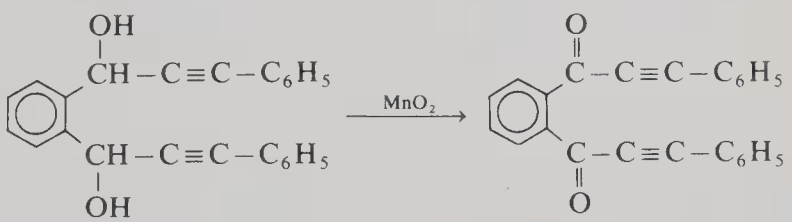
$$C_3H_7C\equiv CH + C_3H_7CHO \xrightarrow[-78°C]{BuLi} C_3H_7C\equiv CCH(OH)\,C_3H_7$$

169a **170a** **171**

$$\xrightarrow{MnO_2} C_3H_7C\equiv CC(O)\,C_3H_7$$

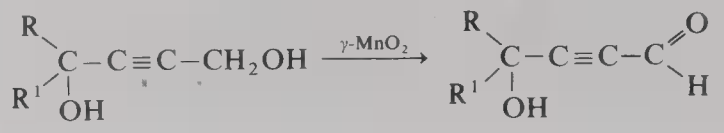
172

In another example, 4,4-dimethyl-1,7-diphenyl-1,6-heptadiyne-3,5-diol was converted with manganese dioxide into the corresponding 3,5-dione in 79% yield,[210] and similar oxidation (MnO_2/petroleum ether/20 h/r.t.)[210] of 1,2-bis(1-hydroxy-3-phenylprop-3-yn-1-yl)-benzene (**173**) gave 1,2-bis(1-oxo-3-phenylprop-3-yn-1-yl)benzene (**174**) in 50% yield. Other



173 **174**

acetylenic diols were similarly converted into diones in 40%–90% yield.[210] However, some substituted acetylenic diols containing primary and tertiary hydroxyl groups, e.g., **175**, on treatment with acidic manganese dioxide at room temperature were converted into γ-oxyaldehydes, e.g., **176** (50%–70% yield).[211] Also, some substituted acetylenic diols containing tertiary and secondary hydroxyl groups, e.g., **177**, on similar treatment were converted into the expected ketols, e.g., **178** (30%–80% yield),[212] thus leaving the tertiary hydroxyl group intact.

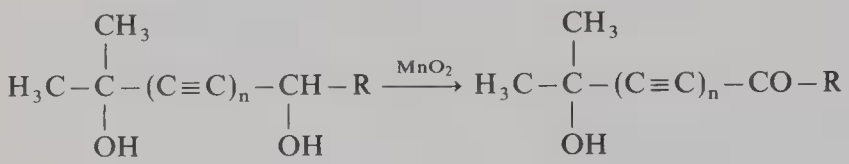


175 176

$R = R^1 = CH_3$

$R = CH_3$, $R^1 = C_2H_5$

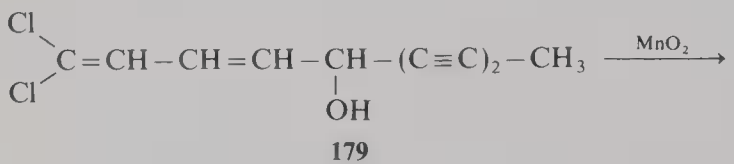
$R = CH_3$, $R^1 = n\text{-}C_3H_7$



177 178

$n = 1$; $R = CH_3$ (33%); C_3H_7 (80%); CCl_3 (54%); C_6H_5 (75%); thienyl-2 (35%); $-CH=CH-CH_3$ (30%); $n = 2$; C_6H_5 (30%);

A sensitive, mixed ethylenic and acetylenic alcohol **179** required a very mild oxidant for the conversion into ketone **180**; the only suitable reagent for this reaction was active manganese dioxide (moderate yield).[213]



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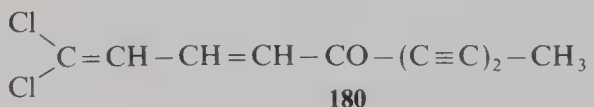
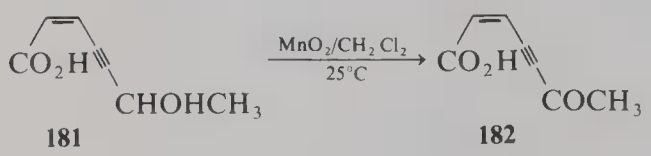
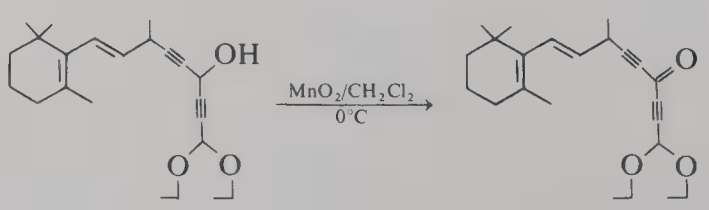


180

Mildness of the oxidant (MnO_2, CH_2Cl_2, 25°C) was necessary for the conversion of the acetylenic alcohol **181** into the ketone **182** [methyl(Z)-6-oxo-2-hepten-4-ynoate] in 74% yield[741] and the conversion of the diacetylenic alcohol **183** (MnO_2, CH_2Cl_2, 0°C) to the corresponding ketone **184** in 76% yield.[742]



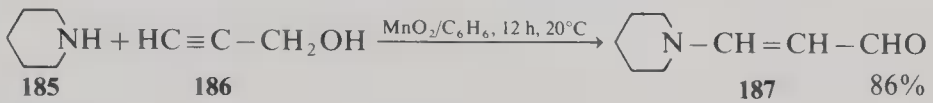
181 182



183 184

3.2.3. Oxidation of Acetylenic Alcohols in the Presence of Amines

An attractive procedure for the preparation of β-alkyl(aryl)aminoacroleins from 2-acetylene alcohol and organic bases has been reported. For example, oxidation of propargyl alcohol (**186**) by manganese dioxide in the presence of piperidine (**185**) at room temperature (12 h) yielded β-piperidinoacrylaldehyde (**187**) in 86% yield. In the presence of other organic bases, e.g., RH [$R=(H_3C)_2N$, $(C_2H_5)_2N$, morpholino, $C_6H_5NCH_3$, H_3CNH, C_2H_5NH, i-C_3H_7NH, i-C_9H_9NH, C_6H_5NH], the corresponding aminoacroleins RCH=CHCHO were obtained in 46%–86% yield.[215] Oxidation of acetylenic alcohols and glycols by manganese dioxide in the presence of amines, alcohols, and phenols has been studied by Vereschchagin and coworkers.[216]



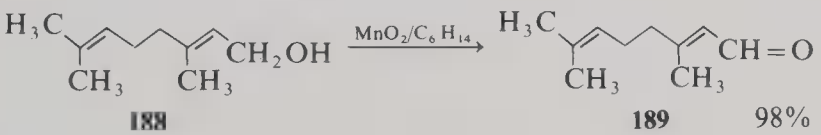
185 **186** **187** 86%

3.3. Terpenes

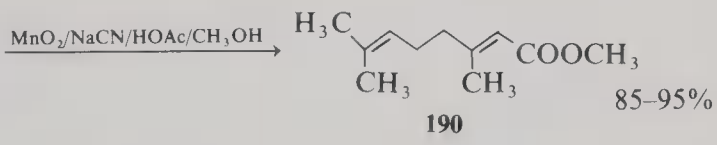
As described earlier, only a few unsaturated terpene alcohols have been selectively oxidized with manganese dioxide (e.g., compounds **34**, **53**, **94**, **117**, **119**, **124**, and **126**).

3.3.1. The Stereospecific Corey Esterification[190]

A stereospecific method for conversion of α,β-unsaturated primary alcohols into carboxylic acid esters via the aldehyde involves manganese dioxide oxidation, first in hexane (to generate the aldehyde), and subsequently in the presence of cyanide ions in methanol to give, via suggested cyanohydrin and acyl cyanide intermediates, the product, a conjugate carboxylic acid ester.[190] Usually, the conversion is high and no *cis–trans* isomerization of the α,β-unsaturated double bond occurs. This can be seen from the conversion of geraniol (**188**) [*trans*-3,7-dimethyl-2,6-octadien-1-ol] via geranial (**189**), into methyl geranate (**190**) in 85%–95% yield.[190] Similarly farnesol, benzyl, cinnamyl, and furfuryl alcohols have been converted into their methyl esters in 91%–95% yield.[190]



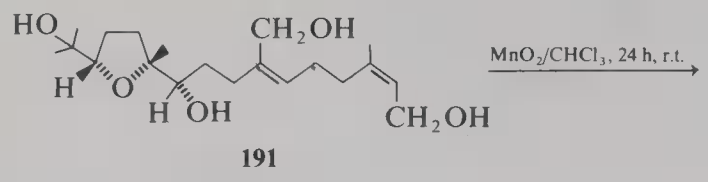
188 **189** 98%



190 85–95%

3.3.2. Selective Oxidations of Terpenes

A selectivity was observed in the manganese dioxide oxidation of a linear, polyoxygenated diterpene alcohol. Thus, on treatment with the reagent in chloroform, geranylnerol (**191**) gave the monoaldehyde **192** and a preponderance of the terminal α,β-unsaturated dialdehyde (**193a**) (15%), believed to exist in equilibrium with an aldehydic hemiacetal (**193b**) (NMR evidence[220]) and all-*trans*-geranylgeraniols[222] were oxidized with manganese dioxide to the corresponding aldehydes. Selectivity in the manganese dioxide oxidation of terpene alcohols is further illustrated by numerous applications. For example, the unsaturated diterpene agathadiol (**194**) was converted by the reagent into the conjugate



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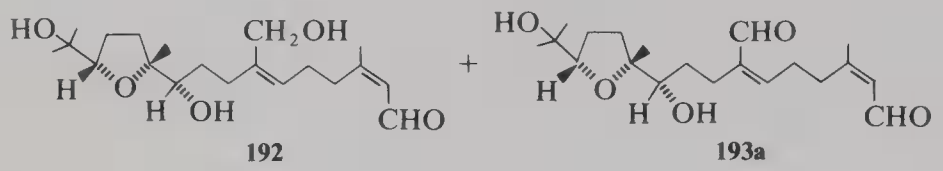
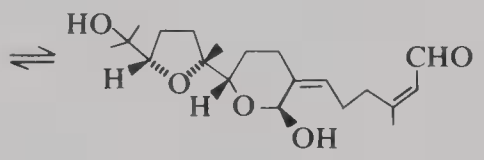
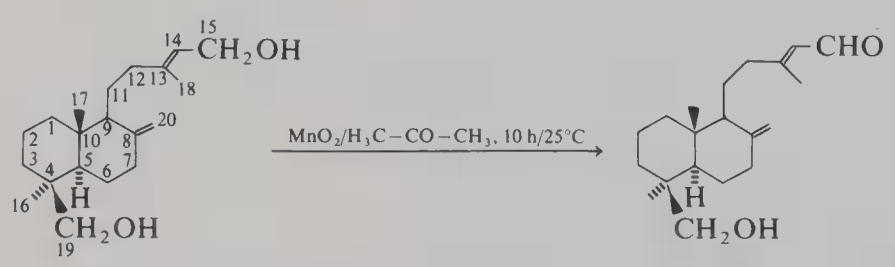


192 **193a**

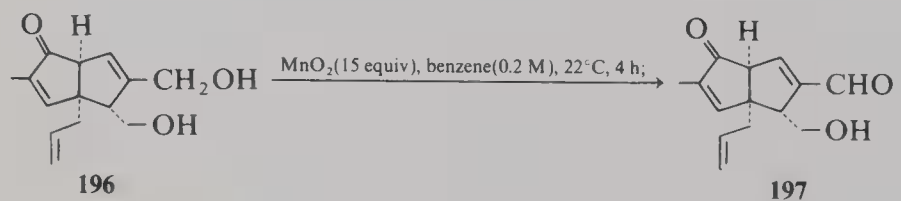


193b

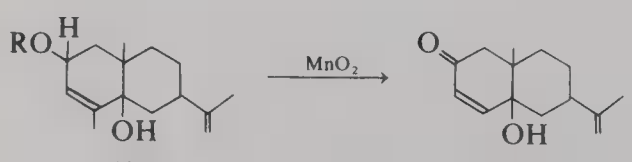
aldol (**195**, agathalal) in 90% yield[223]; similarly, sesquiterpene diol (**196**) was converted into an aldol **197**[224]; the diol **198** into a ketone **199**[225]; and the diol **200** into tricyclic enone **201**.[226] Oxidation of dimethyl shellonate **202** with manganese dioxide (Attenburrow) gave a mixture, identified as the aldehyde **203**, the oxo ether **204**, and the oxo compound **205**. The diol (monoacetate) **206** was converted by the reagent into the ketone **207** (e.g., synthesis of β-damascenone).[228]



194 **195**



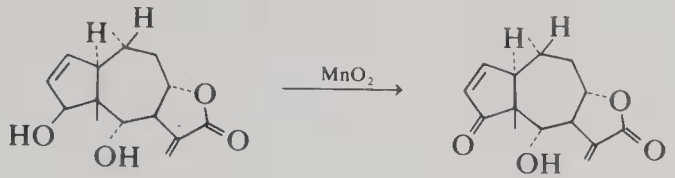
196 **197**



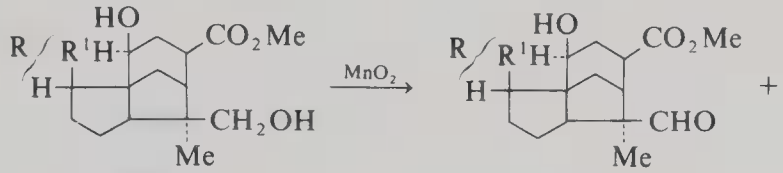
198 **199**

2α–H, R = H — 5β–OH

2β–H, R = H — 5α–OH

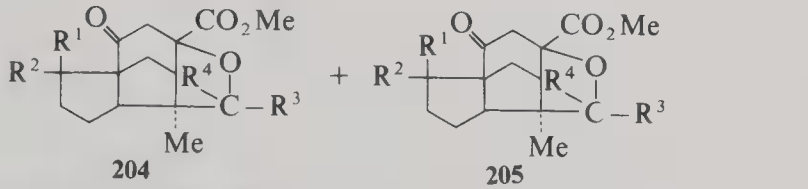


200 **201**



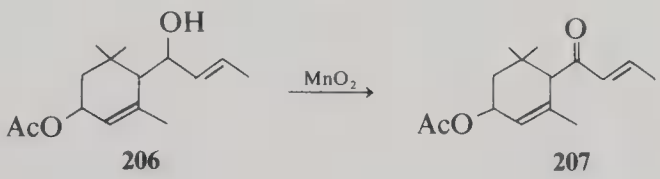
202 **203**

$R^1 = CO_2Me$



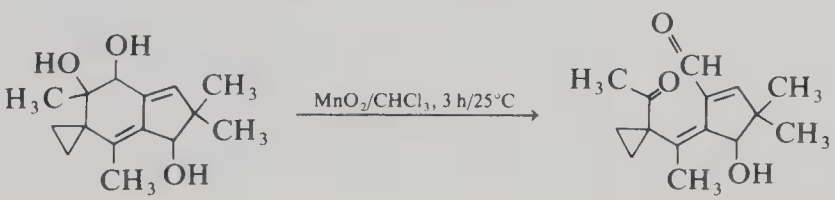
204 **205**

$R^1 = CO_2Me$, $R^2 = R^3 = R^4 = H$ $R^1 = CO_2Me$, $R^2 = R^3 = H$, $R^4 = OH$



206 **207**

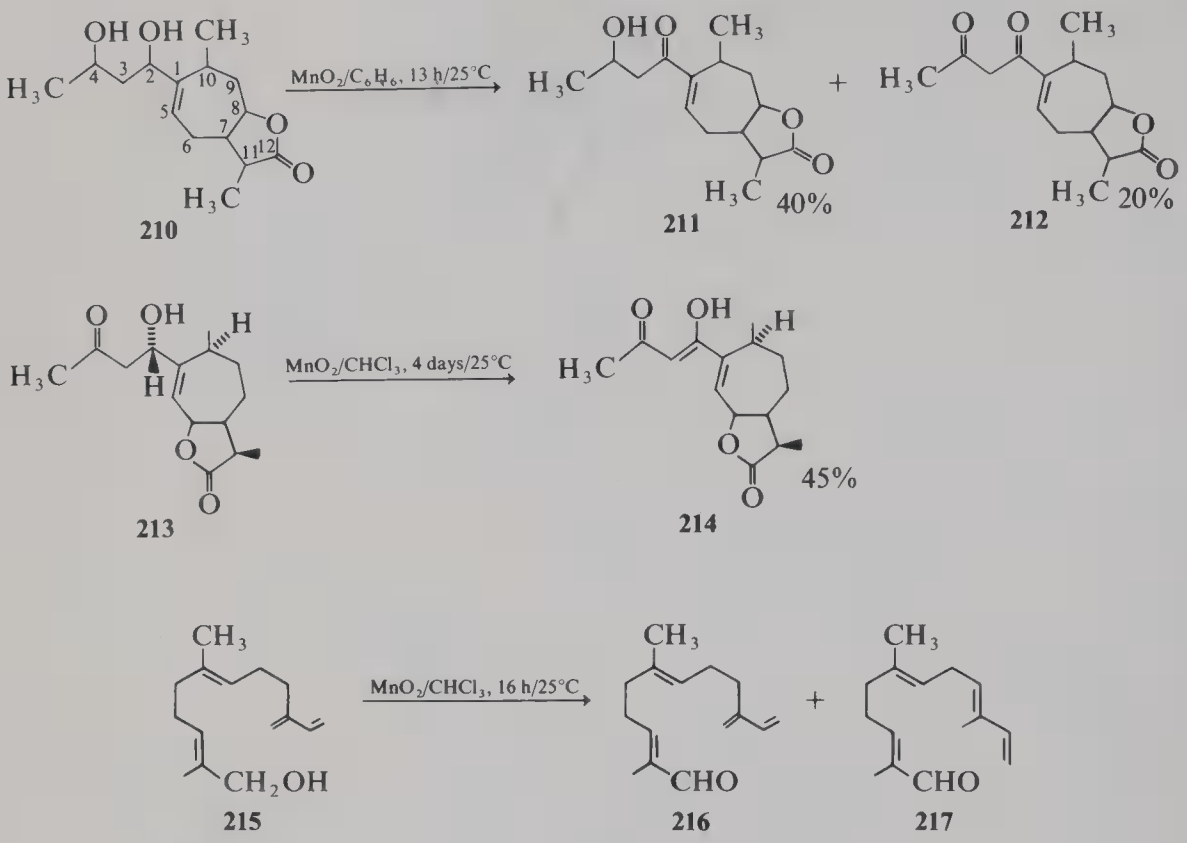
Cleavage of the sesquiterpenoid triol (**208**) was observed on treatment with active manganese dioxide; the keto-aldehyde **209** isolated was identical with the product obtained in the cleavage of **208** with sodium periodate.[229]



208 **209**

However, oxidation of diol **210** (the naturally occurring sesquiterpenoid lactone garfinin) with manganese dioxide gave a mixture containing β-ketol **211** (40% yield) and an enolizable β-diketone **212** ($\sim$20% yield).[230] In contrast, similar oxidation of the isomeric 6,7-lactone **213** produced the diene (parthemollin, **214**) in 45% yield.[231]

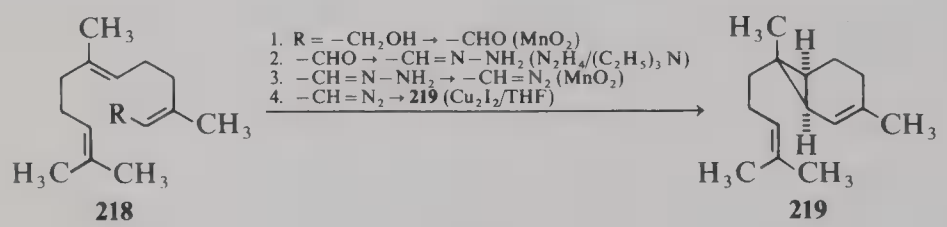
On treatment of the synthetic sesquiterpene all-*trans*-tetraene alcohol (**215**) with manganese dioxide, all-*trans*-β-sinensal **216** (2,6-dimethyl-10-methylene-2,6,11-dodecatrienal) was obtained in 68% yield; this conversion proved that β-sinensal **216**, as well as α-sinensal **217** (2,6,10-trimethyl-2,6,9,11-dodecatetraenal), isolated from Chinese orange, exist in the all-*trans* configuration.[231]



210 **211** **212** **213** **214** **215** **216** **217**

3.3.3. Synthesis of Sesquicarene

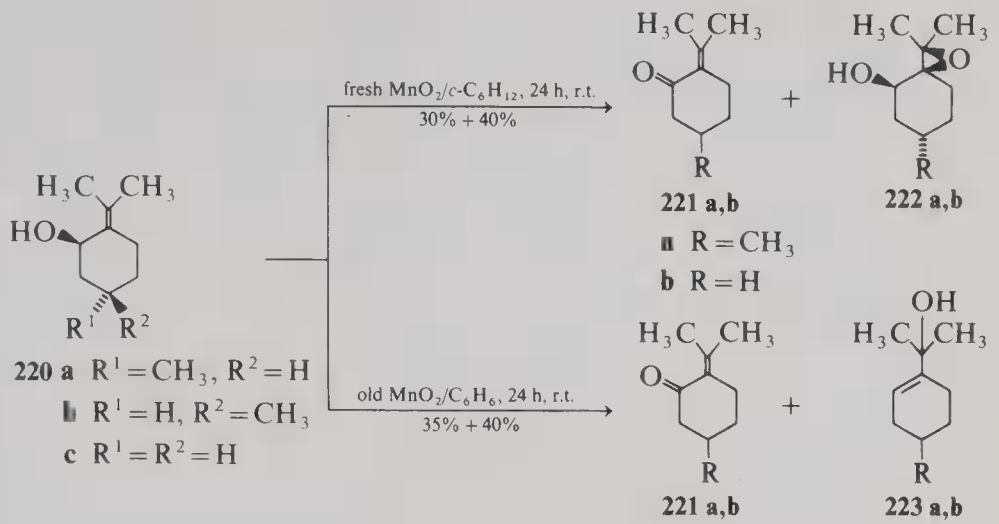
Corey and Achiwa[232] described a simple, four-step synthesis of sesquicarene (**219**) from *cis,trans*-farnesol (**218**) (R = CH_2OH) via intramolecular, diazo olefin cyclization. The alcohol **218** was oxidized to farnesol with activated manganese dioxide; this was then converted into the hydrazone, which was oxidized to the diazo compound; cyclization of the latter gave DL-sesquicarene (**219**) in 25% yield from **218**.



218 **219**

3.3.4. Rearrangement of Terpenes

An interesting, unexpected rearrangement of the allylic terpene alcohols (e.g., *trans*- and *cis*-pulegols) in the presence of the high and low activity manganese dioxide reagent has been described. Thus, treatment of the *trans*- and *cis*-alcohol mixture **220a** and **220b** (2-isopropylidene-5-methylcyclohexanol) with the fresh manganese dioxide in cyclohexane yielded (±)-pulegone (**221a**) (30% yield) and the epoxyalcohol **221b** (40% yield). However, treatment of **220a** and **220b** with the aged manganese dioxide in benzene gave, in addition to **221a**, a new isomerization product, an allylic alcohol (**223a**; 40% yield). Similar oxidation of 2-isopropylidenecyclohexanol **220c** or 2-isopropylidenecycloheptanol with manganese dioxide afforded only a little of a ketone (e.g., **221b**; 10%–20% yield); the major product was either the epoxy alcohol (e.g., **222b**) or a rearranged allylic alcohol (e.g., **223b**) depending upon the batch (activity) of the manganese dioxide. Evidently this remarkable



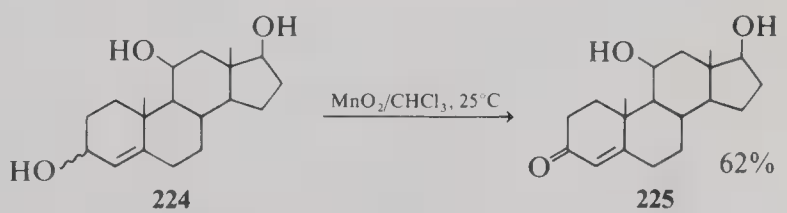
olefin epoxidation reaction depends upon the exact nature of the manganese dioxide, which is possibly a function of its age. The allylic alcohol grouping no doubt also plays a part in the reaction, since a sample of 9-octalin was recovered unchanged after stirring with manganese dioxide in benzene for several days.[233] Applications of manganese dioxide oxidation to the terpene series involve oxidation of geraniol,[28,190] homologs of geraniol and related compounds,[25,107,143–145,183,234,235] farsenol,[217,219] macrocyclic diterpenes (e.g., α- and β-4,8,13-duvatriene-1,3-diol),[236] and some naturally occurring terpenes.[237–242]

3.4. Steroids

Active manganese dioxide oxidations in the steroid field have been reviewed[21]; the mechanistic aspects of steroid oxidations in general (e.g., oxidative rearrangements) have been reported.[9,243–246] The stereochemical aspects of manganese dioxide oxidation of steroid allylic alcohols have been discussed (Section 3.1.3., e.g., compounds **42** and **44**).

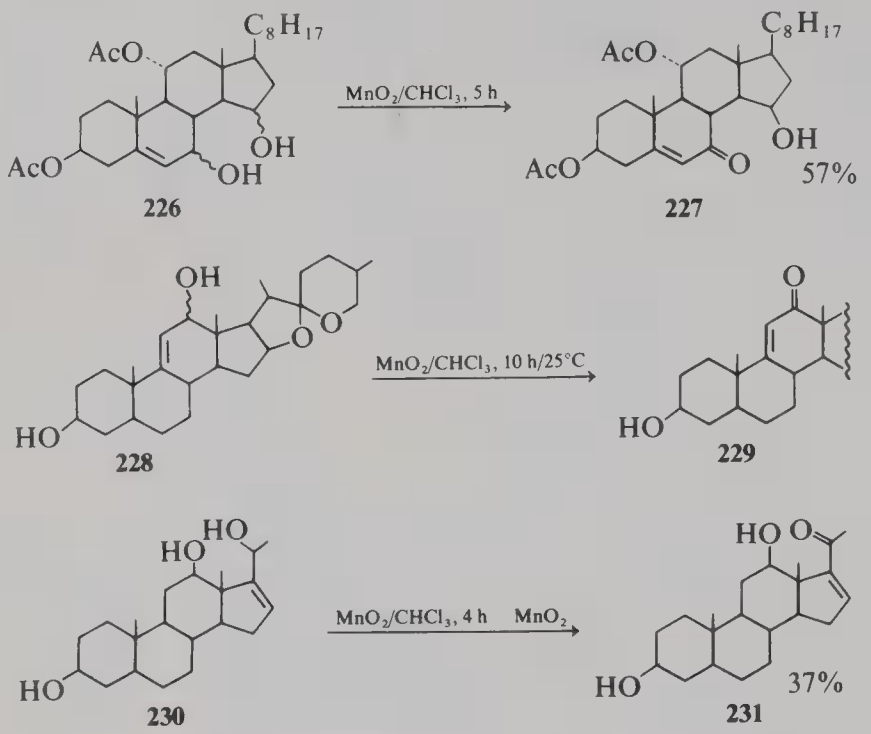
3.4.1. Oxidation of Unsaturated Steroid Alcohols in Ring A, B, C, or D

The manganese dioxide oxidation of steroid alcohols shows some unusual results; preferential oxidation of the allylic hydroxyl groups by the reagent was recognized[26,46,247] in a very early study on steroids. Subsequent work showed[248–252] that, no matter where the unsaturated alcoholic group was located in the steroid molecule (ring A, B, C, or D), it was oxidized first by the reagent, thus giving rise to selectivity in oxidation.[253,254] Thus, a mixture of the 3α-, 11β-, 17β- and 3β-, 11β-, 17β-triols **224** (obtained on reduction of andrenosterone with lithium alanate) was oxidized with manganese dioxide to give 11β-hydroxytestosterone (**225**) in 62% yield; the saturated 17-ol remained intact.[26] Similarly, the steroid alcohol (**226**,



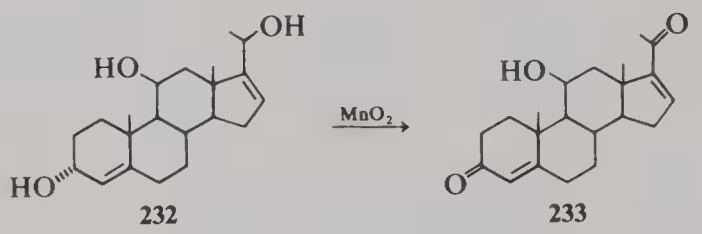
containing an allylic hydroxyl group on ring B) was oxidized with manganese dioxide in chloroform, to give cholest-5-ene-3β, 11α, 15β-triol-7-one-3β, 11α-diacetate (**227**) (57% yield),[255] and Δ^7-androstene-3β, 6α-diol was converted into the conjugate enone (87% yield).[253] The steroid alcohol **228** containing an allylic hydroxyl group on ring C has also

been oxidized to enone **229**.[247] 3β, 12β, 20-Trihydroxy-5α-Δ^{16}-pregnane **230** readily converted into enone **231**.[249]



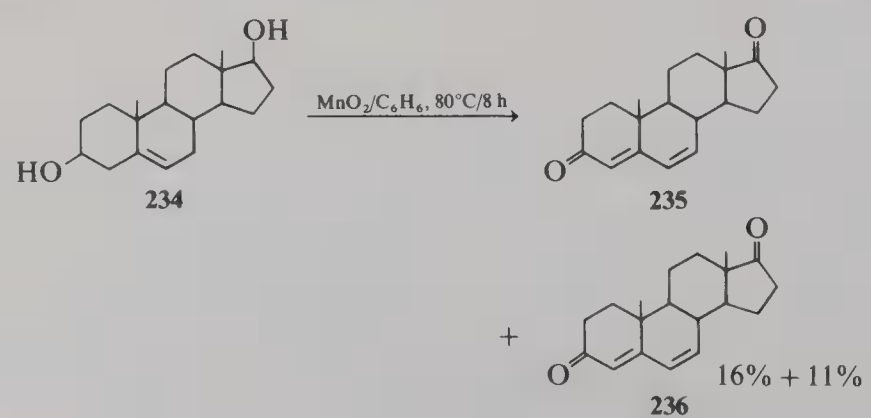
226 **227** **228** **229** **230** **231**

Allylic hydroxyl groups present in both rings (for example, rings A and B,[256] or rings A and D[257]) have similarly been oxidized to the corresponding α,β-unsaturated dienones, even at room temperature (e.g., conversion of **232** into **233**).[257] At elevated temperatures



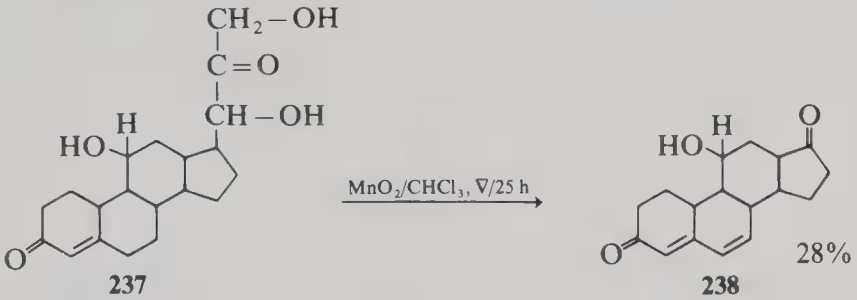
232 **233**

(70–120°C), manganese dioxide reacts vigorously and loses much of its selectivity; oxidation of unsaturated alcohols is often accompanied by dehydrogenation. For example, α,β- and β,γ-unsaturated steroid (cholesterol and other homoallylic Δ^5-3-hydroxysteroids) are converted into conjugate dienones when treated with manganese dioxide in refluxing chloroform or benzene[26,46,247,258]; the Δ^5-3-hydroxysteroid (**234**) affords the mixed dehydrogenation products, e.g., $\Delta^{4,6}$-enone (**235**) and $\Delta^{4,6}$-dienone (**236**) in low to moderate yield.[26]



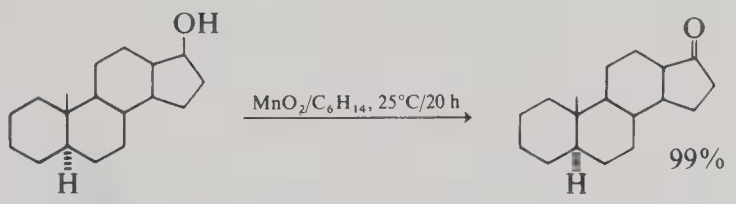
234 **235** **236**

It has been pointed out[26,247,258,259] that manganese dioxide can be used (in refluxing chloroform) to cleave the 1,3-dihydroxyacetone and 17,20-glycol side chains of Δ^4-3-keto steroids (the cortisone family); this is demonstrated by the conversion of 11-hydroxy cortisone (**237**) into 3,17-dienone (**238**) in 28% yield[49,50]; in neutral media, the reaction is accompanied by dehydrogenation.

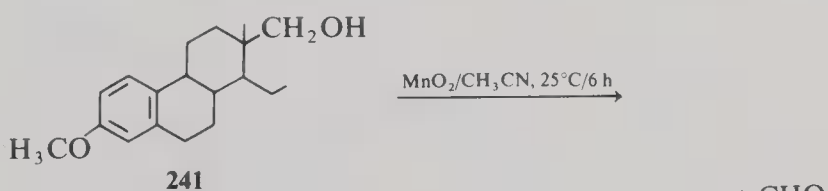


237 **238**

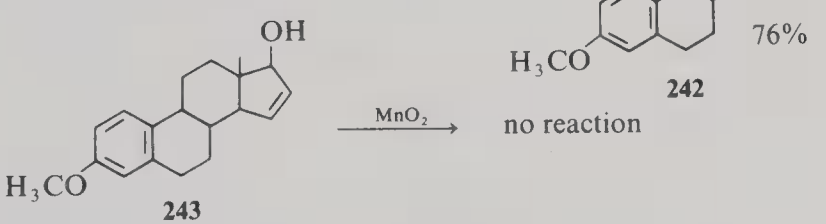
Similar dehydrogenations in refluxing solvents have been observed with other steroid alcohols.[47,248,258–260] Harrison[47] reported that, when sufficient fresh reagent and purified solvents are used, both primary and secondary saturated alcohols can be oxidized in high yield, but slowly. Thus, 100 mg of 5α-androstan-17β-ol (**239**), stirred at room temperature in hexane (or acetonitrile) with manganese dioxide (2 g) for 20 h, gave pure 5α-androstan-17-one (**240**) in practically quantitative yield[47]; similarly, the estrone primary alcohol **241** was oxidized to estrone aldehyde **242** in 76% yield.[47] Surprisingly, however, estrone **243** was unaffected by the oxidant.[261]



239 **240**



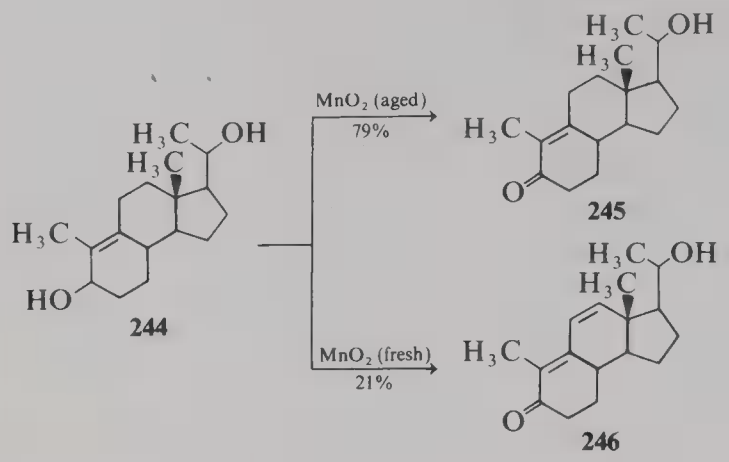
241 **242**



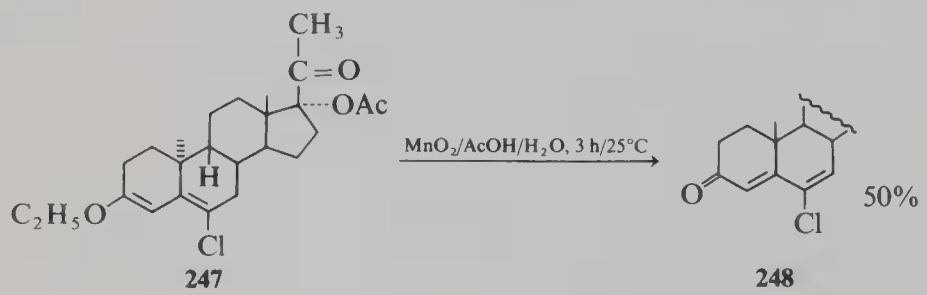
243

The activity of manganese dioxide seems to be an important factor in the oxidation of the steroid alcohols. For example, treatment of des-A-9-pregnene-5β, 20β-diol (**244**) with aged reagent gave 20β-hydroxy-des-A-9-pregnene-5-one (**245**) in 79% yield; however, fresh oxidant gave the overoxidation product (**246**; 20β-hydroxy-des-A-9,11-pregnadien-5-one) in 21% yield.[251]

A procedure involving hydrolytic oxidation by manganese dioxide (in a polar solvent) of a halo-substituted steroid enol ether has been reported. Treatment of 6-chloro-3-ethoxy-17α-



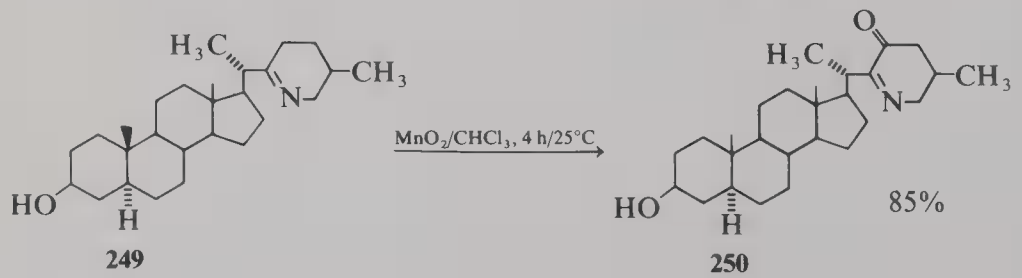
hydroxy-9β, 10α-pregna-3,5-dien-20-one 17-acetate (**247**) with manganese dioxide in aqueous acetic acid at room temperature gave 6-chloro-17α-hydroxy-9β, 10α-pregna-4,6-diene-3,20-dione 17-acetate (**248**) in 50% yield.[262] A 16α-hydroxy-*cis*-6β-fluoro substituted corticoidal steroid has been oxidized with manganese dioxide in ethyl acetate to give the isomerically pure 16-keto-*cis* derivative in 87% yield.[263]



3.4.2. Steroidal Alkaloids

C_{27}-steroidal alkaloids of the 22,26-epiminocholestane type are of particular interest with regard to their biogenetic correlation to other Solanum alkaloid groups[264] which could lead, via redox reactions, to solanidanes[265] as well as to spirosolanes.[266]

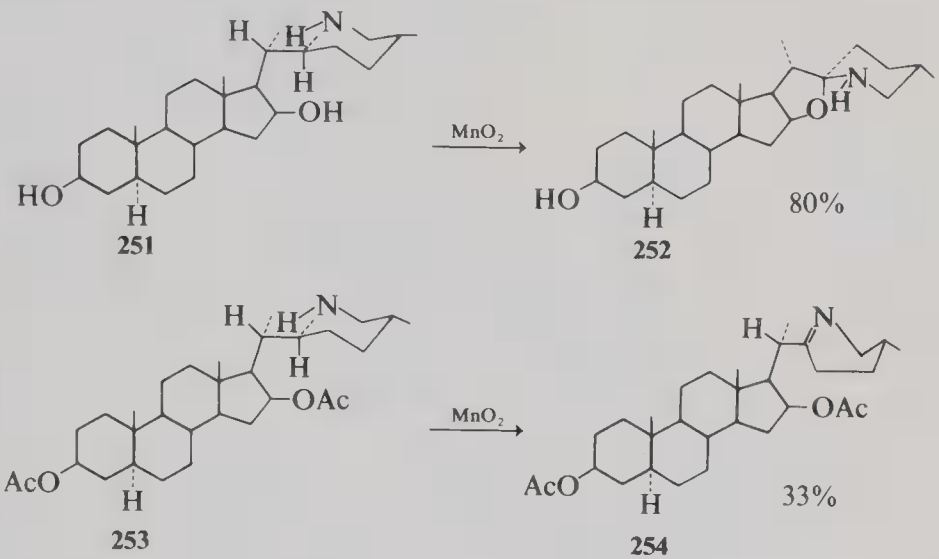
3.4.2a. Oxidation of an Active Methylene Group in Solacongestidine. An interesting case of oxidation of an activated methylene group by active manganese dioxide to give a carbonyl compound was reported.[261] Treatment of solacongestidine (**249**) in chloroform with the oxidant (ACC) gave 23-oxosolacongestidine (**250**) in high yield; **250**, on brief refluxing with



acetic anhydride, was readily aromatized to a pyridine derivative via elimination of the 23-oxo group to give 3β-acetoxy-20[2-(5-methylpyridyl)]-5α-pregnene.[266]

3.4.2b. Active Manganese Dioxide: A Reagent for a Biomimetic Cyclization. Treatment of 16β-hydroxylated 22.26-epiminocholestanes, e.g., dihydrotomatidine A (**251**), with active

dioxide (Attenburrow) leads directly to a biogenetically important cyclization, to afford the corresponding spirosolane alkaloids, e.g., tomatidine (**252**) (80% yield).[267] The mechanism apparently proceeds via a primary oxidation of the piperidine ring in **251** to the corresponding azomethine, followed by spontaneous and stereospecific cyclization to the spirosolane alkaloid (**252**); this view is supported by the conversion of the 3.16-diacetylated epiminocholestane (**253**) with MnO_2 into the azomethine (**254**) (33% yield).[267] Active manganese dioxide has been applied in structural studies, particularly for detecting the presence of allylic groups in steroids[268,269] and some natural products.[232,241,242]



251 **252** **253** **254**

3.5. Alkaloids

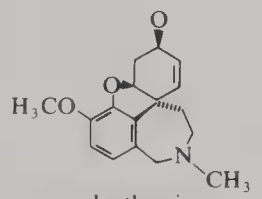
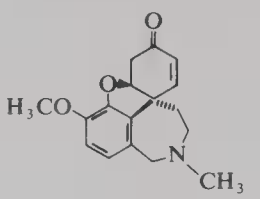
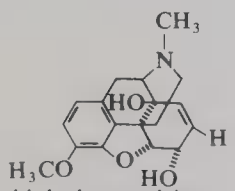
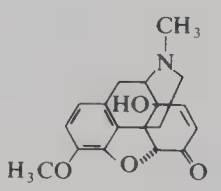
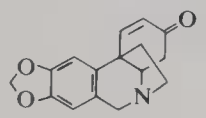
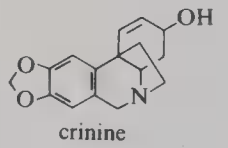
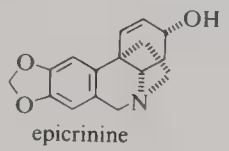
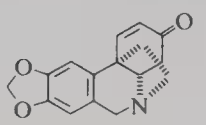
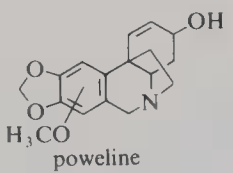
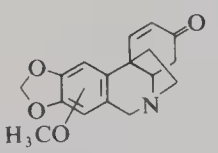
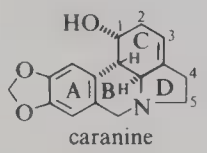
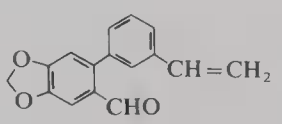
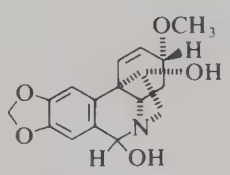
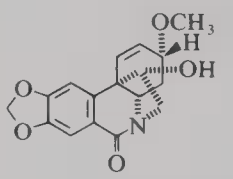
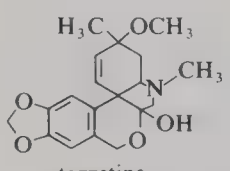
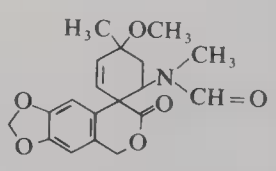
A stereochemical effect in active manganese dioxide oxidation has been observed in the series of alkaloids[87,89] containing either allylic[87] or saturated[89] hydroxyl groups. Based on the favored oxidation of the allylic hydroxy group by the reagent, the correct structures were assigned to the natural alkaloids buphanamine (**47**) and epibuphanamine (**45**). Thus, manganese dioxide oxidation is a particularly useful analytical tool in elucidating the structure of the complex alkaloids[270–286] summarized in Table III.

A direct insertion of oxygen into an allylic alcohol system has been observed following the treatment of codeine with manganese dioxide, to give 14-hydroxycodeinone in 30% yield[271,287] (see Table III). A direct allylic oxidation has also been observed in other systems (e.g., manganese dioxide oxidation of cyclohexene to cyclohexenone)[288] or in oxidation of vitamin A_1 derivatives,[289] or in an oxidative rearrangement of a bicyclic alcohol.[73]

3.6. Benzylic Alcohols

The oxidation of benzylic alcohols and structurally related alcohols by manganese dioxide is well established. Although the oxidant was originally regarded[13,26] as ineffective for conversion of benzyl alcohol into benzaldehyde, subsequent studies showed[28,289] that the more active forms of the dioxide can achieve this in high yield. Thus, manganese dioxide has become widely used in the synthesis of aromatic[27] or heterocyclic[152,153] ketones and aldehydes from substituted and unsubstituted benzylalcohols. The oxidation of benzylic alcohols with manganese dioxide generally stops at the carbonyl stage; however, further oxidation to acids (or lactones), either in neutral media[290,291] or in hot, aqueous solution,[292] have been reported, e.g., conversion **109** → **110**.[154]

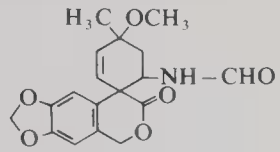
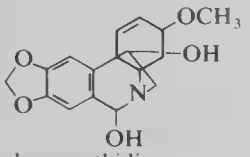
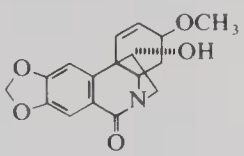
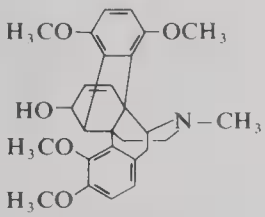
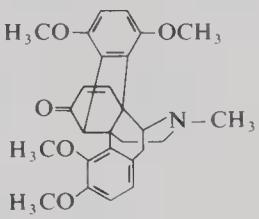
TABLE III. Manganese Dioxide Oxidation for Structural Elucidation of Alkaloids

Alkaloid	Oxidation product[a]	Yield (%)	Reference
 galanthamine		80	270
 14- hydroxycodeine		86	271
	 crinine	78	274–277
 epicrinine		75	278
 poweline		90	274–277
 caranine		30	279[b]
 6-hydroxycrinamine		66	280
 tazzetine			281–283

[a] Absence of reaction is indicated by a line in the product column.
[b] Product of acid hydrolysis.

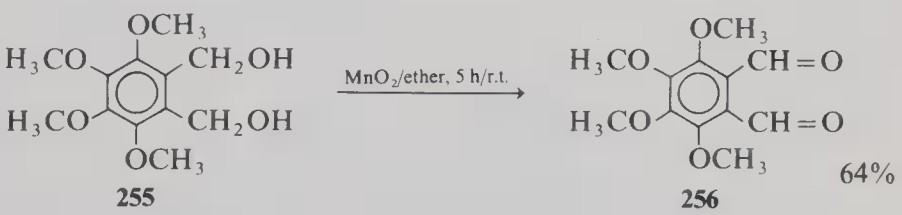
Table continued

TABLE III. *(Continued)*

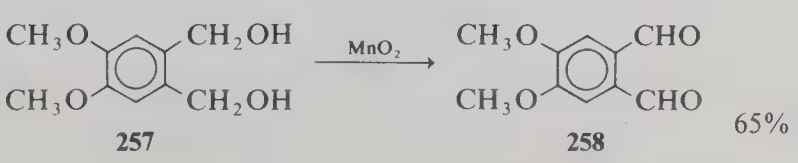
Alkaloid	Oxidation product[a]	Yield (%)	Reference
		50	
 haemanthidine		72	284
 flavothebaone (thebaine)		78	285
45	**46** (see page 133)	60	87
47	—	—	87
48	**49**	70	89

3.6.1. Oxidation of Phthalyl Alcohols

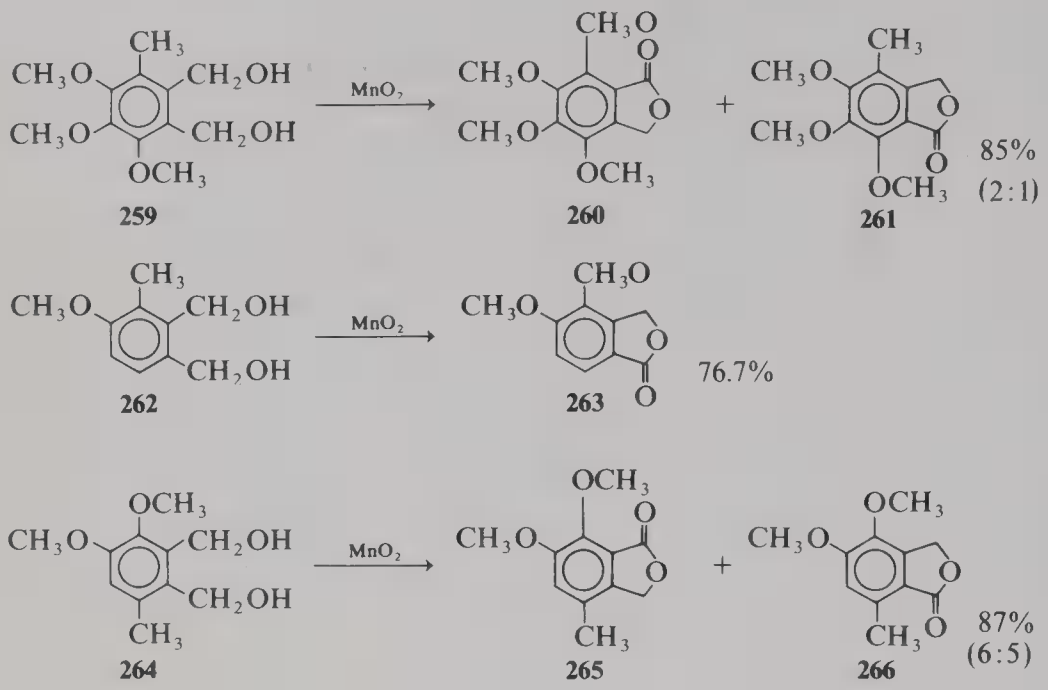
The 3,4,5,6-tetramethoxy-phthalyl alcohol (**255**) was oxidized with manganese dioxide to the phthalaldehyde **256** in 64% yield.[293] However, as recently found by Bhattacharjee and Popp,[294] oxidation of the phthalyl alcohols with manganese dioxide could form either phthalaldehydes or phthalides, depending on the position of the ring substituents. Thus, whereas 4,5-dimethoxy-phthalyl alcohol (**257**) was oxidized with manganese dioxide (methylene chloride, 25°C) to the phthalaldehyde **258** (65%), the phthalyl alcohol **259** (4,5,6-trimethoxy-3-methylphthalalcohol) on similar treatment, gave a mixture of lactones, e.g., 7-methyl-4,5,6-trimethoxyphthalide (**260**) and 4-methyl-5,6,7-trimethoxyphthalide (**261**) (2:1 ratio) (85% yield). Similarly **262** gave **263** (76%) and **264** gave **265** and **266** (6:5 ratio)



255 **256**



257 **258**

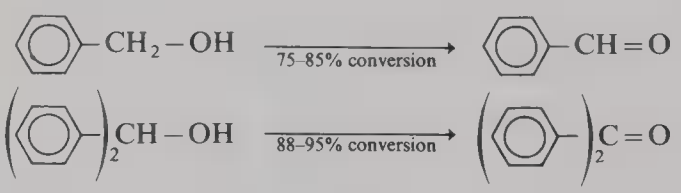


259 260 261 262 263 264 265 266

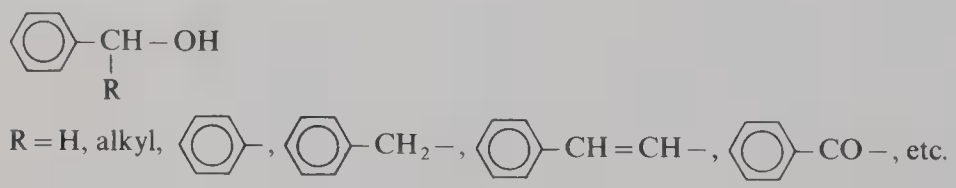
(87% yield).[294] Good conversions of α-substituted benzylic alcohols (e.g., diphenylmethanol, 1,1′-naphthylethanol, tetrahydrophenanthren-1-ol),[27,295] and other substituted benzylic[27,287,295–298] or naphthylic[27,295,296] alcohols have been reported. It is generally accepted[27,29,33,37] that a free-radical intermediate is partially involved in manganese dioxide oxidation of benzylic alcohols.

3.6.2. Oxidation of Benzenemethanols

The oxidation of a variety of benzenemethanols with active manganese dioxide was studied by Pratt and Van der Castle.[27] After refluxing the reagent with benzene until water no longer collected in a Dean–Stark trap, the alcohol was added, and refluxing was continued until evolution of water ceased. The results may be summarized as follows:



In a study of the oxidation of alcohols of the type



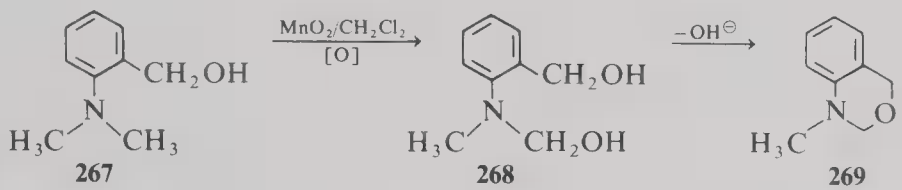
the authors[27] explained the difference in the rates of oxidation of the α-substituted benzyl alcohols as due to the steric effect of substituents capable of preventing rapid adsorption of the alcohol on the surface of the active manganese dioxide, and the effect of the stabilization of free radicals formed in the first stage of the oxidation.

Among the various types of active manganese dioxide, γ-manganese dioxide is considered (Refs. 19, and 37, and this text) to be most reactive form and also a mild oxidant

(Ref. 38, and this text). Recently Crotti and Macchina found[762] that the reagent can oxidize benzylic-type alcohols beyond the arylalkyl aldehyde stage and with degradation of a side chain (to give carboxylic acid). The authors report an unprecedented oxidative degradation or arylethanols and arylacetic acids by means of γ-manganese dioxide as summerized in Table IV.

The oxidation of benzylic alcohols to the corresponding aldehydes by active MnO_2 or a ready oxidation of dialkyl anilines to a variety of products by the same reagent is well known (Ref. 19 and this text). Recently Kienzle found[763] that when both structural features are present in a benzene ring in *ortho* position to one another (for example, *o*-dimethyl aminobenzyl alcohol, e.g., **267**) the predominant product of MnO_2 oxidation is 1,4-dihydro-1-methyl-2H-3, 1-benzoxazine (e.g., **269**) in the range of 80% (possible conversion of **267** → **268** → **269** is given below). None of these *N*-alkylated 1,4-dihydro-2H-3, 1-benzoxazine has been reported in the literature.

Thus, when 2-(dimethylamino)-3-methylbenzyl alcohol (analog of **267**, Table V) is stirred in CH_2Cl_2 solution with a tenfold amount (by weight) of active MnO_2 (Merck) 1, 4-dihydro-1, 8-dimethyl-2H-3, 1-benzoxazine (analog of **269**, Table V) is formed in an exothermic reaction within 10–15 min (84% yield); a small amount of aldehyde is also formed. Table V summarizes these important oxidative transformations of *o*-dialkylamino benzyl alcohols by active MnO_2.



267 **268** **269**

3.6.3. Favored Oxidation of Benzylic Hydroxyl Groups

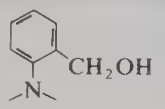
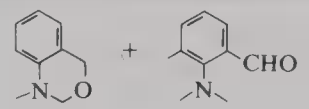
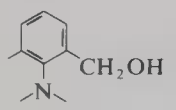
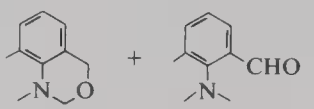
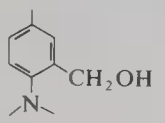
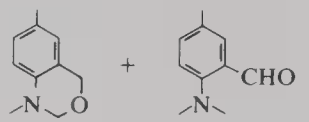
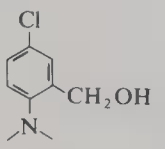
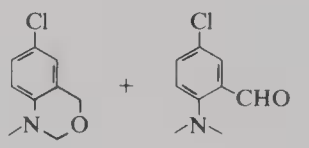
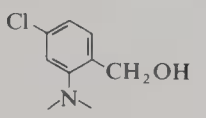
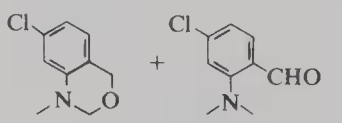
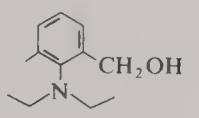
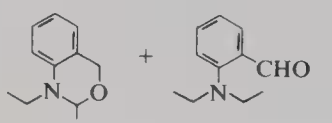
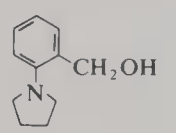
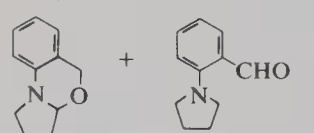
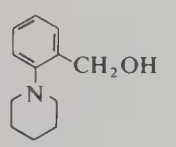
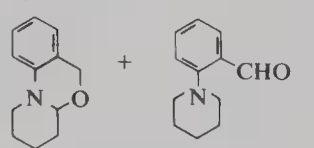
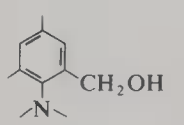
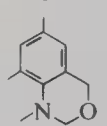
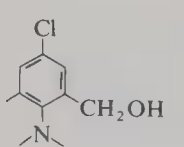
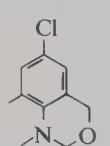
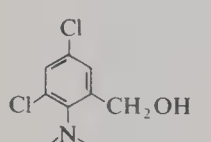
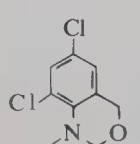
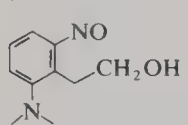
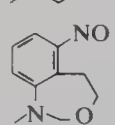
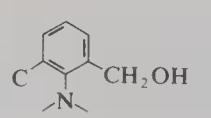
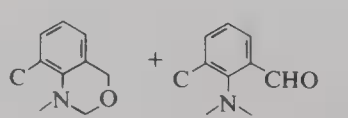
Selective oxidation of benzylic-type alcohols with manganese dioxide has recently been reported,[300] e.g., conversions of **270** → **271**,[301] **272** → **273**,[302] or **274** → **275**[302] without affecting of the epoxide ring. Similarly flavan-3,4-diol (**276**) was converted to the dihydroflavonol

TABLE IV. Products Obtained by Oxidation of p-$XC_6H_4CH_2R$ with Active γ-Manganese Dioxide[a,b]

Reactant, p-$XC_6H_4CH_2R$	Percent product		Percent recovered starting material
	p-XC_6H_4CHO	p-XC_6H_4COOH	
($X = OCH_3$; $R = CHO$)	50	50	
($X = H$; $R = CH_2OH$)	22	23	53[c]
($X = H$; $R = COOH$)	21	37	42
($X = CH_3$; $R = CH_2OH$)	17	45	28[d]
($X = CH_3$; $R = COOH$)	3	55	42
($X = OCH_3$; $R = CH_2OH$)	31	27	42
($X = OCH_3$; $R = COOH$)	22	70	8
($X = H$; $R = OH$)		100	
($X = H$; $R = CH_2CH_2OH$)	9	11	54[e]

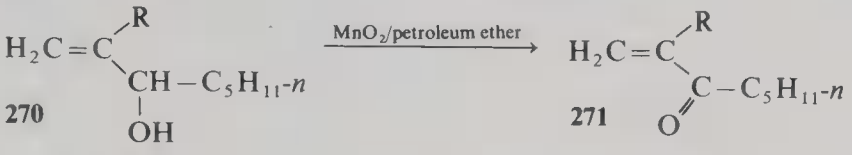
[b] The percentages (weight percent) are calculated by means of ^{1}HNMR spectroscopic analysis of the crude reaction product (reaction time 24 h).
[c] Phenylacetic acid was also present (2%).
[d] *p*-Tolylacetic acid was also present (10%).
[e] $PhCH_2CH_2COOH$ was also present (26%).

TABLE V. Oxidation of *ortho*-Dialkylaminobenzyl Alcohols with Active MnO_2[a]

Substrate	Product	Ratio oxazine/aldehyde
		2/2
		84/1
		3/2
		4/3
		–/1
		5/2
		12/1
		9/1
		1/–
		1/–
		1/–
		1/–
		24/1

[a] Reference 763.

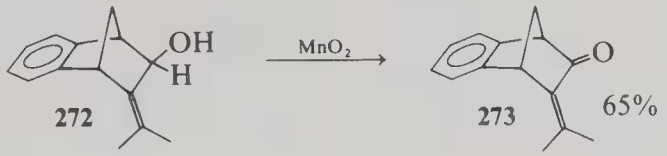
(**277**) with the reagent; in this case no cleavage of the carbon–carbon bond took place, thus indicating selective oxidation of 4-ol.[303]



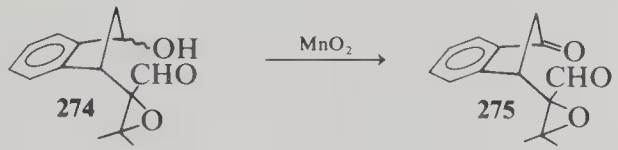
270 **271**

a R = CH_3 **a** 74%

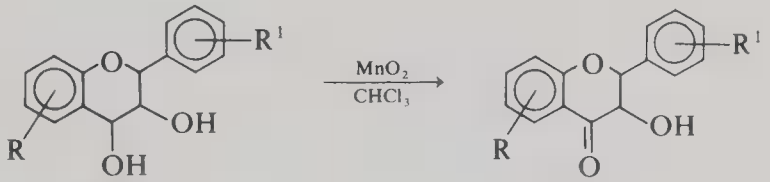
b R = H **b** 70%



272 **273**



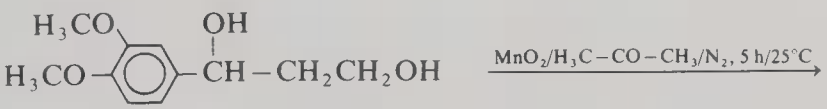
274 **275**



276 **277**

R = R^1 = H

Selective oxidation of a benzylic, secondary alcohol group without attack on saturated primary alcohol groups has been demonstrated. Treatment of 1-(3,4-dimethoxyphenyl)-1,3-propanediol (**278**) with manganese dioxide under nitrogen gave the 1-keto derivative **279** in 94% yield; however. oxidative degradation of the side chain was observed in a similar oxidation of 1-(3,4-dimethoxyphenyl)-glycerol (**280**) to give veratraldehyde (**281**) in 99% yield.[304]



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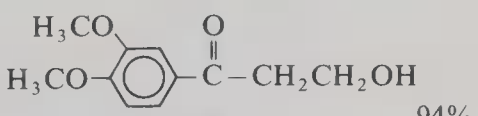
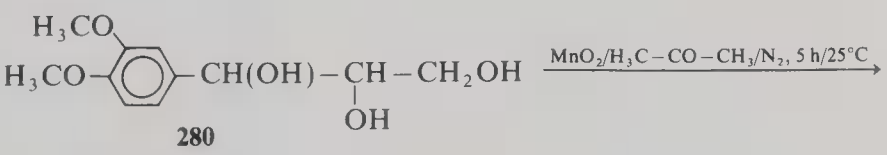


279 94%



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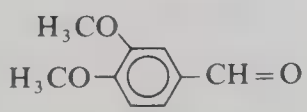
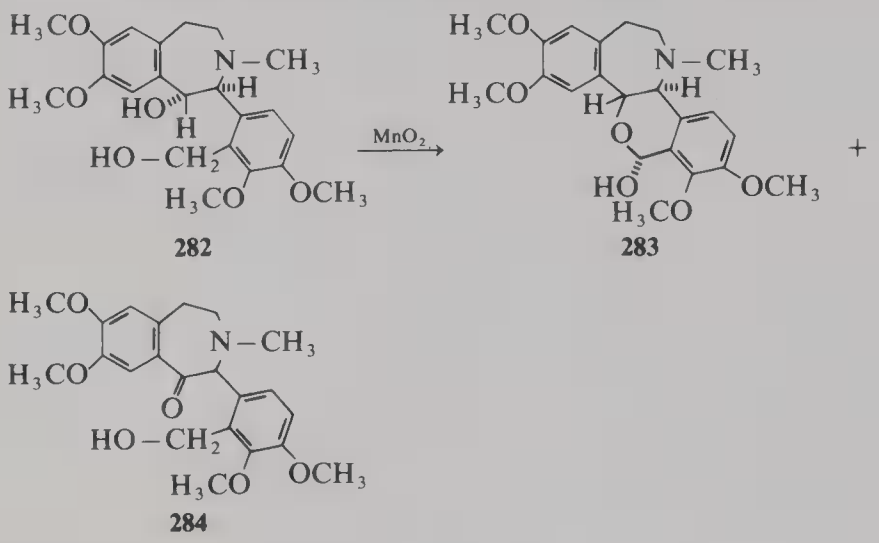
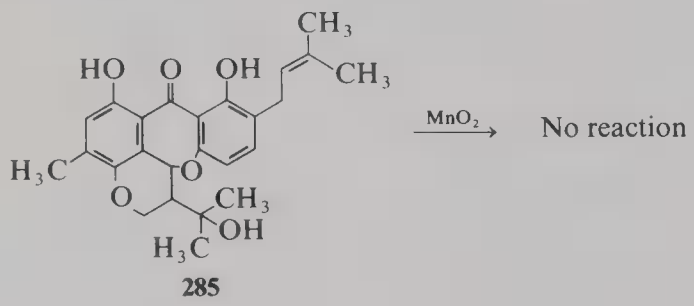


281

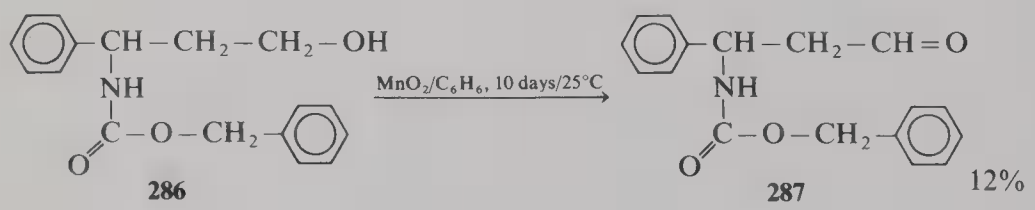
In contrast, manganese dioxide oxidation of the alkaloid diol **282** gave a mixture containing mainly a cyclic (hemiacetal) ether **283** (alkaloid alpinigenine) and some ketol **284**.[305] The structure of the phenolic, optically active metabolite arugosin C (**285**; a dibenzo[b,e]-

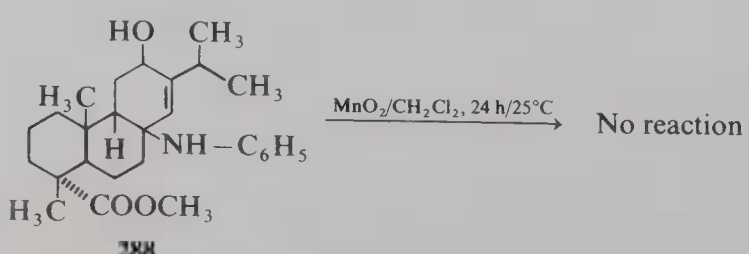


oxepin) was supported, among other factors, by the failure of **285** to be oxidized with active manganese dioxide, a reagent which oxidizes benzylic secondary alcohols.[306]

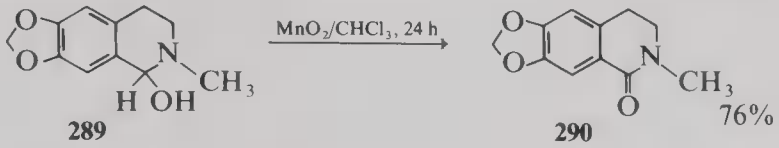


Oxidations of benzyl-substituted β-aminoalcohols with manganese dioxide produce sensitive β-aminoaldehydes in low yield. Thus, treatment of *N*-benzyloxycarbonyl-3-amino-3-phenylpropanol (**286**) with manganese dioxide gave the corresponding β-aminoaldehyde (**287**) in 10%–12% yield (isolated as 2,4-dinitrophenylhydrazone).[307] In contrast, however, the aminoalcohol **288** failed to undergo manganese dioxide oxidation.[308]



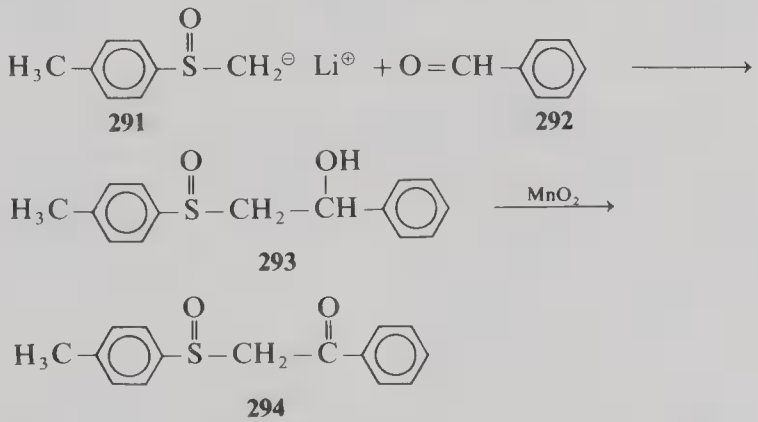


As mentioned in Section 3.5, some natural *N*-methyl aminoalcohols, e.g., the alkaloids tazettine or dihydrotazettine[281–283] or derivatives of tazettine,[283] have been selectively oxidized with manganese dioxide to give *N*-methylamide derivatives (see Section 3.5, Table III); however, aminoalcohol **289** (alkaloid hydrastinine) was converted by manganese dioxide into the corresponding lactam (**290**) in 76% yield.[287]



289 **290**

Treatment of a benzylic alcohol [1-(1,3-dioxolan-2-yl)-3-hydroxy-3-(3,4,5-trimethoxyphenyl)-propane] in refluxing benzene with manganese dioxide (2 h) gave a ketone [1-(1,3-dioxolan-2-yl)-3-oxo-(3,4,5-trimethoxyphenyl)-propane] in 87% yield.[310] Synthesis of ω-(p-tolylsulfinyl)-acetophenone (**294**) involved a manganese dioxide oxidation of 2-hydroxy-2-phenylethyl *p*-tolyl-sufinyl carbanion (**291**) with benzaldehyde (**292**).[311]



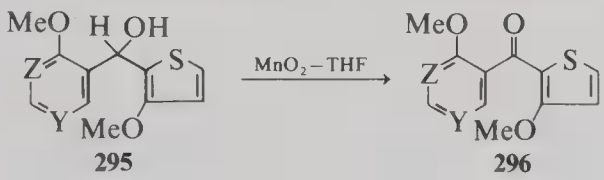
291 **292**

293

294

Active manganese dioxide was the reagent of choice for the oxidation of the isomeric adducts, following the condensation of 1,2,3,4- and 1,2,3,8-tetramethylcyclooctatetraenes with *N*-phenyltriazolinedione[312]; similar isomeric adducts of the dimethylcyclooctatetraene derivatives were also oxidized with manganese dioxide.[313]

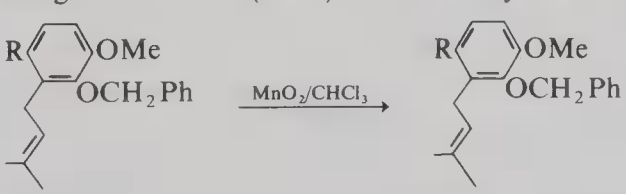
A series of secondary alcohols, e.g., **295**, have been successfully oxidized to the corresponding ketones **296** with active MnO_2 in tetrahydrofuran; this constitutes a convenient synthesis of thioxanthones having two heteroaromatic rings.[744] Recently, the



295 **296**

Y	Z
CH	N
N	CH

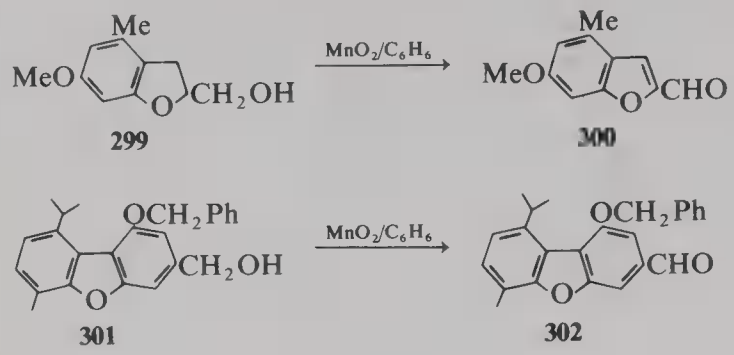
deuterio-benzyl alcohol (**297**) was converted to the deterio-aldehyde **298** by active MnO_2 in 80% yield.[746] Active manganese dioxide (ACC)[25] has recently been used for conversion of



297 **298**

R = CHDOH R = CDO

the benzofuran alcohol (**299**) into the aldehyde **300**[747] and the dibenzofuran alcohol (**301**) into the aldehyde **302**.[748]



3.6.4. Oxidation in the Vitamin D Series

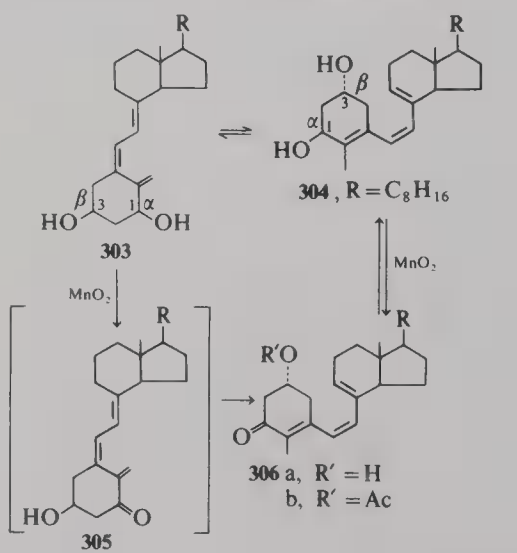
1α,25-Dihydroxyvitamin D_3 (**303**) ($C_{25}-OH$), is a natural hormone,[314,315] inducing the formation of calcium binding proteins, responsible for the calcium transport and its mobilization in the body. 1α-hydroxyvitamin D_3 (**303**) was oxidized with freshly prepared active manganese dioxide in ether resulting in the ketone **306**. Oxidation of 1α-hydroxyprevitamin D_3 (**304**) with an active manganese dioxide resulted also in 1-ketoprevitamin D_3 (**306**). This oxidation, however, proceeded at a faster rate than the corresponding oxidation of **303** and gave the ketone in higher yield.

The formation of 1-ketoprevitamine (**306**) instead of 1-ketovitamin **305** implied that the thermal equilibrium **306** ⇌ **306** is totally on the side of **306**, differing thus from the equilibrium vitamin D_3 ⇌ previtamin D_3 which is predominant on the side of the vitamin. This shift in the position of the equilibrium is consistent with the increased stability due to the linearly conjugated carbonyl system present in the ketone **306**[314] (Scheme 6).

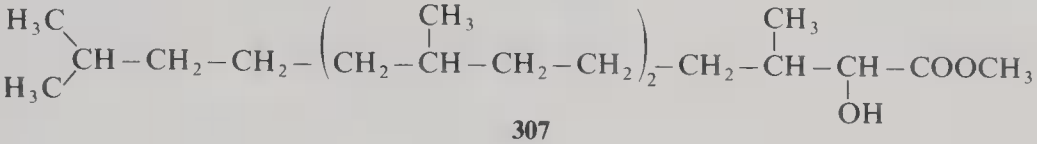
3.6.5. Conversion of α-Hydroxy Acids into Keto Acids

The literature contains a few reports on manganese dioxide oxidation of esters of α-hydroxy acids to the corresponding esters of keto acids. For example, treatment of methyl

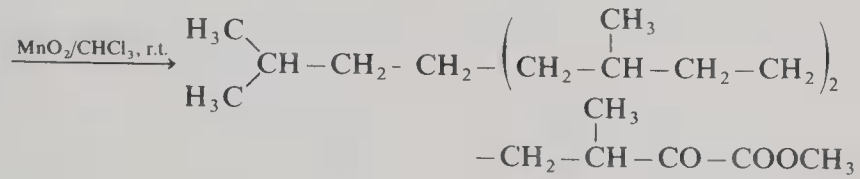
SCHEME 6



α-hydroxyphytanate (**307**), methyl α-hydroxy-3,7,11,15-tetramethylexadecanoic acid) in chloroform with a tenfold excess of the dioxide gave the α-ketophytanate (**308**).[316] However, there is no published report on the direct conversion of an α-hydroxy acid into a keto acid

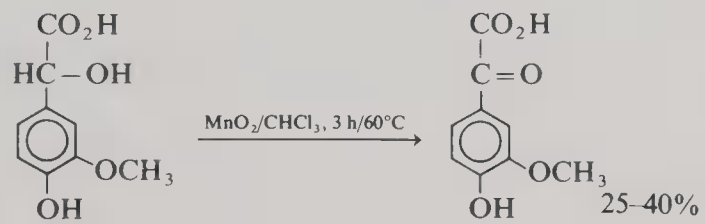


307



308

by manganese dioxide. It has been found for the first time in this laboratory that treatment of **309** (DL-4-hydroxy-3-methoxymandelic acid, "vanillylmandelic acid," a major metabolite of epinephrine, found in urine[317]) with manganese dioxide in chloroform at 55–65°C produces an important metabolic intermediate **310** (DL-4-hydroxy-3-methoxyphenylglyoxylic acid), albeit in only 25%–40% yield.[318]



309 **310**

3.7. Heterocyclic Alcohols

Heterocyclic alcohols and a series of primary and secondary alcohols in which the hydroxyl groups are activated by heteroaromatic conjugation can be selectively oxidized with manganese dioxide to the corresponding carbonyl compounds; these include xanthene-9-ol,[58,295] cumenol alcohol ethers,[320–322] 2-hydroxytetrahydropyran,[287] furan,[175,323] substituted furans,[175,324,325] benzofuran,[326] and benzodioxin[327] alcohols, amino alcohol,[328] (hydroxymethyl)pyridines: 2,3,4, or 6; disubstituted: 2,6,[329] (hydroxymethyl)-pyridine-*N*-oxide,[329] (hydroxymethyl)methylpyridines,[330] (hydroxymethyl)-pyridine derivatives,[331,332] pyrrole,[333] indole,[334–336] carbazole,[337] quinazoline[338] alcohols, 2-(hydroxymethyl)-imidazoles,[339–341] substituted imidazoles,[342,343] benzimidazole[341] alcohols, 5-(hydroxymethyl)uracil,[344] (hydroxymethyl)-1,2,4-triazole,[345] also thienyl,[148,175,346,347] and ferrocene[348–355] alcohols. A series of naturally occurring compounds containing benzylic hydroxyl groups have been successfully oxidized with manganese dioxide, e.g., indole alkaloids.[336,357] dibenzazonine alkaloids,[358] codeine,[287] codeine derivatives,[89] lycorenine,[287] and other related benzylic or heteroaromatic alcohols.[93,359–365]

Some examples of the selective oxidation by manganese dioxide of benzylic, heterocyclic, or heteroaromatic alcohols (with different degrees of activation of the hydroxyl groups) are shown in Table VI.

TABLE VI. Selective Oxidation by Manganese Dioxide of Some Benzylic, Heterocyclic, or Heteroaromatic Alcohols

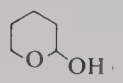
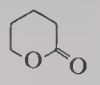
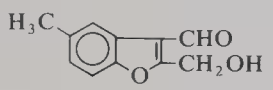
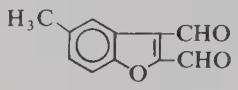
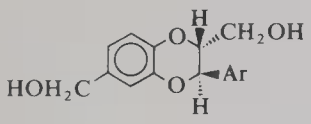
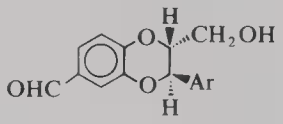
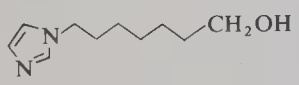
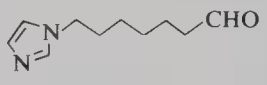
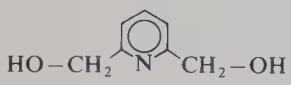
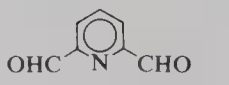
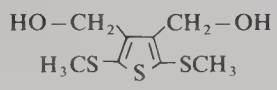
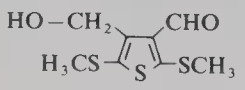
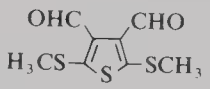
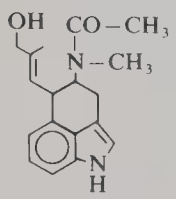
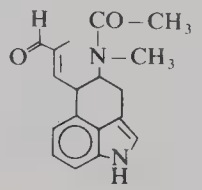
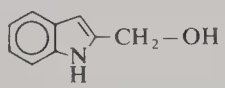
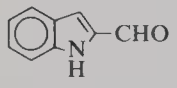
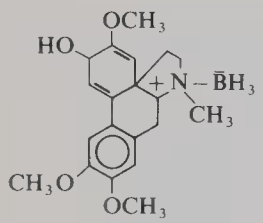
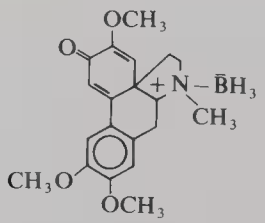
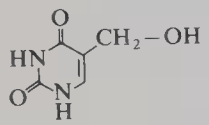
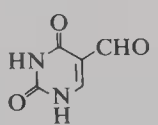
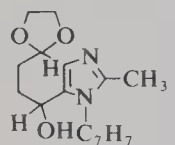
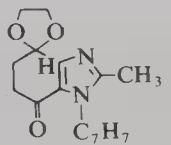
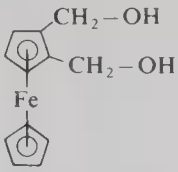
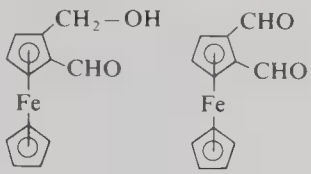
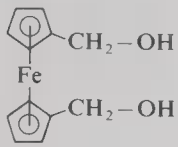
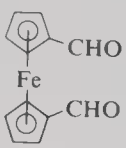
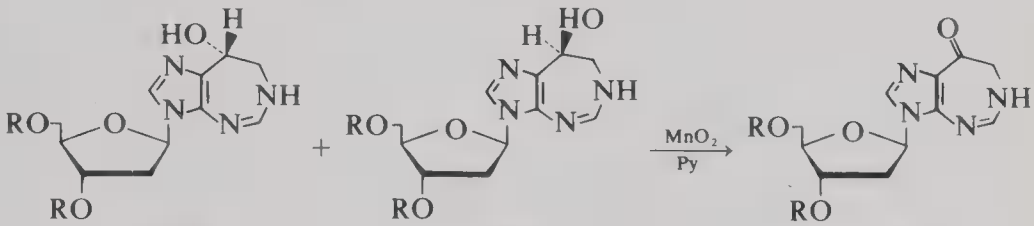
Substrate	Product	Reaction conditions	Yield (%)	Reference
		MnO_2CHCl_3, 24 h/r.t.	>50	287
		MnO_2	68	326
		MnO_2 1,4-dioxane 8 h, 60°C	80	327
		MnO_2CCl_4	70.5	342
		MnO_2CHCl_3 5 h/r.t.	54	329
		MnO_2CHCl_3, 16 h/r.t.	90	347
		MnO_2CHCl_3, 5 h/r.t.	60	347
		MnO_2 acetone, 1.5 h, 56°C	50–80	333
		MnO_2 ether, 24 h/r.t.	65	335
		MnO_2	47	358
		MnO_2/DMSO, 15 min/100°C	85	344
		MnO_2/C_6H_6, 24 h/r.t.	81	343

Table continued

TABLE VI. *(Continued)*

Substrate	Product	Reaction conditions	Yield (%)	Reference
		$MnO_2/CHCl_3$, 12 h/r.t.	50 + 50	338
		$MnO_2/CHCl_3$	33	149

A specific oxidation of heterocyclic moiety, e.g., the tetrahydroimidazo[4,5-d][1,3]-diazepin-8-ol (**311**) (**311a** and **311b**, 8S, 8R isomers), to give an important adenine keto nucleoside (**312**) has recently been achieved with active MnO_2 in pyridine; all other reagents produced an incomplete oxidation.[743]



311a + **311b** $\xrightarrow[Py]{MnO_2}$ **312**

R = –*p*-foluoyl R = –*p*-foluoyl

3.8. Saturated Aliphatic Alcohols

Oxidation of saturated primary and secondary aliphatic alcohols with manganese dioxide in neutral media can be achieved provided that fresh reagent, a suitable solvent, and sufficient time and quantity of the oxidant are applied.[28,47] The rate of oxidation of saturated alcohols, is, however, lower compared to allylic or benzylic alcohols, because of the greater ease with which the C–H bond is cleaved in the unsaturated alcohols. Oxidation of isobutyl, capryl, or C_{14}- alcohols in neutral media,[29] or propyl or isopropyl alcohols[29] to the corresponding carbonyl compounds, and conversion of a benzene solution of butyl alcohol into butyraldehyde (70%) and of 4-methylcyclohexanol (in acetonitrile) into

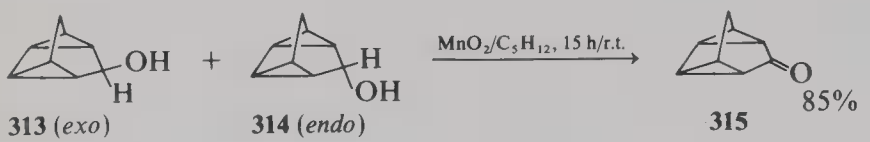
$$H_3C-CH_2-OH \xrightarrow{50\%} H_3C-CH=O \tag{5}$$

$$\begin{matrix} H_3C \\ \diagdown \\ \quad CH-OH \\ \diagup \\ H_3C \end{matrix} \xrightarrow{50\%} \begin{matrix} H_3C \\ \diagdown \\ \quad C=O \\ \diagup \\ H_3C \end{matrix} \tag{6}$$

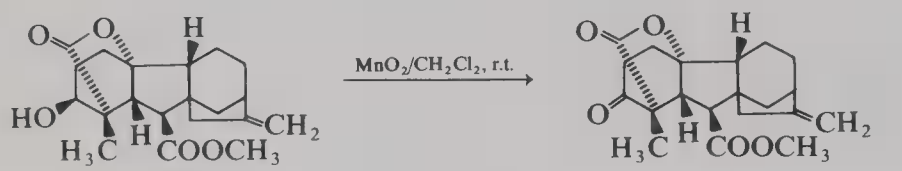
$$\begin{matrix} H_3C \\ \diagdown \\ \quad CH-CH_2-OH \\ \diagup \\ H_3C \end{matrix} \xrightarrow{50\%} \begin{matrix} H_3C \\ \diagdown \\ \quad CH-CH=O \\ \diagup \\ H_3C \end{matrix} \tag{7}$$

4-methylcyclohexanone (71%)[47] has been reported. Many, saturated, aliphatic alcohols have been oxidized with manganese dioxide at the reflux temperature, e.g.,[292] Eqs. (5)–(7). As discussed earlier, several saturated alcohols were successfully oxidized with manganese dioxide, e.g., cyclopropane alcohols (conversions **128** → **129** and **130** → **131**,[178] bicyclic alcohols (**2** → **4**),[73] steroid alcohols (**239** → **240** and **241** → **242**),[47] and oxidation of α-santonin (conversion **119** → **120**),[159] or oxidation of 2-hydroxytetrahydropyran to lactone.[287] Treatment of a mixture of *exo*- and *endo*-tetracyclo[3.3.0.0.^{2,8}.0^{4,6}]-3-octanols (compounds **313** and **314**, respectively) with manganese dioxide gave tetracyclo[3.3.0.0.^{2,8}.0^{4,6}]-3-octanone (**315**) in 85% yield; both epimers seemed to be readily oxidized by the reagent.[187,367]

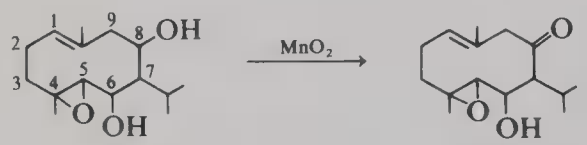
Oxidation of the nonallylic hydroxy group with manganese dioxide in dichloromethane (but not in 1,4-dioxan) may be illustrated with the conversion of the natural gibberellin A_7 methyl ester (**316**) into its 2-oxo derivative **317**[45] or conversion of the homoallylic alcohol shiromodiol (**318**) into the hydroxyketone **319**[368] [Eqs. (8) and (9)].



313 (*exo*) 314 (*endo*) 315



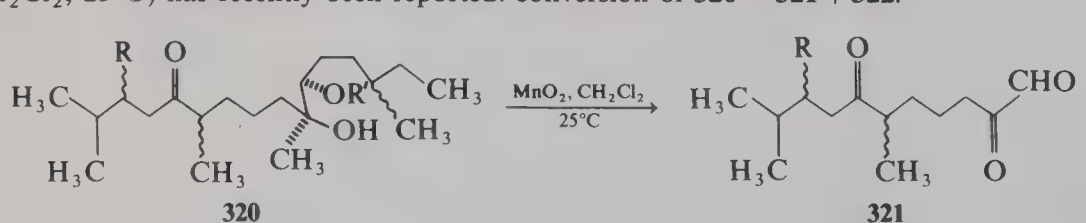
316 317 (8)



318 319 (9)

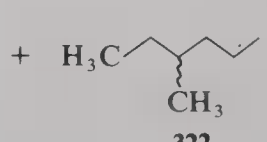
As mentioned earlier (Sec. III, 3a), a stereochemical preference in manganese dioxide oxidation of certain saturated, vicinal diols (to give the dicarbonyl compounds) in neutral media has recently been observed.[92] Only 1,2-*cis*-diols and analogous *trans* compounds having a flexible arrangement of their hydroxy groups can be oxidized; sterically hindered diols, e.g., 9,10-*trans*-decalindiol, remain inert. If the hydroxy groups are secondary, dehydrogenation is observed, instead of complete oxidation. For example, dodecanedial, as the oxidation product of 1,2-*cis*-cyclododecanediol, is accompanied by 1,2-cyclododecanedione (14%) and traces of 2-hydroxycyclododecanone.[92] Several useful synthetic preparations of some otherwise difficulty accessible carbonyl compounds from 1,2-diols are summarized in Table VII.[92]

A novel diol cleavage reaction using surprisingly gentle reaction conditions (MnO_2, CH_2Cl_2, 25°C) has recently been reported: conversion of **320** → **321** + **322**.[74]



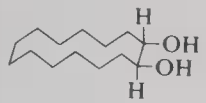
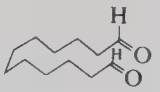
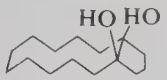
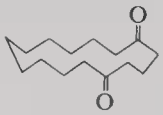
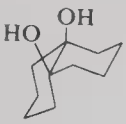
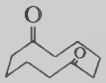
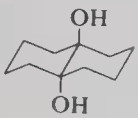
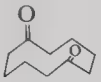
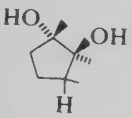
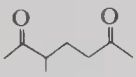
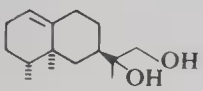
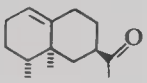
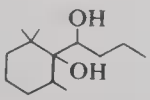
320 321

R = H; R^1 = H



322

TABLE VII. Products of Oxidation of 1,2-Diols by Manganese Dioxide[a]

Starting material	Product	Time (h)	Conversion (%)	Yield (%)
		4	100	85
		2	100	70
		1	100	90
		72	0	—
		5	100	70
		1	100	60
		2	100	90

[a] Reference 92.

Saturated aliphatic α-hydroxyketones were readily oxidized with active manganese dioxide in refluxing organic solvents to the corresponding 1,2-diones in yields comparable to those given by other methods; for example, 3-hydroxyhexanone gave 3,4-hexanedione (52% yield) and 4-hydroxyoctanone was converted into 4,5-octanedione in 58% yield[329] [Eqs. (10) and (11)].

$$C_2H_5-\underset{\displaystyle OH}{\underset{|}{CH}}-\underset{\displaystyle O}{\underset{\|}{C}}-C_2H_5 \xrightarrow[52\%]{} C_2H_5-\underset{\displaystyle O}{\underset{\|}{C}}-\underset{\displaystyle O}{\underset{\|}{C}}-C_2H_5 \qquad (10)$$

$$n\text{-}C_3H_7-\underset{\displaystyle OH}{\underset{|}{CH}}-\underset{\displaystyle O}{\underset{\|}{C}}-C_3H_7\text{-}n \xrightarrow[58\%]{} n\text{-}C_3H_7-\underset{\displaystyle O}{\underset{\|}{C}}-\underset{\displaystyle O}{\underset{\|}{C}}-C_3H_7\text{-}n \qquad (11)$$

Manganese dioxide has been applied in the synthesis of *p*-nitrophenyl 3-hydroxy-2,2-dimethylpropyl ether (from *p*-chloronitrobenzene and neopentyl glycol in an auqueous potassium caronate solution).[369] The reagent was also used in oxidation of saturated, naturally occurring alcohols,[370–374] for the analysis of mixtures of saturated and unsaturated alcohols,[367] and for other functional-group analysis.[375]

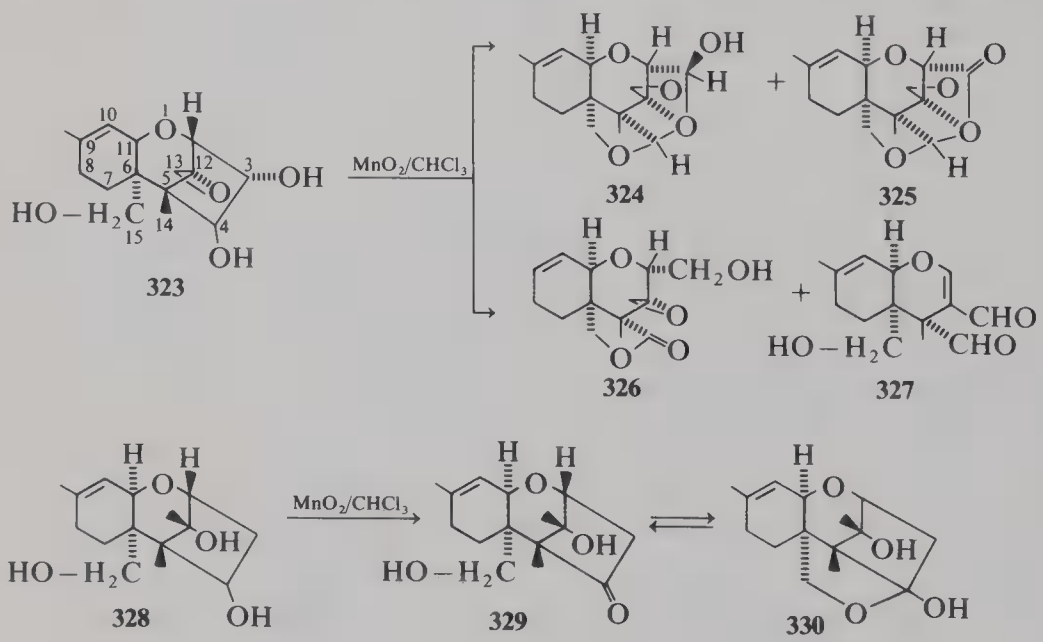
3.9. Polyhydroxy Compounds

Selectivity in the manganese dioxide oxidation of polyhydroxy compounds in neutral media has been pointed out earlier (e.g., conversion **113** → **114**,[156] **117** → **118**,[157] or **194** → **195**[223]). Nonselectivity has usually been observed when the oxidation is performed in hot, polar solvents; thus, ethylene glycol, glycerol, D-mannitol, and inositol were all degraded to carbon dioxide and water when refluxed with an suspension of manganese dioxide.[292] Similarly, hydroxy acids are oxidized, e.g., tartaric acid to give carbon dioxide and acetaldehyde; citric acid → acetone; malonic acid → ethylene + carbon dioxide.[292]

Cleavage of the side chain with manganese dioxide has been reported for certain polyhydroxy, benzylic type alcohols and acids[304,376]; however, some of the dihydroxybenzylic alcohols have been selectively oxidized with the reagent to give keto-alcohols in high yields.[304,377]

An interesting, selective oxidation by manganese dioxide in neutral media of a mould metabolite triol has been recently reported. Thus, whereas the *trans*-α,β-glycol structure in **323** (12, 13-epoxytrichothec-9-en-3α, 4β, 15-triol) was stable to periodate oxidation,[378,379] **323** was easily oxidized (on ring C) with manganese dioxide in chloroform, to give three major 3,4-*seco* products,[379] viz., hemiacetal **324**, δ-lactone **325**, and γ-lactone **326** (formed via an intramolecular, crossed-Cannizzaro reaction), and a minor product, the α,β-unsaturated dialdehyde **327**.

A reasonable mechanism[379] for the formation of **327** involves oxidation of 4β-secondary alcohol **323** to the 4-keto compound, followed by a base-catalyzed isomerization of the epoxide to a keto-aldehyde, and by the retro-Michael fission of ring C between positions 2 and 3; finally, the newly formed α-ketol is then oxidized to the product. This pathway is supported by the report[380] that the related triol **328** (dihydroverrucarol B) was rapidly and quantitatively oxidized by manganese dioxide, giving 4-keto derivative **329**, isolated as the hemiacetal **330**.



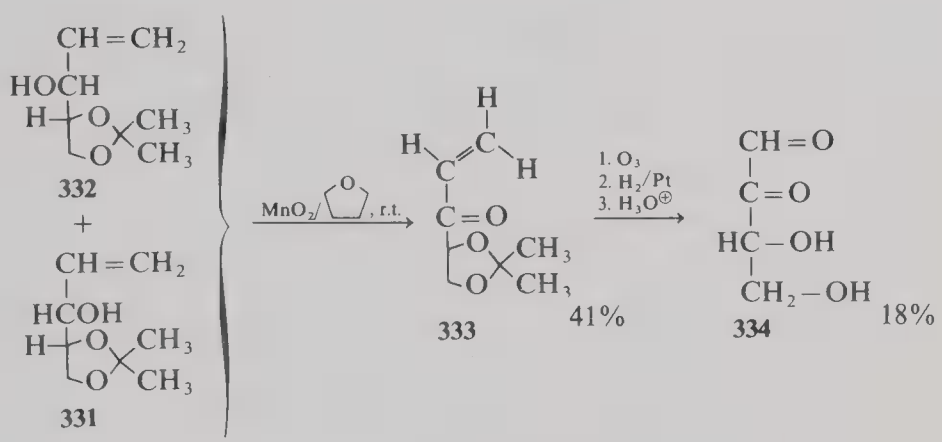
3.10. Carbohydrates

Manganese dioxide oxidation is at present of limited scope in the carbohydrate field; however, progress in this direction is on the horizon. Particularly interesting are the stereospecific oxidations of certain allylic carbohydrates that have been discussed (com-

pounds **36**, **37**, **38**, **39**, **40**, and **41**); some novel synthetic or structural applications of the reagent inthe field are described here.

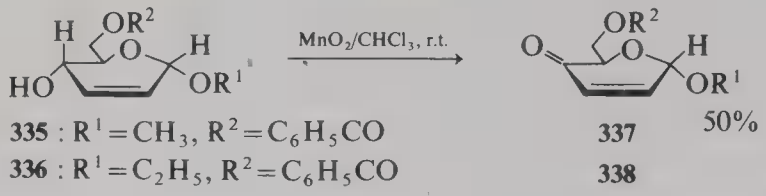
An early study[381] of the action of manganese dioxide on simple carbohydrates in aqueous solution (at 25°C and at 95°C) revealed that hexoses yield pentoses and some acidic products; the fragmentation was also observed with heptoses (to give hexose and pentose); surprisingly, erythrose was oxidized completely by the reagent, and galactose gave some epimerication products. Oxidation was generally observed with aldoses having the 2-hydroxy group free; the substituted aldoses (e.g., 2-deoxy, 2-acetamido-2-deoxy, or 2-*O*-methyl derivatives) were not affected.[381] Disaccharides generally gave less complex mixtures on treatment with manganese dioxide; although the (1 → 2)-linked disaccharide sophorose did not react, the (1 → 3) (laminarabiose), (1 → 4) (maltose or cellobiose), or (1 → 6) (melibiose) disaccharides were degraded to give, mainly, (1 → 2)-, (1 → 3)-, and (1 → 5)-linked hexosylpentoses (18%–31% yield) and glycosylglycuronic acids (18% yield).[382] A limited selectivity has also been observed in the oxidation of D-fructose with manganese dioxide (at 25°C in aqueous solution); the main oxidation product was D-*arabino*-hexosulose [D-glucose, isolated as quinoxaline or as the (2,4-dinitrophenyl)osazone].[383] Under vigorous conditions (refluxing aqueous solution) manganese dioxide loses much of its selectivity and, for example, the sugar alcohols D-mannitol and *myo*-inositol were completely oxidized by the reagent to carbon dioxide.[292] When a sample of DL-*epi*-inosose-2 was refluxed with aqueous manganese dioxide for 1 h and the filtered solution was carefully neutralized with potassium carbonate, among the degradation products were found (isolated as potassium salt) mesoxalic (2-ketooxalic), oxalic, and croconic acids[318]; similar oxidation of inosose was observed[382]; however, no degradation products were reported.

A new route to the preparation of aldosuloses (osones) involves manganese dioxide oxidation of epimeric pairs of the allylic carbohydrate alcohols to give the vinyl ketons as reaction intermediates. Thus, when a solution of 1,2-dideoxy-4,5-*O*-isopropylidene-D-*threo*- (and D-*erythro*)-pent-1-enitol (compounds **331** and **332**, respectively) was treated with manganese dioxide in tetrahydrofuran, compound (**333**; 1,2-dideoxy-4,5-*O*-isopropylidene-D-*glyceropent*-1-en-3-ulose) was isolated in 41% yield. Degradation of **333** by reductive ozonolysis and hydrolysis gave D-*glycero*-tetros-2-ulose (**334**) in 18% yield; similarly, D-*arabino*-hexosulose was obtained in 37% yield.[384,385]



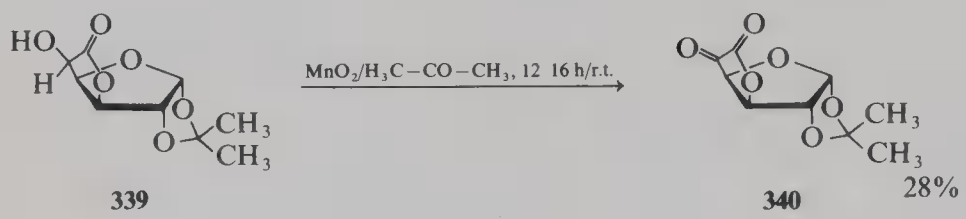
332 + **331** → **333** → **334**

The allylic pyranosides **335** and **336** were oxidized with manganese dioxide to give the alkyl hex-2-eno-pyranosid-4-uloses, **337** and **338**, respectively, a new class of α,β-unsaturated ketoses, in 50% yield.[386] Similarly, 1,2-*O*-isopropylidene-α-D-glucofuranur-ono-6,3-lactone (**339**) on treatment with manganese dioxide in acetone was converted into the 5-ulose-6,3-lactone (**340**) in 28% yield,[387] and 2′,3′-*O*-isopropylidene-6,5′ (S) cyclouridine (**341**) was oxidized to 2,3′-*O*-isopropylidene-5′-oxo-6,5′-cyclouridine (**342**) in 93% yield.[388]

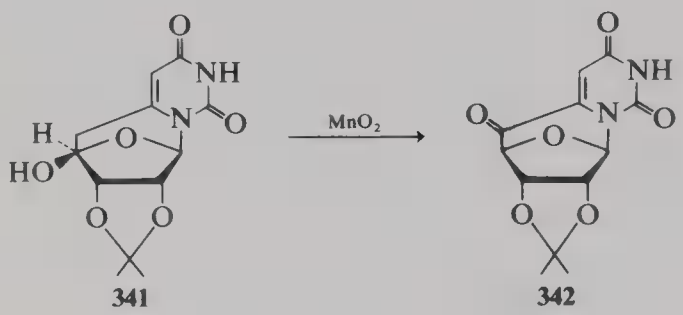


335 : $R^1 = CH_3$, $R^2 = C_6H_5CO$
336 : $R^1 = C_2H_5$, $R^2 = C_6H_5CO$

337
338



339 **340**



341 **342**

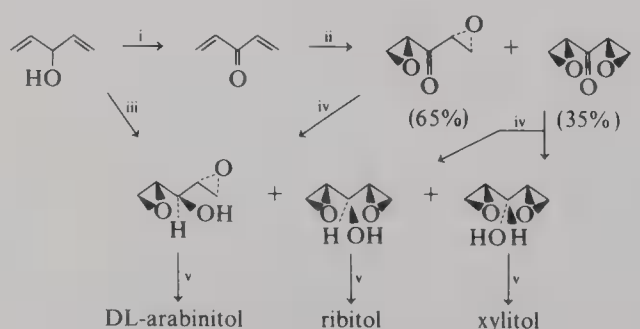
3.10.1. Synthesis of Alditols

DL-Arabinitol, ribitol, and xylitol have been synthesized from 3-hydroxypenta-1,4-diene (divinyl carbinol) by the routes outlined in Scheme 7.[389]

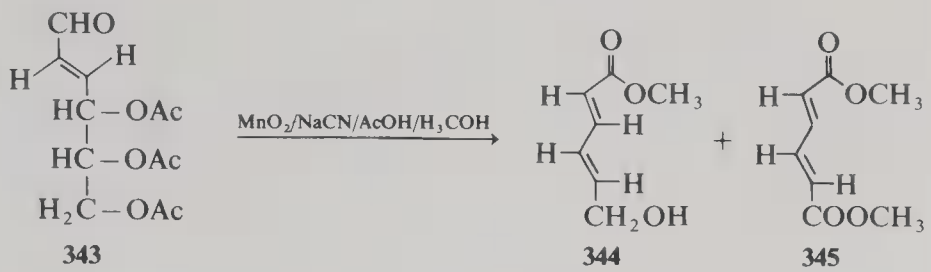
3.10.2. Application of the Corey Procedure

A useful extension of the Corey procedure[190] to the carbohydrate field was the preparation of a mixture of the conjugated diene compounds **344** and **345** from **343**. Thus the 2,3-dideoxyhex-2-enose triacetate (**343**) was oxidized by a mixture of sodium cyanide, acetic acid, and manganese dioxide in methanol to give a mixture of **344** and **345**, a reaction pathway for this conversion was suggested.[390]

SCHEME 7



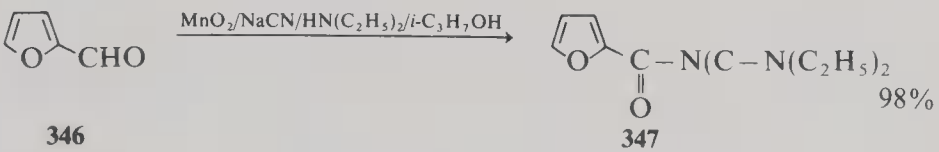
Reagents: i, MnO_2-CHCl_3; ii, $H_2O_2-HO^-$;
iii, p-$NO_2C_6H_4CO_3H$; iv, $NaBH_4$; v, NaOH



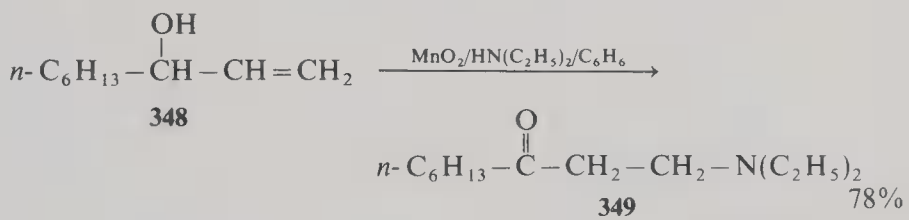
343 **344** **345**

3.10.3. Application of the Mannich Base

A method closely related to the Corey method is a procedure that could be of interest to carbohydrate chemists for converting an aldehyde into a carboxylic acid amide [e.g., conversion of 2-furaldehyde (**346**) into 2-furoic diethylamide (**347**) in 98% yield][391] or preparation of β-aminoketones from 2-ethylenealcohols [e.g., preparation of 1-diethylamino-3-nonanone (**349**) from 1-nonene-3-ol (**348**) in 98% yield].[392]

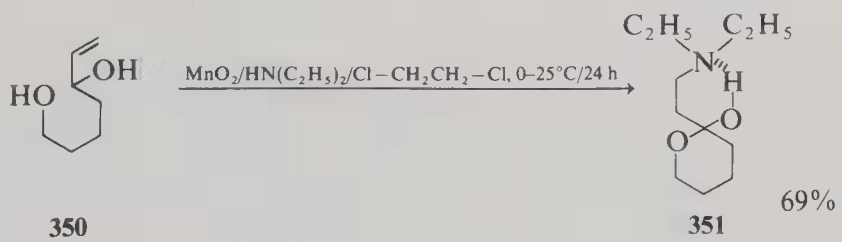


346 **347**



348 **349**

Similar oxidation of 6-heptene-1,5-diol (**350**) with manganese dioxide in the presence of diethylamine yielded the Mannich base[393] 2-(2-diethylaminoethyl)tetrahydropyran-2-ol (**351**) in 69% yield, an important intermediate in the synthesis of novel spiro heterocyclics[394,395]; in addition, for example, compare the Mannich base structure in the natural antibiotics **358** and **359**.

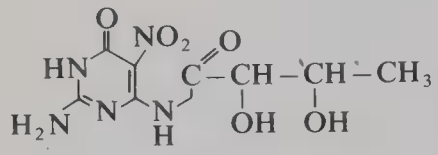


350 **351**

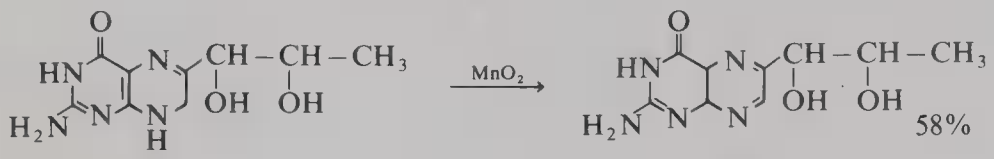
3.10.4. Other Applications

An example of incorporation of a side chain reducing sugar into a conjugate heteroaromatic system is a synthesis of pterins from 4-amino-5-nitropyrimidines. Thus, hydrogenation over Raney nickel of 1-(2-amino-1,6-dihydro-5-nitro-6-oxopyrimidin-4-ylamino)-1,5-dideoxy-L-*erythro*-2-pentulose (**352**) gave 7,8-dihydropretin (**353**); this was then oxidized with manganese dioxide at low temperature to give biopretin (**354**) in 58% yield[396]; the relative stability of the above heteroaromatic diol, as compared to facile cleavage by the reagent of the comparable aromatic diol (e.g., compound **280** → **281**)[304] may be noted.

An interesting oxygen-insertion reaction has been observed following the oxidation of

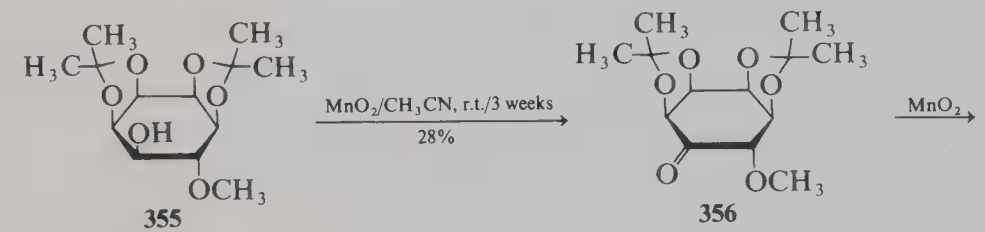


352

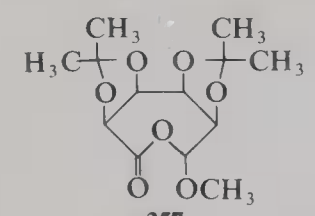


353 354

the substituted inositols with active manganese dioxide. Thus, treatment of 1,2,3,4-di-*O*-methyl-*epi*-inositol (**355**) with the reagent in acetonitrile gave, instead of the expected inosose derivative **356**, an oxygen-insertion product, the hemi-acetal lactone **357** in 28% yield; compound **356** was the reaction intermediate (compare the other oxygen insertion, e.g., conversion **2** → **4**). Compound **357** could be regarded as the key intermediate in the synthesis of hexoses and pentoses (e.g., DL-allose and DL-ribose) from inositols (e.g., cyclitols).[397] Although the yield is moderate, the synthetic procedure is novel and warrants further exploration. The previous oxygen-insertion reactions that led to the new class of carbohydrate derivatives have been performed by Baeyer–Villiger oxidation (perbenzoic acid in moist chloroform) or by using ruthenium tetraoxide reagent.[398]



355 356

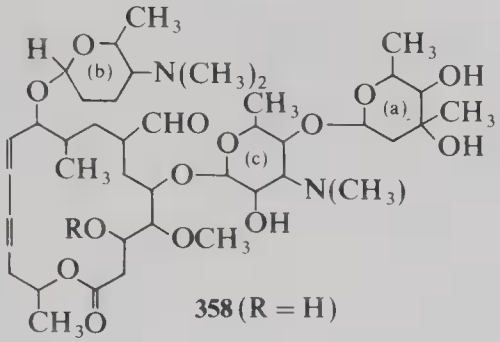


357

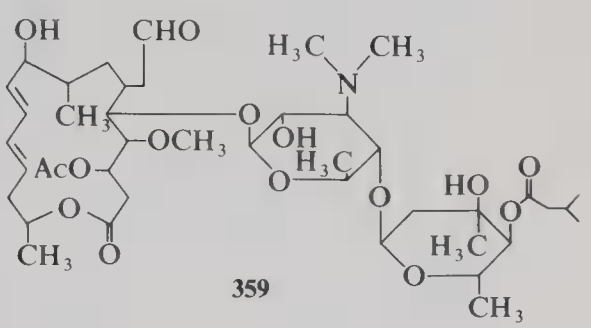
Manganese dioxide has been succesfully applied in structural and diagnostic studies of complex natural products. For example, the structure of the antibiotic spiramycin (**358**, R = H) was confirmed, among use of other evidence, from the manganese dioxide oxidation of the partially hydrolyzed products. Thus, treatment of the mild acid hydrolysis product, forocidine [after splitting off the sugar moiety (ring A) and forosamine moiety (ring B) in **358**] with the oxidant gave a dienone, thus confirming the allylic attachment of ring B to the spiramycin aglycon.[399] In another case, the structurally related antibiotic leucomycin A_3 (**359**) was oxidized with manganese dioxide to dehydroleucomycin A_3, thus confirming the presence of an allylic ($\alpha,\beta,\gamma,\delta$-unsaturated) alcohol group in **359**.[400]

Acid hydrolysis of the glycoside amorphin gave glucose, arabinose, and the aglycon amorphigenin (**360**); the presence of an allylic primary alcohol group on the dihydrofuranoid ring (e) of **360** was confirmed by conversion of the latter with manganese dioxide into an unsaturated keto-aldehyde derivative.[401]

Freudenberg and co-workers[402–404] in their comprehensive study of the structure of the lignin monomer[404] have shown that the structurally related coniferyl alcohol (**361**, R = H),



358 (R = H)



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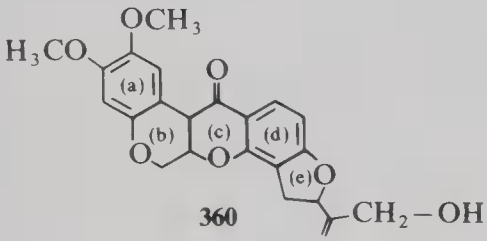
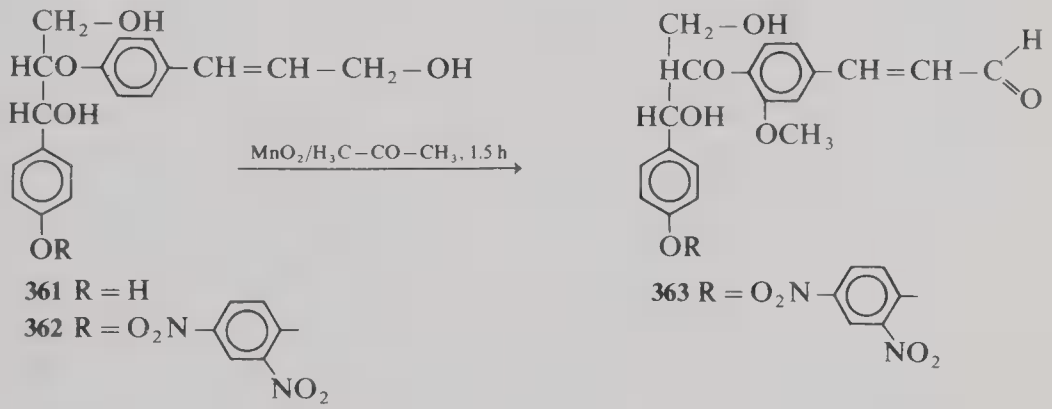


360

when oxidized with manganese dioxide, gives an oligomeric mixture, whereas its 2,4-dinitrophenyl ether (**362**) is selectively oxidized by the reagent to coniferyl aldehyde 2,4-dinitrophenyl ether (**363**) in good yield.

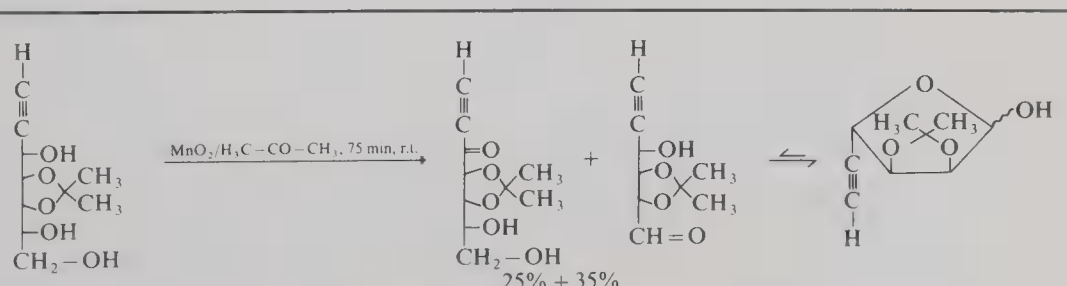


361 R = H
362 R = O_2N–C$_6$H$_3$(NO$_2$)–

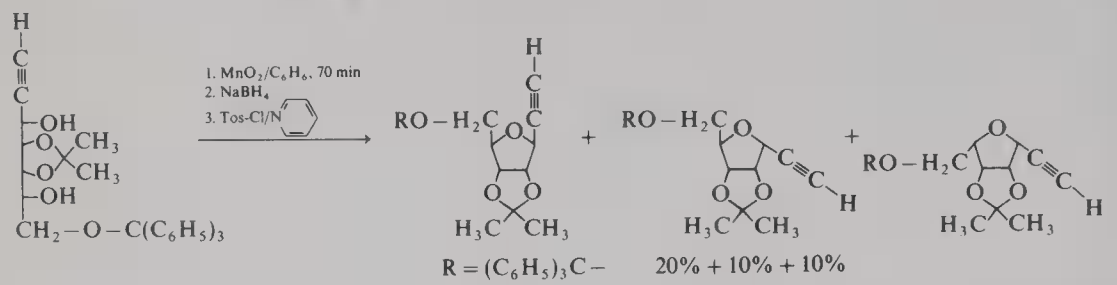
363 R = O_2N–C$_6$H$_3$(NO$_2$)–

In an interesting example,[405] an acetylenic triol (1,2-dideoxy-4,5-*O*-isopropylidene-D-*allo*-hept-1-ynitol) was oxidized with manganese dioxide to give a rare sugar (1,2-dideoxy-D-*ribo*-hept-1-yn-3-ulofuranose, 25% yield), along with an aldehyde (2,3-*O*-isopropylidene-D-*ribo*-hex-5-ynofuranose ⇌ hemiacetal) via an unexpected oxidative cleavage of the C-6—C-7 bond in the triol (Scheme 8).

SCHEME 8



SCHEME 9



Similar oxidation[405] of the ethyne trityl ether with manganese dioxide, followed by borohydride reduction and treatment with *p*-toluenesulfonyl chloride, gave an isomeric mixture separated by chromatography (Scheme 9).

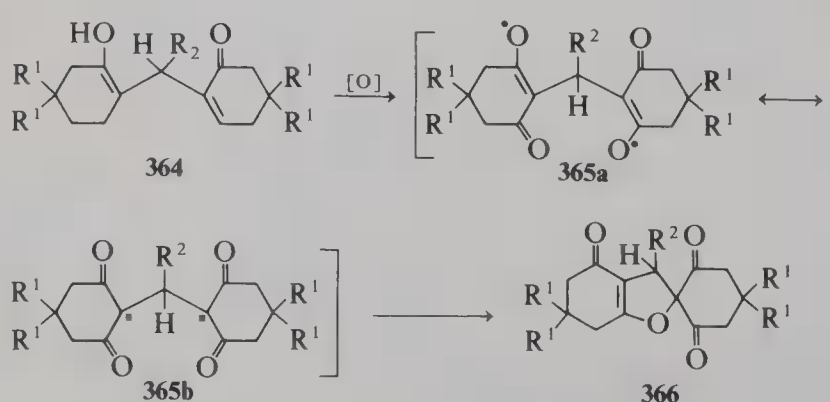
3.11. Phenols

3.11.1. Oxidative Coupling of Phenols

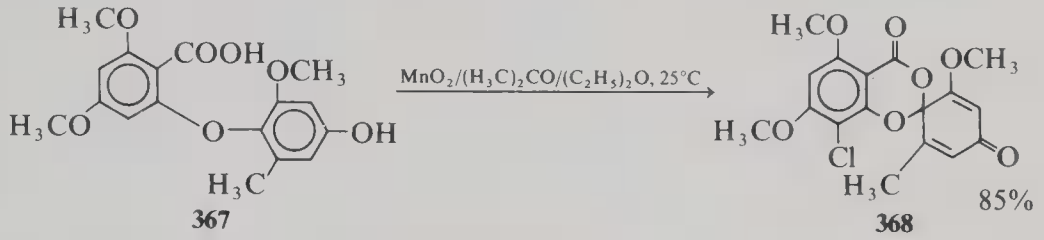
Oxidative cyclization is of great importance to synthetic and biogenetic studies; significantly, a key step in the biosynthesis of many complex natural products is the oxidative coupling of a phenol.[406–420]

Phenolic oxidation has become one of the new research areas of synthetic organic methodology, and many successful syntheses of natural products, particularly those involving formation of new C—C, C—O, or C—N bonds can now be explained by pairing radicals from the substrate involved in the oxidative step. As originally syggested by Barton and Cohen,[406] many alkaloids owe their biosynthesis to intramolecular, radical-coupling reactions, and this was later verified by extensive tracer experiments.[412,416]

Oxidative coupling of phenols can be performed with any one of a series of reagents, e.g., alkaline hexacyanoferrate(III), neutral iron(III) chloride, hydrogen peroxide/iron(II) sulfate (Fenton reagent), lead(IV) oxide, nickel peroxide or lead(IV) acetate; however, active manganese dioxide occupies a special place.[408,413] Various oxidants convert phenols into mono- or diradicals which can either dimerize or couple intramolecularly to form a new bond. A model radical cyclization—for example, chemical oxidation[421] of methylenebis[dimedone] **364** ($R^1 = CH_3$, $R^2 = H$)—leads to intramolecular oxidative carbon–oxygen coupling to yield the spiro enol ether **366**. The latter may arise via a short-lived stabilized biradical (**365a** ↔ **365b**) which undergoes exclusive carbon–oxygen intramolecular coupling; the carbon–oxygen bond has as much bond energy (85 kcal/mol) as a carbon–carbon bond (82 kcal/mol).

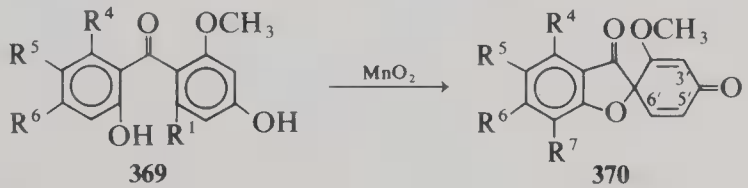


Similar carbon–oxygen coupling has been observed in a synthesis of griseofulvin derivatives either from diphenyl ether[422] or substituted benzophenones.[423] Thus treatment of **367** (6-carboxy-2-methylphenyl ether) with manganese dioxide in acetone/ether gave *rac.*-dehydrogriseofulvoxin (**368**) in 85% yield.[422]



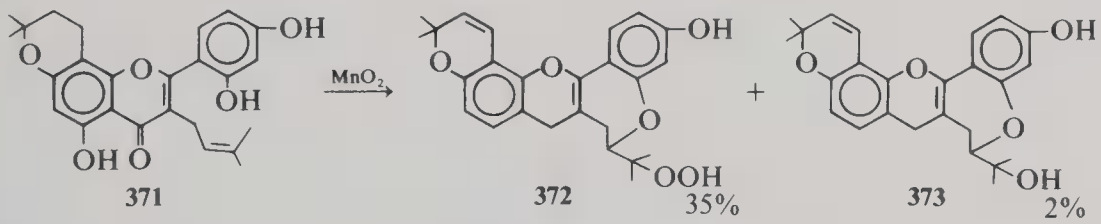
367 **368**

The substituted benzophenones shown **369** are cyclized to Δ^5-dehydrogriseofulvin derivatives (**370**, $R^1 = CH_3$, $R^4 = R^6 = OCH_3$, $R^5 = H$, $R^7 = Cl$ or F) by manganese dioxide[422,423]; only C—O coupling is sterically feasible. The fungal metabolites geodin and erdin (**370**, $R^4 = OH$, $R^5 = R^7 = Cl$, $R^6 = CH_3$, $R^1 = COOCH_3$, or COOH, respectively)[424] are closely related compounds. The oxidative cyclization of morusin (**371**) by using one-electron transfer oxidants (e.g., manganese dioxide) afforded C—O coupling products, e.g., the



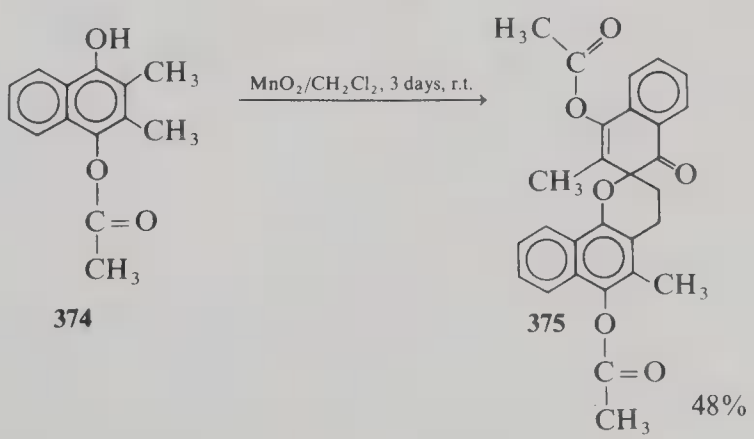
369 **370**

hydroperoxide **372** (35% yield) and the coupling product **373** (2% yield). The radical mechanism involved in the formation of **372** and **373** was supported by conducting the reaction in the presence of 2,4,6-tri-*tert*-butylphenol, a radical quencher, to give products coupled with 2,4,6-tri-*tert*-butylphenoxyl radical.[425]



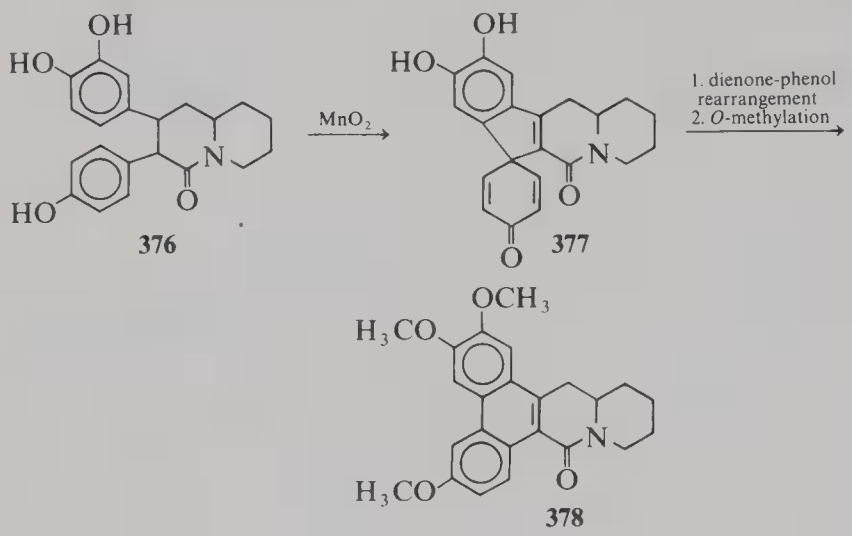
371 **372** **373**

Oxidation of the quinol ester **374** (2,3-dimethyl-1,4-naphthalenediol monoacetate) with activated manganese dioxide (dichloromethane, 72 h, room temperature) gave a novel coupling product, the yellow 4′,6-dihydroxy-3′,5-dimethyl-3,4-dihydrospiro[2H-naptho[1,2-*b*]pyran2′,2-naphthalen-1′-one] diaacetate (**375**), m.p. 148–150°C in 40% yield.[426]



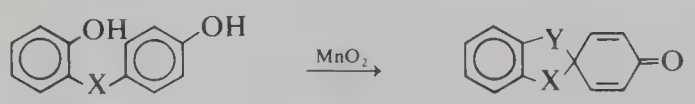
374 **375**

In another intramolecular cyclization process involving carbon–carbon coupling, for example in the phenolic oxidation of the alkaloid quinolizidine **376** with active manganese dioxide,[416,417] the intermediate oxidized product, which can be isolated, is a spiran derivative **377** that can undergo a dienone–phenol rearrangement[412,418] to give the biphenyl derivative **378** (alkaloid cryptopleurine). The synthesis of spiroheterocycles, e.g., the spirobenzoxazole



376 **377** **378**

(**380**) by oxidation with active manganese dioxide of the dihydroxydiphenylamine (**379**) (via an oxidative coupling) has recently been reported.[427]



379 **380**

X = NTs Ts = 4-$MeC_6H_4SO_2$ X = O, Y = NTs

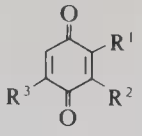
Manganese dioxide has been applied in several enzyme-mimicking syntheses of other phenolic natural products, e.g., diplocin,[428] depsidone,[429] picrolichenic acid,[430] the alkaloid galanthamine [via norwedine and *p*-hydroxy-*N*-(3-hydroxy-4-methoxybenzyl)-*N*-methylphenethylamine intermediate],[270,431] and in the synthesis of several morphine alkaloids[36,432]; the reagent has also been used in the preparation of spirodienone [from *O*-(4-hydroxyphenyl)-benzoic acid],[433] 1,3-benzodioxole-2-spirocyclohexanediene-4-one from 4-(2-hydroxyphenyl)-1-naphthol[434]; also in the oxidative dimerization of totarol to podototarin.[436]

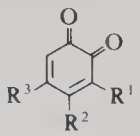
Other examples of intramolecular cyclization of phenols in the presence of manganese dioxide are formation of *bis*-spirodienone[437] or dioxepin derivatives,[438] preparation of a stable phenoxyl radical,[439,440] of a diradical,[441] and synthesis of a *bis*-dienone (from 5,5′-dihydroxy-2,2′-dimethylbibenzyl),[442] or oxidative coupling of mesitol.[443]

Recently Cassis and Valderrama[764] described the preparation of a variety of quinones by oxidation of hydroquinones with active manganese dioxide prepared by reduction of potassium permanganate with methanol (Table VIII). Manganese dioxide is not quite suitable for the preparation of highly reactive quinones such as 1,2-benzoquinone and 1,4,5,10-anthraquinone. However, the authors[764] found that the synthesis of these quinones can be successfully carried out with manganese dioxide impregnated with nitric acid in methylene chloride solution (Table IX).

The authors[764] also noted that the above impregnated manganese dioxide reagent has the capability to induce oxidative demethylation on *p*-methoxyphenol and 1,4-dimethoxybenzene in high yield. As far as we know these are the first examples of oxidative demethylation of aromatic ethers with acid impregnated manganese dioxide.

TABLE VIII. Preparation of Benzoquinones from Hydroquinones Using Active MnO_2[a]

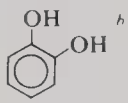
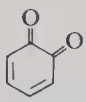
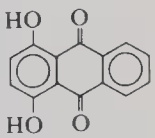
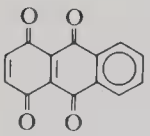
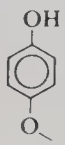
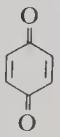
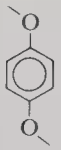
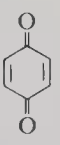

A(a–e)


B(a–b)

Product	R^1	R^2	R^3	Yield (%)[b] found
A(a)	H	H	H	90
A(b)	Me	H	H	95
A(c)	Me	Me	Me	95
A(d)	COMe	H	H	95
A(e)	CO_2Me	H	H	88
B(a)	H	*t*-But	H	99
B(b)	*t*-But	H	*t*-But	100

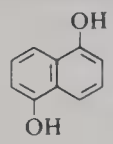
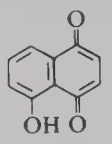
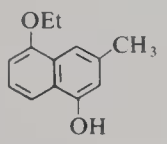
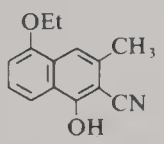
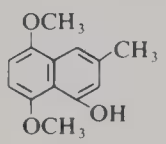
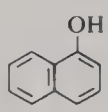
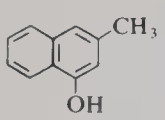
[a] Reference 764.
[b] Performed by G.L.C. and/or ^{1}H-NMR on crude product.

TABLE IX. Quinones Prepared by Oxidation of Hydroquinones with Manganese Dioxide Impregnated with Nitric Acid[a]

Substrate	Product	Reaction time (h)	Yield (%)
 [b]		0.25	68
		2.0	86
		0.5	96
		1.5	93

[a] Reference 764.
[b] Hydroquinone in CH_2Cl_2 solution.

TABLE X. Oxidation of 1-Naphthols with Active MnO_2 in Benzene Solution[a]

Substrate	Product of oxidation	Yield (%)
		60
	5-Ethoxy-3-methyl-1,4-naphthaquinone	90
	2-Cyano-5-ethoxy-3-methyl-1,4-naphthaquinone	91
	5,8-Dimethoxy-2-methyl-1,4-naphthaquinone	80
	4,2′-Binaphthol 4,4′-Binaphthol	15 15
	Polymerized	Nil
5-Methoxy-1-naphthol	Polymerized	Nil

[a] Reference 765.

Another recent report by Kumari and Pardhasaradhi[765] described a selective oxidation of 3.5-disubstituted 1-naphthols to the corresponding *p*-quinones using active manganese dioxide. The authors also observed that very good yield 1,4-quinones are obtained when the starting phenols are 3,5-disubstituted.

Table X summarizes some of the oxidation of 1-naphthols to 1,4-naphthoquinones applying active manganese dioxide in benzene solution. Recently Bruce *et al.*[766] reported the application of commercial precipitated manganese dioxide for the preparation of a broad range of quinones from the corresponding hydroquinones.

3.11.2. Oxidative Polymerization of Phenols

As shown by McNelis,[449] dimeric and polymeric products are formed on treatment of 2,6-xylenol (**381**) with active manganese dioxide in neutral media (Scheme 10). The head-to-tail polymer (polyphenylene ether **382** $n = x$) is the principal product (60%–90% yield) with an excess of the oxide, with some 2,2′,6,6′-tetramethyl-*p*,*p*′-biphenyl (383) and 3,3′,5,5′-tetramethyldiphenoquinone (**384**); whereas the tail-to-tail dimer **384** (60% yield) and trimer **382** ($n = 1$, 30 % yield) are formed when a molar excess of **381** is used. The proposed[449] quinol ether mechanism (Scheme 10) for the formation of **382** or **384** involves the phenoxyl radicals (**381a**, **381b**) that may couple at the oxygen atom to give (via **382a** and

382b) a trimer **382** ($n = 1$) (head-to-tail) (or an oligomer chain **382**, $n = x$), or at the *para* position to give, via **384a**, a dimer **384** (tail-to-tail). However, it may be exclusively *para* coupling if steric hindrance limits reaction at an oxygen atom, for example, such as in 2,6-di-*t*-butylphenol to give, exclusively, dimer 3,3′,5,5′-tetra-*t*-butyldiphenoquinone in 98% yield,[439,443] or the reaction may be conducted in a more polar solvent, for example, in dichloromethane, for preparation of **384** from **381**.[444]

The pathway outlined[449] (Scheme 10) does not require equilibration of large or small radicals, and, consequently, it is a fast reaction where one oligomer chain polymerizes at the expense of other chains ("*unzipping*" polymerization reaction); this mechanism is different from a nonclassical, electron mechanism suggested for a similar reaction.[445]

As recently pointed out by Price,[446] in oxidation, for example, of phenol (**381**), with excess manganese dioxide there might be only one phenol coordinated on manganese (complex A), while for excess phenol, there might be two or more (complex B). The manganese in complex A, as compared to complex B, would be more "neutralized" by hydroxy groups, would thus be a weaker Lewis acid, and could thus more readily liberate a free phenoxyl radical (e.g., **381a**) that would tend to form C—O coupling (e.g., **382a** → **382b**). In complex B, the manganese would be a stronger Lewis acid and would form a stronger bond to

SCHEME 10

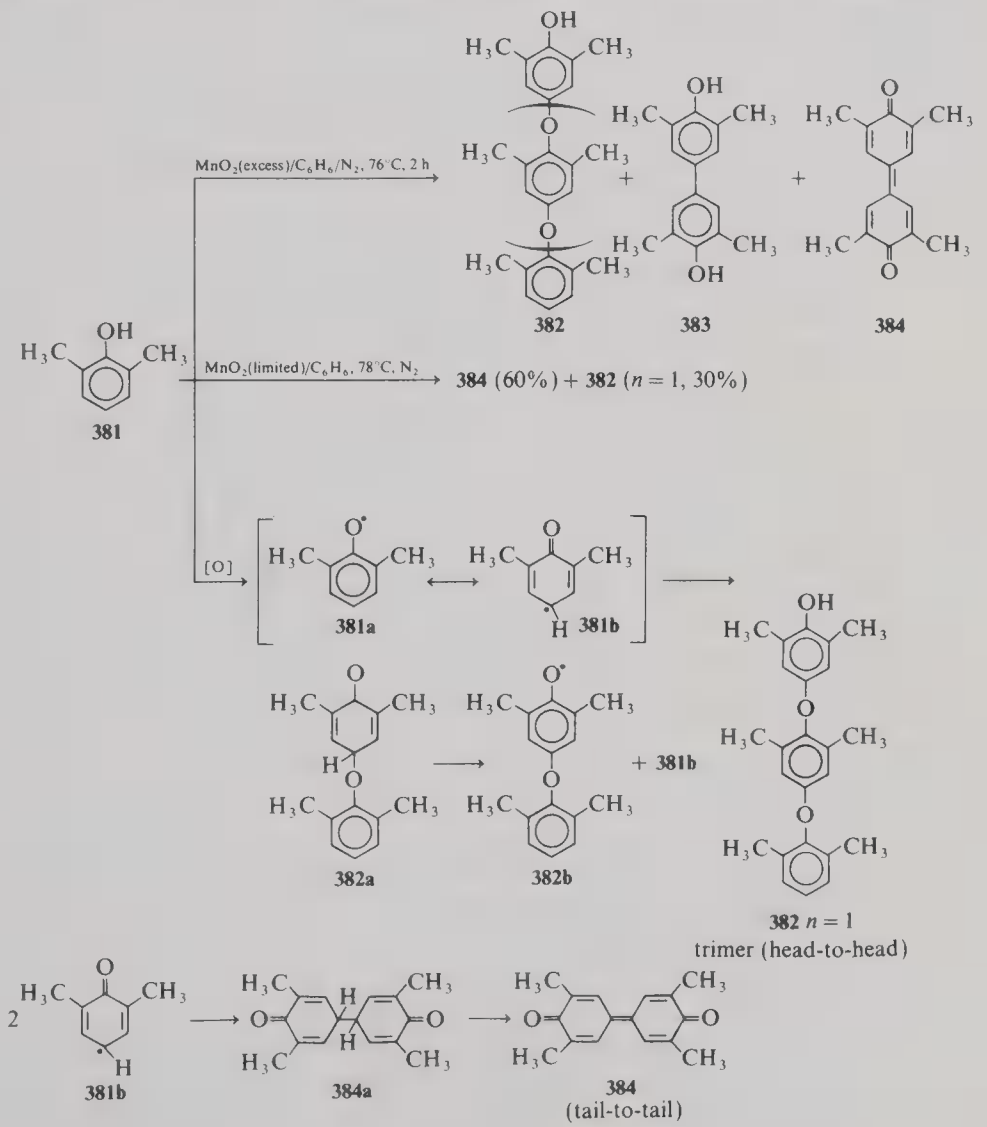
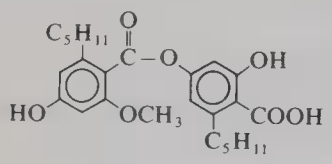
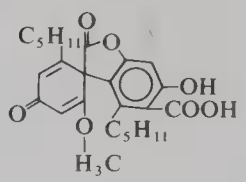
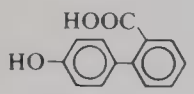
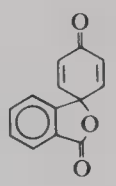
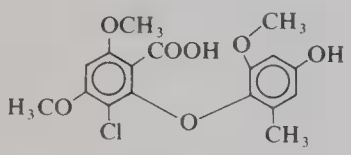
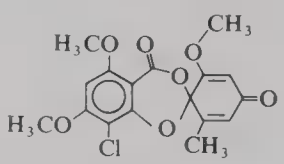
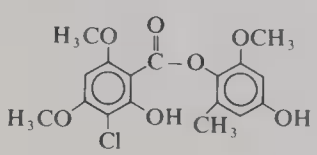
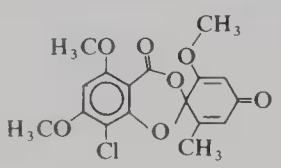
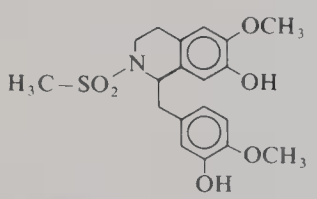
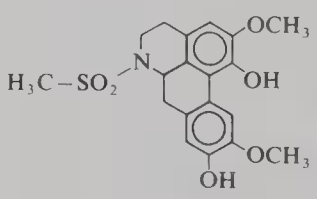


TABLE XI. Oxidative Coupling of Phenols

Substrate	Product	Reaction conditions	Yield (%)	Reference
		MnO_2/C_6H_6, 0.5 h	15–20	430
		MnO_2/ether, 18 h	40	433
		MnO_2/acetone, 2 h	88	422
		MnO_2/acetone	50	423
		MnO_2[a]/$CHCl_3$	40	36

[a] Supported on silica gel.

the phenyl oxygen (complex C), would not liberate the free phenoxyl radical, and would therefore give C—C coupling product (e.g., **384a** → **384**) (Scheme 11).

Oxidation of 2,6-xylenol trimer (**382**, $n = 1$) with manganese dioxide in refluxing acetic acid (2 h) gave 2,6-dimethyl-*p*-benzoquinone (96% yield) and a small proportion of dimer **384**. The suggested[447] ionic-radical mechanism apparently involves an oxidation step, with the formation of the phenonium ion, followed by a homolytic cleavage via an attack by the acetate ion to form two phenoxyl radicals.

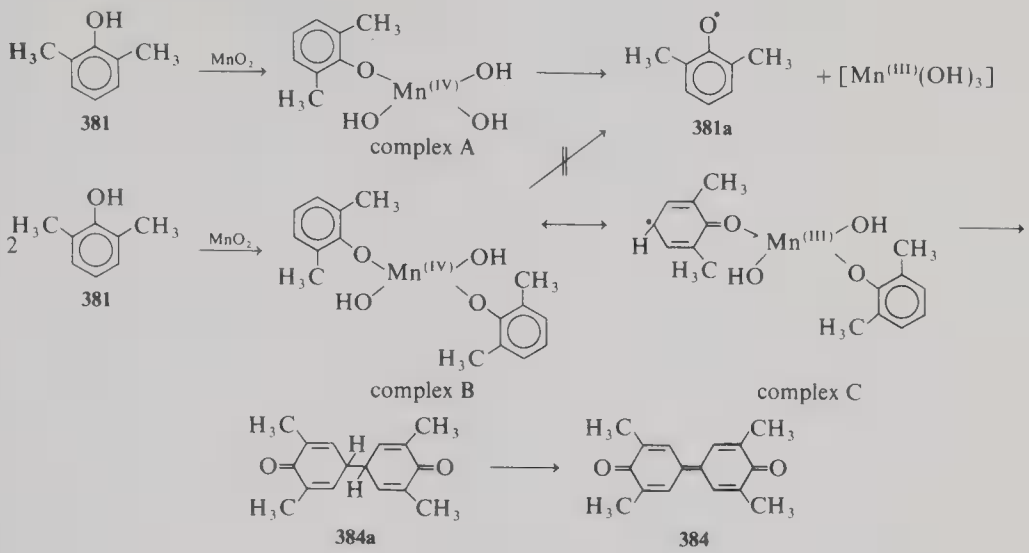
Surprisingly, mesitol, on treatment with manganese dioxide in benzene, undergoes unusual oxidative dealkylation reaction to give a mixture of C—C and C—O coupling products[443] (Table XI).[443]

Organic reaction mechanisms are generally characterized by two-electron changes (e.g., electron-pair processes), whether they proceed by ionic or free-radical pathways; in inorganic chemistry, one-electron changes (e.g., electron-transfer processes) are well established in a variety of redox reactions.

Although a number of qualitative mechanisms have been proposed, there is almost no fundamental insight into how bonds between carbon and metals are made and broken in organometallic compounds; see for example, Ref. 450.

Becker[448] has oxidized a series of 3,5-disubstituted 4-hydroxyphenyldiphenylmethanes **385** with manganese dioxide in benzene to obtain Fuchsones **386** (α,α-diphenyl-1,4-

SCHEME 11



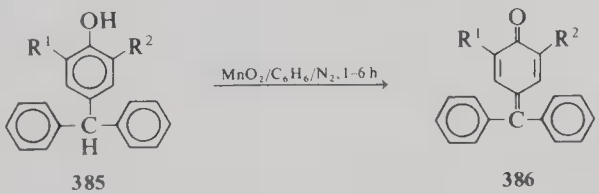
benzoquinonemethide); this is a convenient synthesis of important triphenylmethane dyes (Table XII).

The intermediate phenoxyl radical from **385** can be trapped with the 2,4,6-tri-*t*-butylphenoxyl radical to give a dimer (a quinol ether).[439]

The manganese dioxide oxidation of the sulfone **387** afforded 2,6-di-*tert*-butyl-7-phenyl-7-phenylsulfonylquinone methide (**388**) (73% yield).[451] Similar quinone methide was obtained by oxidation with the reagent of 2,6-diethyl-4-benzhydrophenol.[452]

Oxidation of 2,4,6-tri-*t*-butylphenol (**389**) with manganese dioxide in benzene[439] gives a deep-blue[453] resonance-stabilized phenoxyl radical (**389a** ↔ **389b** ↔ **389c**); this radical can

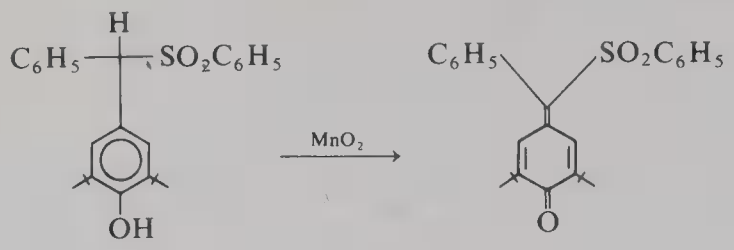
TABLE XII. Preparation of 3,5-Disubstituted Fuchsones[a]



385 386

R^1	R^2	Yield (%)
H_3C	H_3C	84
i-C_3H_7	*i*-C_3H_7	94
		99
		92
H_3C		92
	*t*-C_4H_9	94

[a] Reference 448.



387 388

attack other radicals, or easily dissociated molecules, to form cyclohexadienones or aryl ethers, e.g., a dimeric product **390**. However, when the oxidation of **389** has been performed in the presence of other phenols, dienone phenyl ethers **391** are formed (Scheme 12) (Table XIII) in high yields.[439,448] Similar products have also been isolated from the oxidation of 4-bromo-2,6-di-*t*-butylphenol and pentachlorophenol.[439]

In a recent study of nonphenol oxidative coupling of benzylisoquinolines (required for a synthesis of alkaloids dibenzazonine and appophine), Kupchan and co-workers[454,455] have oxidized with active manganese dioxide a series of *N*-bridged dienol intermediates; e.g., conversion of *N*-methyldienol into *O*-methylflavinantine (29% yield)[454] and conversion of a mixture of the epimeric (±)-*O*-methylsalutaridinols into (±)-*O*-methylsalutaridine (MnO_2, $CHCl_3$, 60% yield)[455] (compare oxidation of alkaloid tazzetine, Refs. 281–283).

3.12. Benzilic Acid Type Rearrangements

The oxidative, ring contraction (transformation of a hydroxy- or oxo-hydroxy-benzene of the oxo-hydroxy-dihydrobenzene compounds into oxo-cyclopentane derivatives) can be effected by means of active manganese dioxide in chloroform,[456] acetone,[168] or aqueous[30] reaction media.

Transformation of hexahydroxybenzene **392** (or its oxidation products, e.g., tetrahydroxy-*p*-benzoquinone, rhodizonac acid, or triquinolyl)[30] into croconic acid **393** in 68%–75% yield requires an alkaline medium and a special type of active manganese dioxide.[30] Possible chemical transformations[44] of **392** into **393** are shown in Scheme 13; this conversion may involve the manganese ester intermediate **392a**, an oxidation process to give intermediates **392b** and **392c**, and benzilic acid-type (or α-oxoalcohol type) of rearrangements[457,458] of intermediates **392d** and **392e**, to give via carbonium ion **392f**,

SCHEME 12

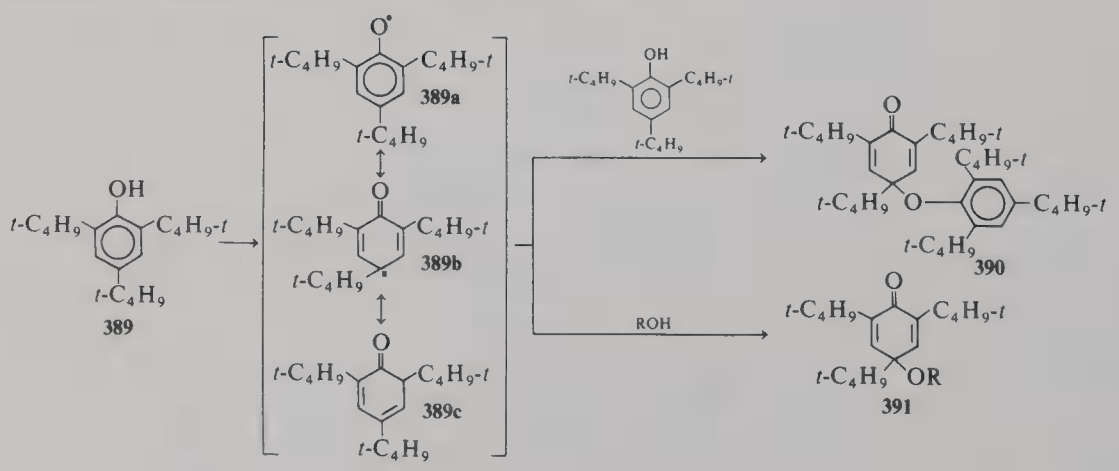
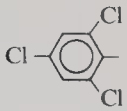
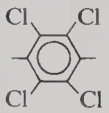
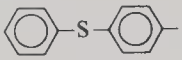
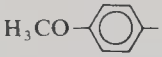
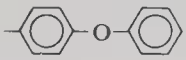
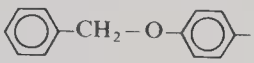
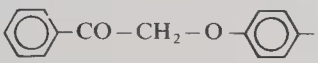
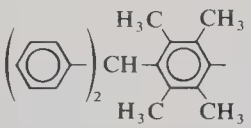
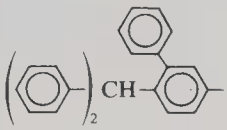
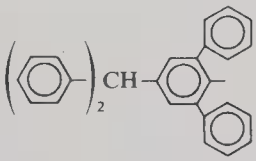


TABLE XIII. Preparation of Cyclohexadienonyl Phenyl Ethers (**391** Scheme 12)[a]

R	Yield (%)	Reference
	73	439
	93	439
	90	439
	86	439
	91	439
	82	439
	71	439
	87	439
	85	448
	75	448
	62	448

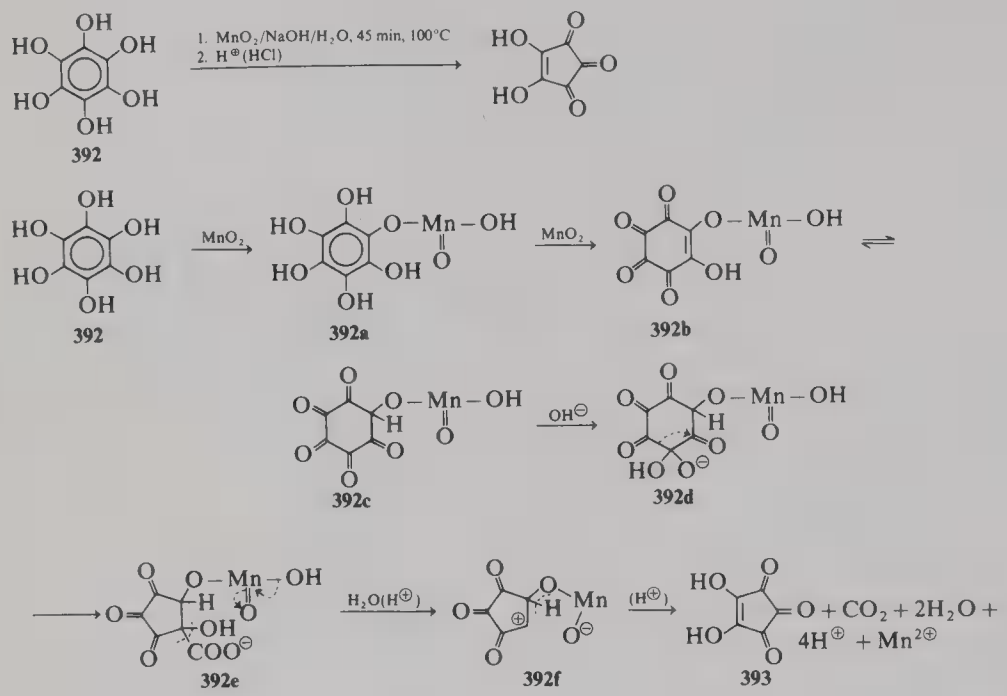
[a] Some additional examples of oxidative coupling of phenols are summarized in Table XI.

product 393. Steps from **392a** to **392c** can be reconciled by invoking radical participation. Thus, conversion of **392** into **393** by manganese dioxide presumably proceeds by a concerted mechanism involving ionic and free-radical pathways.[44]

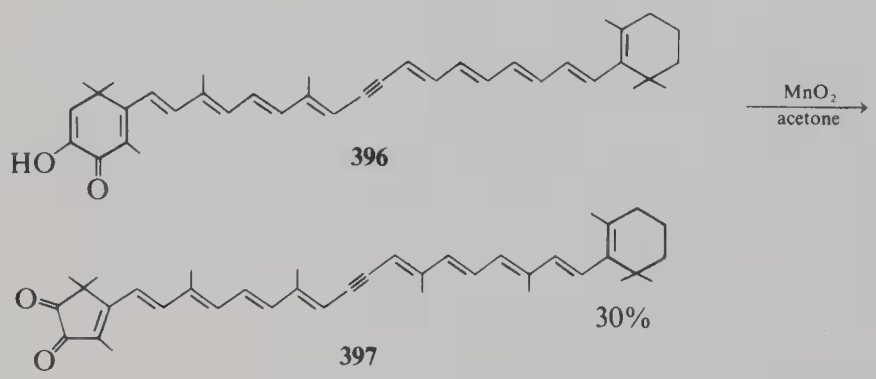
3.12.1. Oxidative Ring Contraction of Carotenoid Diosphenols

An interesting oxidative rearrangement has been observed with the carotenoid diosphenol. Treatment of **394** (15,15′-dehydro-β-carotene-3,4-dione) with manganese dioxide in acetone at 20°C gave the purple cyclopentanedione **395**. Carotenoids with end groups corresponding to those of **394a** have been isolated.[107] Similarly carotenoid diosphenol (**396**) was converted into the 2-nor-carotenoid (**397**) (30% yield) via a ring contraction[459] (Scheme 14).

SCHEME 13



392 392a 392b 392c 392d 392e 392f 393

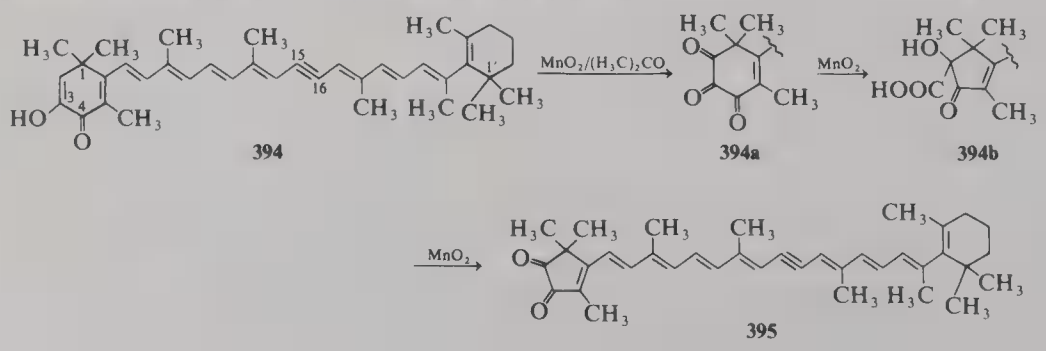


396 397

3.12.2. *Oxidative Ring Contraction of Steroids*

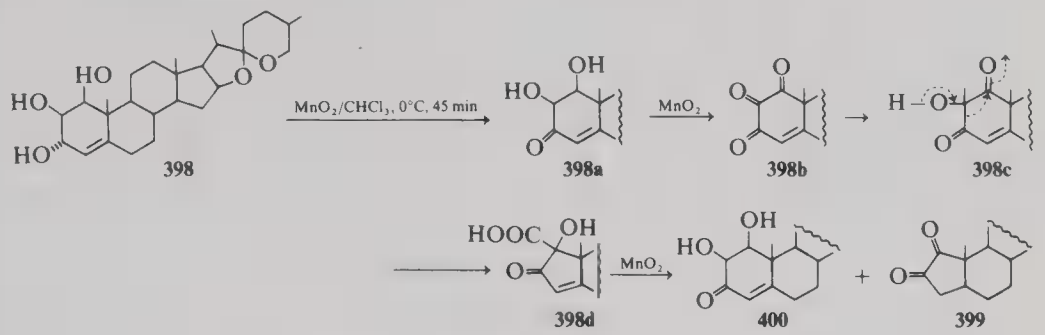
The foregoing reaction pathway is substantiated by the results of an earlier report[456] describing the conversion of the trihydroxysteroid **398** by manganese dioxide in chloroform (under unusually mild conditions) into the cyclopentanedione derivative **399**. The following

SCHEME 14

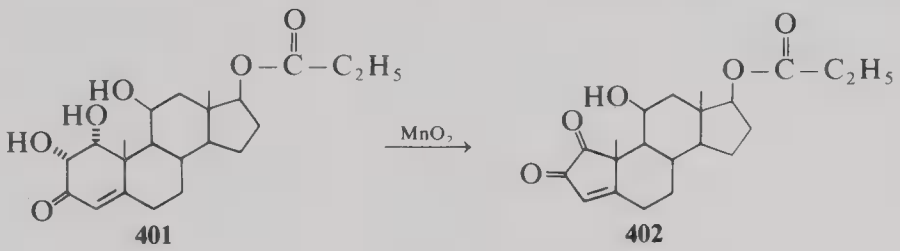


394 394a 394b 395

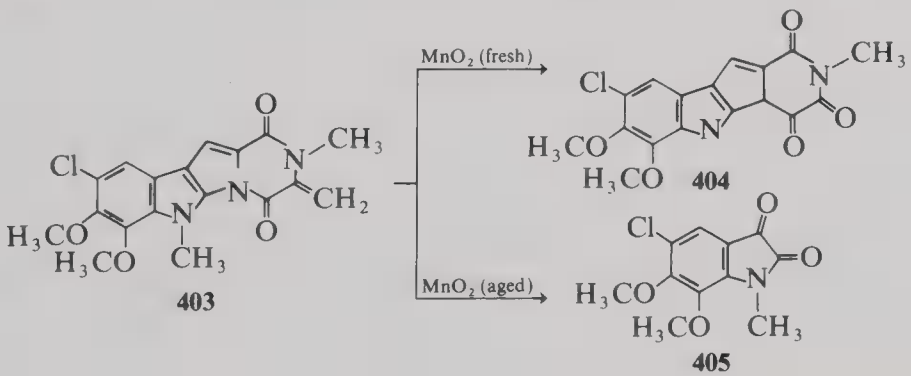
SCHEME 15



sequence **398a** → **398d** has been proposed[456] to explain the formation of **399** and **400** (Scheme 15). By a similar mechanism, on treatment with manganese dioxide the steroid oxodiols of type **401** also undergo ring contraction, to give **402**.[460,461]. This reaction pathway is probably typical for manganese dioxide oxidation; consequently, ring-contraction rearrangements can be expected with all other polyhydroxy or polyoxo ring systems.



The oxidation of the indole derivative **403** with manganese dioxide to give the isatin derivative **405**[462] apparently involves an oxidative rearrangement similar to that of the benzilic acid type; the loss of the methylene side chain and isolation of the trione **404** constitute supporting evidence; in addition, the efficiency of the aged and the freshly prepared reagent may be noted.



4. DEHYDROGENATION AND OXIDATIVE AROMATIZATION

4.1. Dehydrogenation

Introduction of a double bond, referred to as a dehydrogenation process,[463] can proceed either by hydride ion abstraction (an ionic mechanism) or abstraction of a hydrogen atom or an electron (a free-radical mechanism). Hydrogen can be removed from the saturated com-

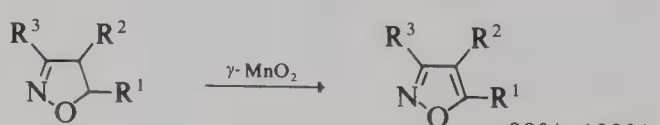
pounds either catalytically or chemically. Catalytic dehydrogenation over a metal catalyst (e.g., Pt, Pd, MoO_3/Al_2O_3, etc.) is extensively used in industry (e.g., conversion of straight or branched alkanes into aromatic hydrocrbons), whereas chemical dehydrogenation (e.g., by use of sulfur, selenium, bromine, high-potential quinones,[464] e.g., DDQ, chloranil, also $Pb(OAc)_4$, SeO_2, or $Hg(OAc)_2$, etc.) can have both industrial and laboratory application.

In the series of chemical dehydrogenating agents, manganese dioxide is also known as a selective dehydrogenating agent[465] particularly noted for its unexpected dehydrogenation (and even aromatization) of steroids,[21] e.g., introduction of a carbon–carbon double bond adjacent (alpha, beta) to the steroid carbonyl group or in position allylic to it (gamma, delta to an alpha, beta unsaturated carbonyl group) (Section 1). The high redox potential of manganese dioxide (Section 3.2) permits many dehydrogenation and aromatization reactions. Stereoelectronic effects apparently influence the rate of dehydrogenation; generally, a *trans* elimination of two hydrogen atoms is a process energetically more favorable than *cis* elimination; similarly, dehydrogenation of the ketosteroids by manganese dioxide proceeds stereoselectively with the preferential loss of the axial hydrogen atom.

Literature reports are numerous on the application of active manganese dioxide as a selective dehydrogenating reagent. In addition to examples mentioned earlier in the text (compounds **234**, **237**, **244**, **353**), a partial list of dehydrogenations by the reagent in the carbocyclic series includes a bicyclic compound (to give a 5,6,7,8-tetralin derivative),[466] conversion of 2,3-dihydro-1,4-dioxonaphthalene into 1,4-dioxonaphthalene (72% yield, MnO_2/ethyl acetate/acetonitrile, under reflux for 3 h)[318] or dehydrogenation of oxygen heterocyclics, natural products dolineone or nepsidine[466] or leucomycin A_3[400,467] or DL-4′-*O*-methylcoclaurin (a phenolic isoquinoline alkaloid).[468] The dehydrogenation of nitrogen heterocyclics with manganese dioxide is widely used; the procedure, for example, has been successfully applied to converting 1,2,3,4-tetrahydroquinoline into quinoline,[60] 2,3-dihydroindole into indole,[60] acridane into acridine,[60] pyrroline into dihydropyrrazoline,[24] 4,5-dihydro-1,2-oxazole into 1,2-oxazole,[38] or indolines,[60,469,470] imidazolines,[471] benzimidazolines,[472,473] anthraquinoneimidazolines,[474] and pyrazolines[475–477] into the corresponding indoles, imidazoles, and pyrazoles; also to produce pyrroles,[478,479] carbazoles,[480] quinazolines (e.g., conversion of 1,2,3,4-tetrahydroquinazoline into the 2,3-dihydroderivative),[481] diazepines,[482] and thiazoles[483] from the corresponding hydro compounds.

4.1.1. Dehydrogenation at Carbon or Carbon-Hetero Atom

Active γ-MnO_2,[37] as described in Ref. 19 (see also Section 1.1.4), has recently been found[38] to be the only oxidant examined that is suitable for quantitative conversion of 4,5-dihydro-1,2-oxazoles (**406**) into 1,2-oxazoles (**407**) (98%–100% yield). The experimental simplicity and lack of by-products recommend the present method for the conversion of both alkyl and aryl 3,5-disubstituted 4,5-dihydro-1,2-oxazoles into 1,2-oxazoles. Moreover, the essentially neutral conditions involved can be tolerated by several functions and protective groups, thus making this procedure a useful synthetically transformation.

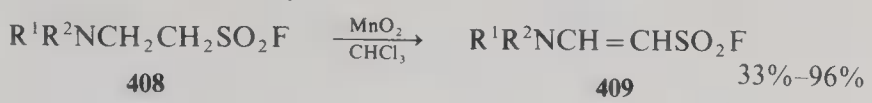


406 **407** 98%–100%

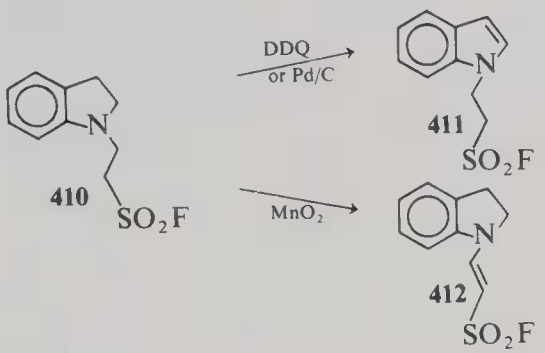
R^1, R^3 = alkyl, aryl, COOMe
R^2 = H, NO_2

Hyatt and Krutak[484] described an unusual manganese dioxide oxidation of 2-aminoethanesulfonyl fluorides. For example, β-fluorosulfonylethylamines, e.g., **408** were dehydrogenated by active manganese dioxide to afford novel 2-aminoethenesulfonyl fluorides (**409**) (33%–96%). Whereas the indole derivative **411** could be prepared from indoline **410**

by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or palladium on carbon, the reaction of **410** with active MnO_2 afforded a new compound **412**, which was isomeric with **411**.

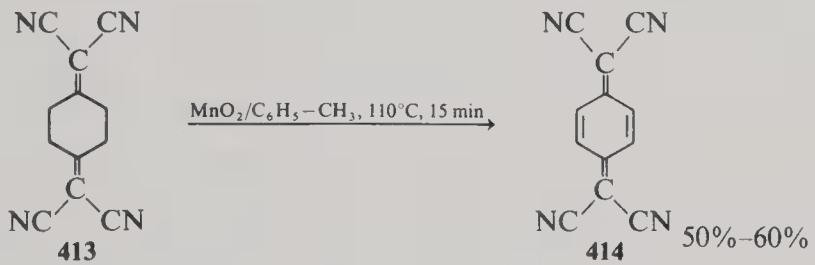


408 **409**



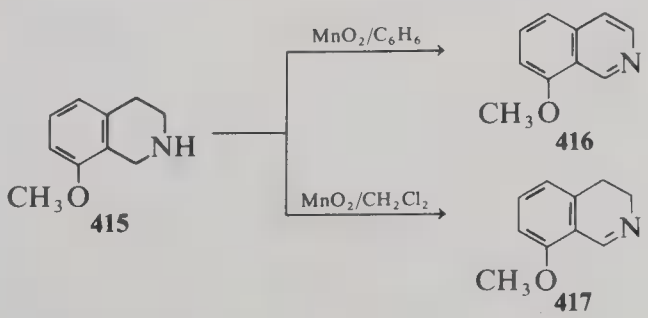
Similar dehydrogenation of the α-pyron side-chain alkane group following treatment with manganese dioxide has recently been reported.[485]

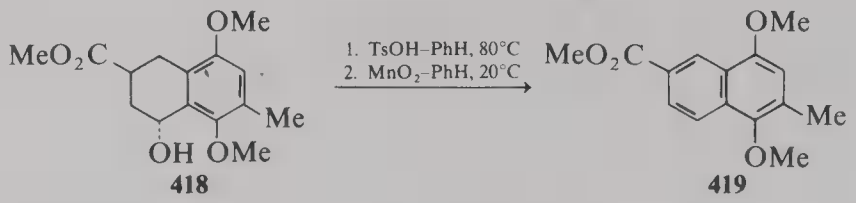
A new, rapid procedure for dehydrogenating **413** (2,3,5,6-tetrahydro-1,4-dicyanomethylenecyclohexane) to **414** (7,7,8,8-tetracyanoquinonedimethane, TCNQ)[486] was developed in this laboratory by application of active manganese dioxide in warm toluene.[318] Although the conversion of **413** into **414** was moderate (50%–60% yield), the procedure is rapid compared to other methods.[487,488] Moreover, the procedure can be a useful diagnostic test for detection of small concentrations of **413** in mixtures (by TLC, NMR, or visible spectrum of the yellow-orange solution due to **414**). The relative stability of the cyano groups in **413** and **414** against attack by manganese dioxide (e.g., no amide formation) should be noted. Similar oxidation of *p*-phenylenedimalononitrile[487] (with manganese dioxide in warm toluene), produced **414** in 80% yield.[318]



413 **414**

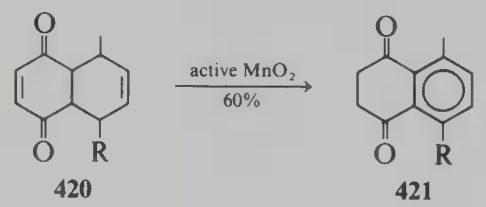
As recently shown by Rapoport *et al.*,[750] dehydrogenation of 1,2,3,4-tetrahydroisoquinoline (**415**) with active manganese dioxide depends very much on a solvent used. Thus, oxidation of **415** with MnO_2 in benzene led predominately to the fully aromatized 8-methoxyisoquinoline (**416**); with dichloromethane as solvent, oxidation was more selective,



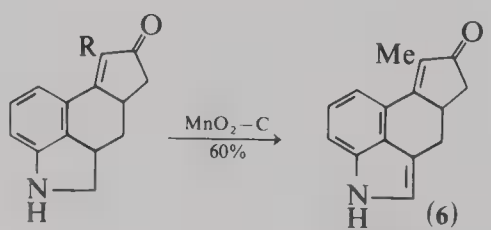


418 **419**

and the dihydroisoquinoline (**417**) was the major product. Similarly, dehydrogenation of **418** (MnO_2, benzene, 20°C) gave the naphthalene **419** in 77% yield.[751] Recently active manganese dioxide proved to be the reagent of choice to effect an oxidative aromatization (e.g., dehydrogenation) of carbocyclic[767] and heterocyclic[768,769] systems, e.g., conversions **420** → **421**,[767] **422** → **423**[768] (using manganese dioxide on activated carbon), and **424** → **425**.[769] Some additional dehydrogenation reactions using manganese dioxide are depicted below.[470,472,473,490–494]

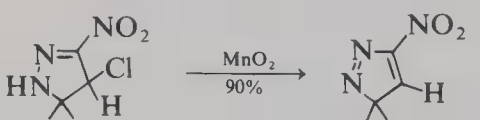


420 **421**

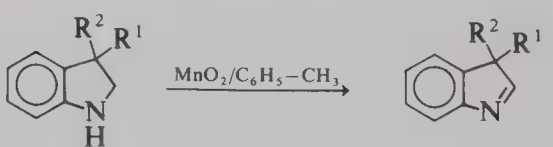


422 **423**

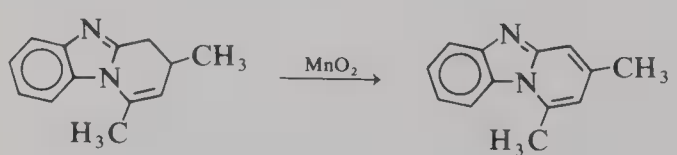
$R = CH_3$



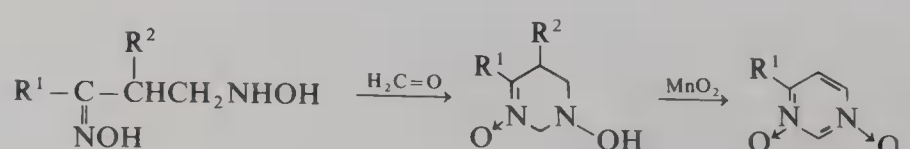
424 **425**



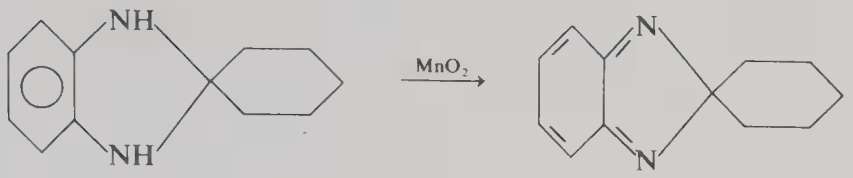
(Ref. 470)



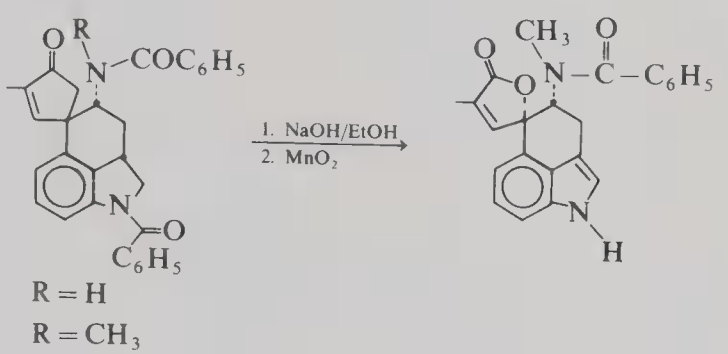
(Ref. 473)



(Ref. 490)



(Ref. 472)



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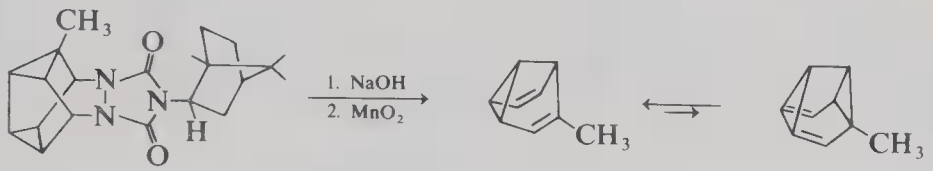
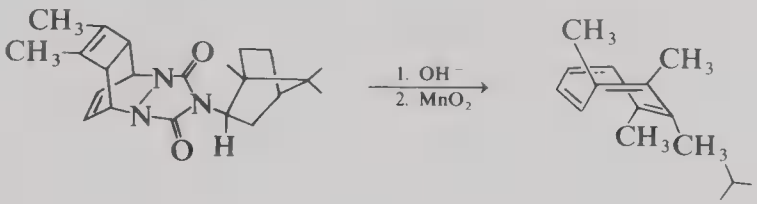


(Ref. 492)



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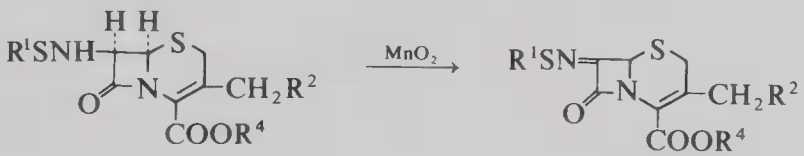

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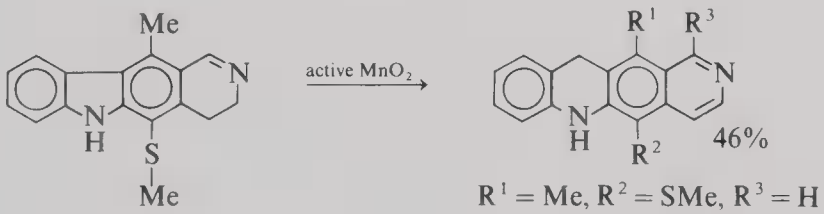
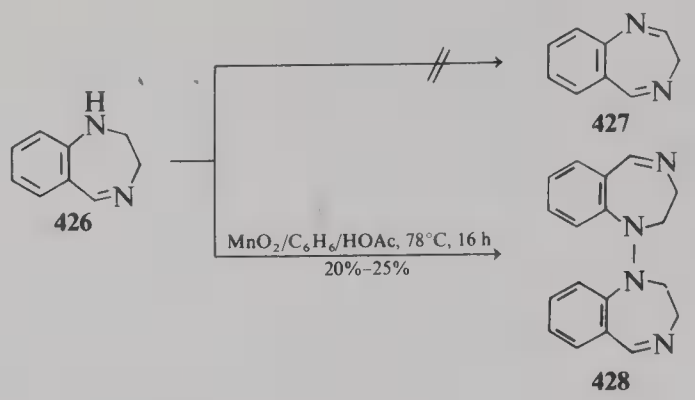


(Ref. 494a)

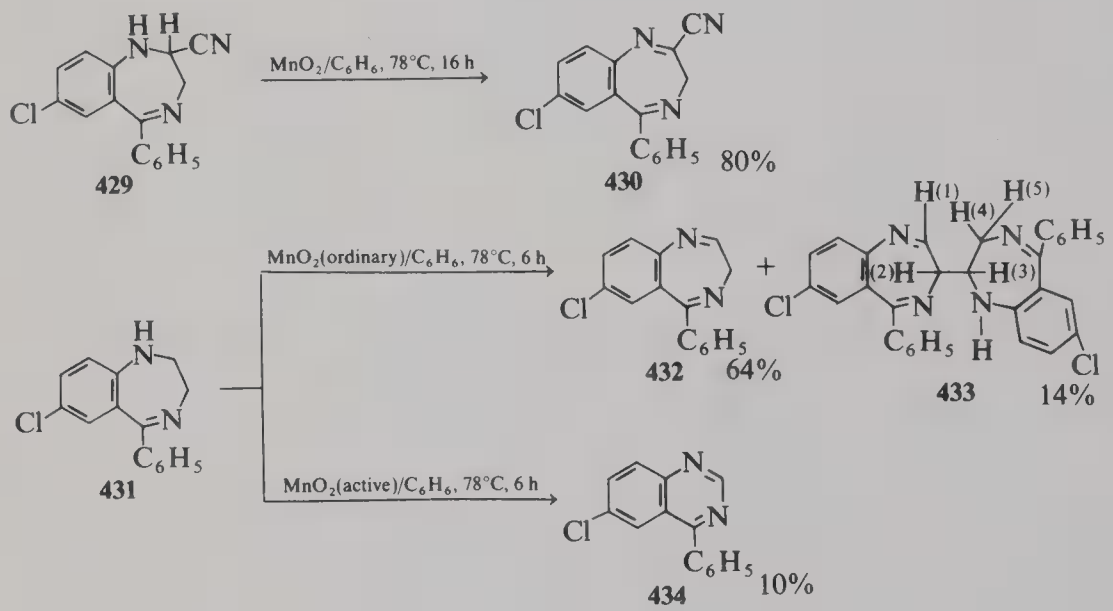
4.1.2. Dehydrogenation in the Diazepine Series

A synthesis of benzodiazepines[495] utilized manganese dioxide for dehydrogenation of the corresponding 1,2-dihydrobenzodiazepines.[496] An attempt to prepare the unsubstituted 3H-1,4-benzodiazepine (**427**) by manganese dioxide dehydrogenation of dihydrobenzodiazepine (**426**) resulted in the formation of dimer **428**, 1,1-bis[2,3-dihydro-1H-1,4-benzodiazepinyl] in 20%–25% yield.[495] However, dehydrogenation of 7-chloro-2-cyano-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine (**429**) with manganese dioxide gave 7-chloro-2-cyano-5-phenyl-3H-1,4-benzodiazepine (**430**) in 80% yield. The cyano group in **429** or **430**



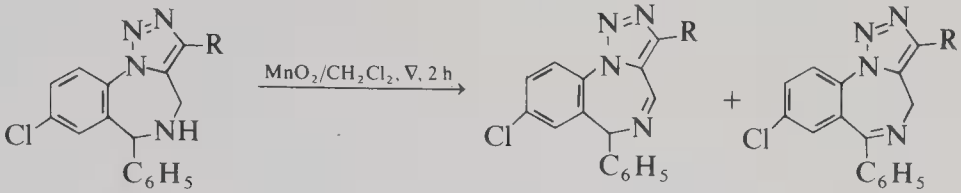
was not affected by the oxidant. Surprising results have been observed in dehydrogenation of dihydrobenzodiazepines with ordinary and activated manganese dioxide. Whereas treatment of 7-chloro-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine (**431**) with ordinary manganese dioxide gave benzodiazepine (**432**) (64% yield) and the dimer **433** (14% yield), treatment of **431** with the activated reagent gave an elimination and aromatization compound **434** (6-chloro-4-phenylquinazoline), in 10% yield, as the only product isolated.[495]

The final step in a total synthesis of the ergot alkaloid *dl*-isosetoclavine involved dehydrogenation; this step was carried out in 36% yield by means of activated manganese dioxide in chloroform at 25°C.[496]



New, 1,4-benzodiazepines have been conveniently prepared by dehydrogenation of the corresponding dihydro-compounds with active manganese dioxide. Thus, the amine (**435**; R = H, 8-chloro-5,6-dihydro-6-phenyl-4H-v-triazolo[1.5-*a*][1,4]benzodiazepine) on treatment with manganese dioxide in refluxing dichloromethane (2 h) gave a mixture of two products (separated by column chromatography), the 6H-isomer **436** (8-chloro-6-phenyl-6H-v-triazolo[1,5-*a*][1,4]benzodiazepine in 30% yield and more polar 4H-isomer **437** (8-chloro-6-phenyl-4H-v-triazolo[1,5-*a*][1,4]benzodiazepine) in 28% yield. Similarly **435** ($R = CH_3$) was oxidized and the resulting two compounds separated.[497]

Dehydrogenation of the 8-aza steroid intermediate **438** [*N*-(*β*-3,4-dimethoxyphenethyl)-1,2,3,4,5,6,7,8-octahydroquinoline-2,5-dione] was effected with manganese dioxide in dichloromethane at room temperature to give **439** [*N*-(*β*-3,4-dimethoxyphenethyl)-

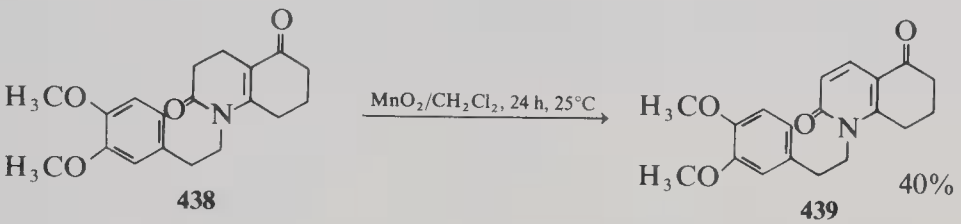


435a R = H
b R = CH_3

436a (30%)
b (22%)

437a (28%)
b (42%)

1,2,5,6,7,8-hexahydroquinoline-2,5-dione] in 40% yield.[498] Additional dehydrogenation that include intramolecular cyclization reactions will be presented in discussion of amines and hydrazines (Section 5).



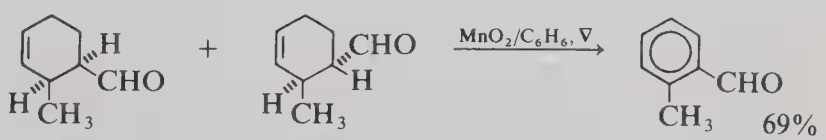
438

439

4.2. Oxidative Aromatization

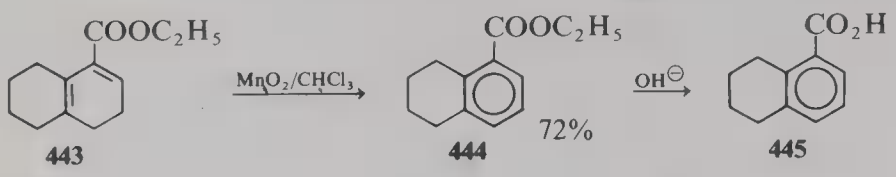
Solid manganese dioxide has a high oxidation potential ($E_0 = 1.23$ V)[18,499,500]; in acid solution, it is a strong oxidant [Mn(IV) couple, $E_0 = 1.57$ V][18,500]; however, in neutral medium, it is only a mild oxidizing agent, and in alkaline solution, its potential[499] is close to zero [Mn(IV)/Mn(II) $E_2 = -0.05$ V]. Thermodynamically, manganese(IV) could be both a very powerful, two-equivalent oxidant and a vigorous, one-electron oxidant.[501] Although the oxidation potential of manganese dioxide is high, it is generally a mild oxidizing agent under neutral conditions, seldom effecting aromatization reactions.[465] However, the oxidation potential of the reagent also permits many dehydrogenation reactions, and even complete aromatization of many saturated ring systems [to give systems containing $(4n+2)\pi$ electrons].[502]

Aromatization effected by manganese dioxide has been observed for a variety of carbocyclic and heterocyclic compounds; these include substituted cyclohexenes,[503] dihydrobenzenes,[466,504,505] steroids,[261] carbazoles,[480,506] a bicyclic alcohol (conversion **2** → **5**),[73] and acyclic acetylene derivates.[203] A mixture of *cis*- and *trans*-2-methylcyclohexene-3-carbaldehydes (**440** and **441**, respectively) but not esters, and an excess of activated manganese dioxide, refluxed in benzene under anaerobic conditions, gave *o*-tolualdehyde (**442**) in 69% yield; similarly, 4-acetylcyclohexene is oxidized to acetophenone in 71% yield; a slight kinetic preference for aromatization of the *cis* isomer **440** has been noted.[503]



440 **441** **442**

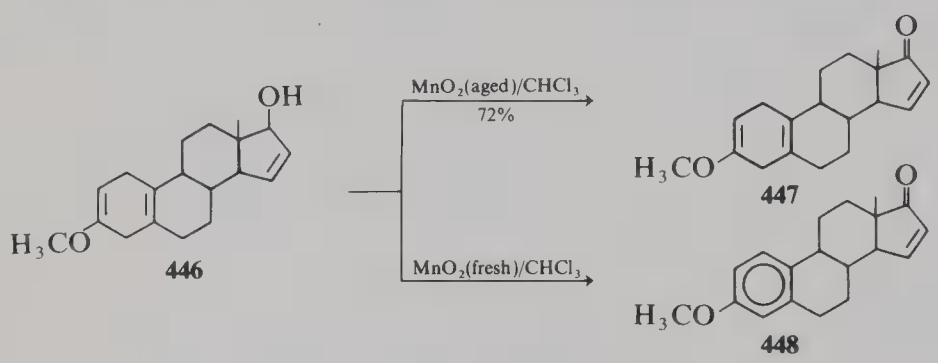
An example of oxidative aromatization of an ester is the conversion of **443** by active manganese dioxide (ACC) to give **444** [recovered, after hydrolysis, as **445** (5,6,7,8-tetrahydro-1-naphthoic acid)].[506] The variable activity of manganese dioxide may give unexpected products on oxidation. Thus, treatment of 3-methoxy-2,5(10),15-estratrien-17β-ol (**446**) with a two-year-old sample of active manganese dioxide have the 17-dione **447**, whereas fresh



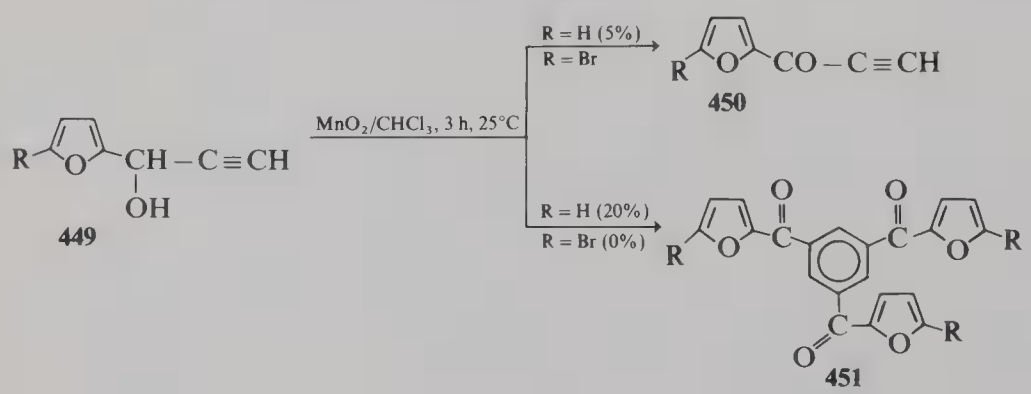
443 444 445

reagent caused aromatization of ring A, to give **448** (3-methoxy-1,3,5(10)-estratetraen-17-one) in addition to **447**.[261]

An unusual aromatization of an acetylenic alcohol has been reported by Sasaki and Suzuki.[203] Treatment of 1-(2-furyl)-1-hydroxyprop-2-yne (**449**; R = H) with active manganese dioxide (ACC) gave expected ethynyl ketone **450** (R = H, 5% yield) and the unexpected, symmetrical, trisubstituted benzene derivative **451** (R = H, 20%, yellow crystals); this is an example of heteroaromaticity as the result of an oxidative cyclization of the acetylenic alcohol **449**.[203] However, similar oxidation of the substituted alcohol **449** (R = Br) gave the keto derivative **450** (R = Br) as the only product.[175]



446 447 448



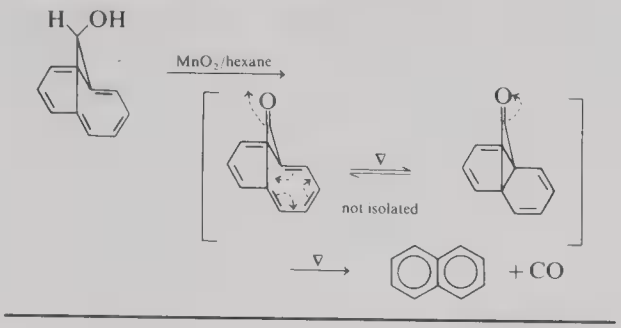
449 450 451

Cyclization and aromatization of **449** to **451** parallels the classical example of the thermal polymerization of acetylene to benzene,[502] and the aromatization of the dipotassium salt of dihydroxyacetylene to the hexapotassium salt of hexahydroxybenzene,[507,508] a precursor of the aromatic oxocarbons.[509]

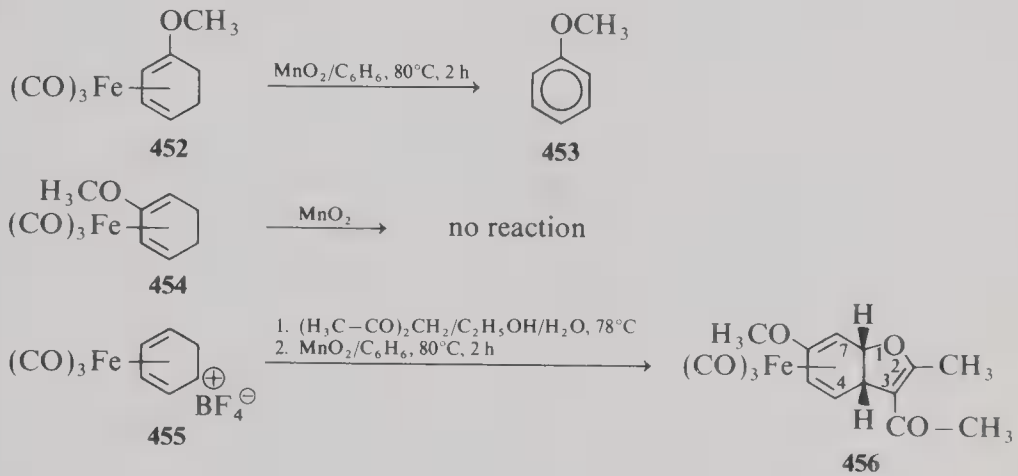
An interesting stereospecific aromatization that involves an organoiron complex has recently been observed. Thus, manganese dioxide removes the tricarbonyliron group from its complex with 1-methoxycyclohexa-1,3-diene (**452**) to give anisole (**453**) whereas the isomeric complex **454** (2-methoxycyclohexa-1,3-dienetricarbonyliron) remains unaffected following treatment with the oxidant.

However, tricarbonylcyclohexadienylironcarbonium tetrafluoroborate (**455**) after successive treatment with a β-diketone (e.g., acetylacetone) and manganese dioxide, cyclizes stereospecifically to give **456** (3-acetyl-*cis*-6-methoxy-2-methyl-3a,7a-dihydrobenzofurantricarbonyliron) in 90% yield.[510] The oxidative cyclization reaction, as suggested,[510] may be a concerted attack by the enol hydroxyl and may proceed with the transfer of the *endo* C—H electrons to the oxidizing agent via iron.

SCHEME 16



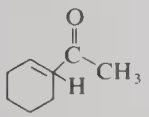
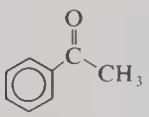
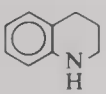
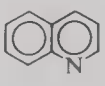
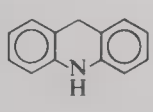
Manganese dioxide dehydrogenations (and aromatizations) are subject to fewer competitive side-reactions than those accomplished by selenium dioxide,[465] or by the Oppenauer type of reaction. Among compounds aromatized by the manganese dioxide treatment are



6-methyl-3-(*p*-tolyl)-3,4-dihydroquinazoline,[481] 1,2,3,4-tetrahydroquinoline, 2,3-dihydroindole, acridane,[60] and other dehydroheterocyclics.[283,466,468,495,511,512]

Vogel and co-workers[512] in their comprehensive study of chemistry of a novel 10π-electron annulene system (e.g., 1,6-methanocyclodecapentaene) observed an unusual type of aromatic isomerization, for example, in an attempted preparation of a ketone (e.g., 11-oxo-1,6-methanocyclodecapentaene) by oxidation of the corresponding annulene alcohol with manganese dioxide. The observed products were naphthalene and carbon monoxide arising

TABLE XIV. Manganese Dioxide-Induced Aromatization

Substrate	Product	Reaction conditions	Yield (%)	Reference
		$MnO_2/C_6H_6/N_2$	71	503
		$MnO_2/C_6H_6/\sim 1$ h	79	60
		$MnO_2/C_6H_6/0.75$ h	93	60

via cheletropic fragmentation of the intermediate ketone. The reaction products were also accompanied by some α-naphthaldehyde (which is isomeric with the above ketone). The indicated (Scheme 16) four-electron process is symmetry allowed to occur thermally via a concerted, nonlinear, cheletropic process. The thermodynamic stability of the products, naphthalene and carbon monoxide, provides ample driving force the concerted decarbonylation process. Some other exampes examples of aromatization are shown in Table XIV.

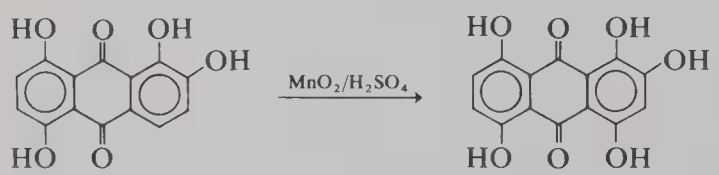
5. HYDROCARBONS

5.1. Some Chemical Applications of Precipitated Manganese Dioxide in Acid Media (e.g., Oxidation of Conjugated CH_3-, CH_2-, and $=CH-$ Groups)

5.1.1. Aromatic Systems

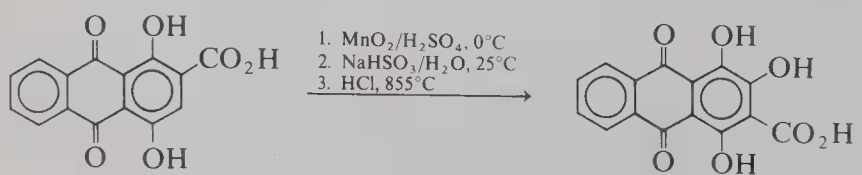
An early application of natural manganese dioxide, pyrolusite, more than 100 years ago, was either in acid media (strong mineral acids or acetic acid) or in an alkaline suspension, often with application of heat, and generally involving the oxidation of compounds having stable nuclei (e.g., aromatic compounds).

In 1835, Liebig[513] first converted ethanol into acetaldehyde by use of pyrolusite and precipitated manganese dioxide "Braunstein" in sulfuric acid, and Nietzki[514] used the reagent for oxidation of hydroxy aromatics in an alkaline medium. Bohn[515] in 1888, discovered that hydroxy groups can be introduced into anthraquinone by use of fuming sulfuric acid and manganese dioxide; in this way, the quinalizarin dye Violet blue (**457**) was converted into the important Alizarin Cyanin R (blue) (**458**) in high yield.



457 **458**

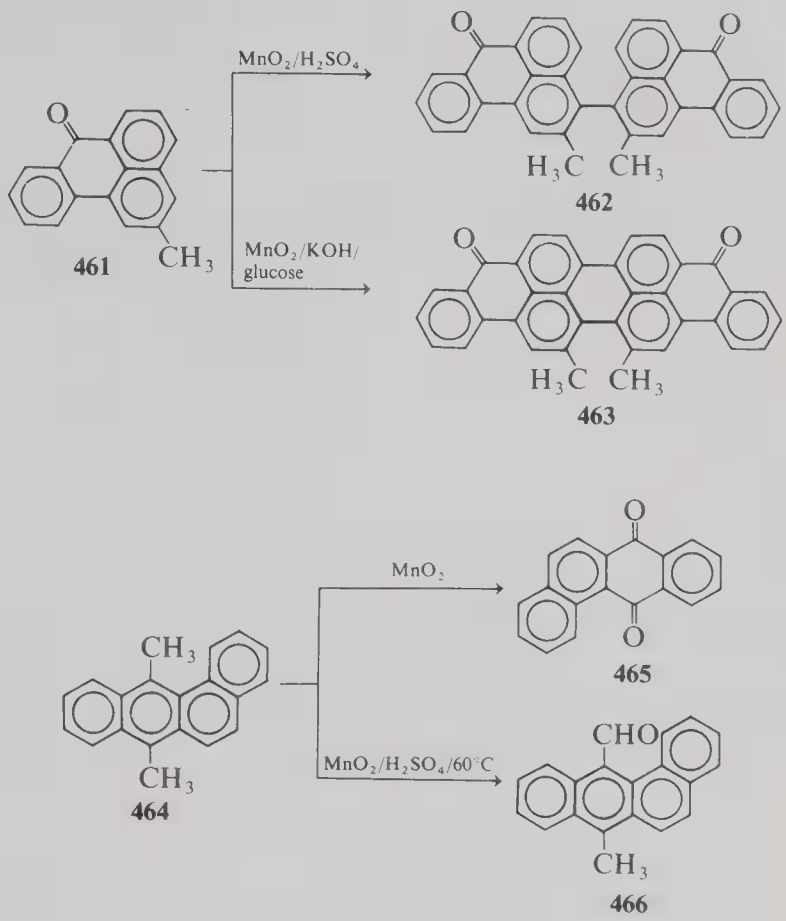
Another example of a similar hydroxylation of the aromatic ring by manganese dioxide in acid media is the conversion of 1,4-dihydroxy-2-anthraquinonecarboxylic acid (**459**) into 1,2,4-trihydroxy-3-anthraquinonecarboxylic acid (**460**) in good yield.[516] However, the oxidation[517] of 2-methyl-*meso*-benzanthrone (**461**) with manganese dioxide in sulfuric acid at 0–5°C gave the coupling product 2,2′-dimethyl-3,3′-bibenzanthryl-7,7′-dione (**462**) in 78%



459 **460**

yield, whereas in alkaline medium containing D-glucose, the product was 16,17-dimethylviolanthrone (**463**); this is an oxidative coupling with ring closure.

The reaction medium is very important in the oxidation of hydrocarbons. For example, the oxidation of 7,12-dimethyl benz[a]-anthracene (**464**) with manganese dioxide in a neutral medium gave 7,12-quinone (**465**), whereas similar oxidation in sulfuric acid yielded 7-methyl-12-formyl benz[a]anthracene (**466**).[518]



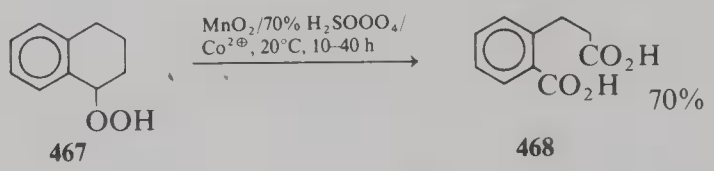
An early procedure[519] that constitutes a quick route to toluquinone consists in steam distillation of a mixture of *o*-toluidine, precipitated manganese dioxide, and sulfuric acid. The reagent has also been used to oxidize hydroquinone (quinol) to *p*-benzoquinone,[520] to oxidize[521] pyridoxamine 5′-phosphate to pyridoxal 5′-phosphate (a most important form of vitamin B_6), to convert 2-furaldehyde (with manganese dioxide/concentrated hydrochloride acid) into[522] mucochloric acid (via a β-chloro-γ-hydroxylactone intermediate),[523] for commercial manufacture of *p*-benzoquinone (aniline/manganese dioxide/sulfuric acid[524,525]), and for preparation of pyridoxal-*p*-toluidine Schiff base.[526] Manganese dioxide in acid medium has also been applied for the conversion of methyl- and ethylbenzene to the corresponding benzaldehyde and acetophenone[527] and in oxidation of similar systems (e.g., alcohols, phenols, and amines).[528–533]

5.1.2. Other Systems

Kinetics of the oxidation of the aliphatic acids by manganese dioxide in an acid medium have been studied[534]; the oxidation of malic acid proceeds at a lower rate than the corresponding reaction with oxalic acid,[535] and both are faster than that of malonic acid.[536] Malic and tartaric acids[537] showed an induction period in similar oxidations. It is believed that the rate-controlling step in these oxidations is the dissolution of the solid.[3]

An interesting procedure for preparation of dicarboxylic acids involves cleavage of a carbon–carbon bond in cyclic hydroperoxides. Thus, tetralin-α-hydroperoxide (**467**) was added dropwise at 15–20°C to a stirred mixture of the calculated amount of manganese dioxide and 70°C sulfuric acid containing a little copper(II) or cobalt(II) acetate to prevent tar formation; after stirring for 10–40 h, tetralic acid (**468**) was isolated in 70% yield.[538]

Manganese dioxide (along with other oxidants) promotes the oxidation (e.g., hydroxylation) of ethylene by palladium(II) acetate in acetic acid to give 1,2-disubstituted



467 468

alkanes, e.g., ethylene glycol mono- and diacetate.[539] The reagent has also been applied for oxidation of palladium dichloride/alkene complexes, in a novel method for synthesis of α,β-unsaturated aldehydes and ketones.[540]

5.2. Oxidation of Conjugated CH_3-, CH_2-, and $=CH-$ Groups by Manganese Dioxide in Neutral Media

A direct oxidation of methylene or methine groups (in cyclic and acyclic compounds) by active manganese dioxide in a neutral organic solvent to give either hydroxyl, carbonyl, or ether derivatives has been demonstrated on several occasions in this survey, e.g., conversions of **2** → **3** → **4**,[73] of **249** → **250**[266] or conversions of 2-butanone into 2,3-butanedione[329] [Eq. (12)], of isobutene into 2-methylacrolein[15,540] [Eq. (13)], also of oxidation of pyrene to give a mixture of 1,6- and 1,8-pyrenediones,[44] and further a conversion of codeine into 14-hydroxycodeine,[271,287] of cyclohexene into cyclohexanone,[541] or of the allylic methylene group in the vitamin A_1 series into the keto derivatives.[3,15,50,99,542]

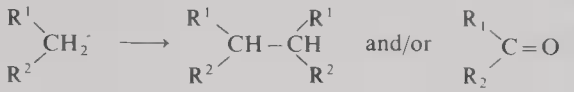
$$H_3C-CH_2-\overset{\overset{O}{\|}}{C}-CH_3 \xrightarrow{MnO_2} H_3C-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-CH_3 \quad (12)$$

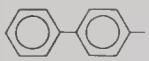
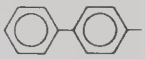
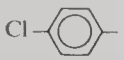
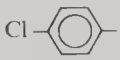
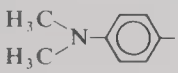
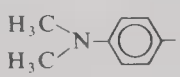
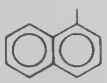
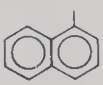
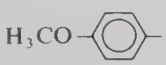
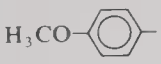
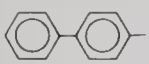
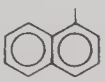
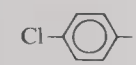
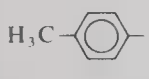
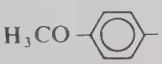
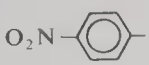
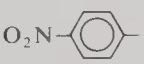
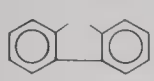
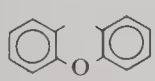
52%

$$H_2C=\overset{\overset{CH_3}{|}}{C}-CH_3 \xrightarrow{MnO_2} H_2C=\overset{\overset{CH_3}{|}}{C}-CHO \quad (13)$$

As shown in Section 5.1, oxidation of aromatic compounds with manganese dioxide in acid medium has been extensively studied; however, use of the reagent in neutral medium for oxidation of aromatic hydrocarbons (e.g., activated methylene group) is still of limited scope. Pratt and Suskind[59] studied the oxidation of a series of diarylmethanes by active manganese dioxide; the authors[59] demonstrated that the same hydrocarbon could form different products under different oxidizing conditions. Thus, when, for example, diphenylmethane (Table XI) was treated with manganese dioxide in a refluxing mixture of benzene and biphenyl, the major product was the coupling compounds, tetrahenylethane (81% yield) with some elimination by-product, tetraphenylethylene (15%–20%). However, when this hydrocarbon was heated directly with an excess of the oxidant (ratio 1:10) in the absence of solvent, benzophenone was the main reaction product (74% yield, Table XIV); a free-radical intermediate was suggested for the formation of the coupling product. The authors[59] found it to be a general reaction with all symmetrical and unsymmetrical diarylmethanes; the rate of the reaction and the yield of tetraarylethanes depend on the electronic properties of the phenyl ring substituents (compare the effect of the electron-donating and electron-withdrawing groups on the yield of coupling product, summarized in Table XV). Formation of benzophenone was also explained[59] by a free-radical mechanism, e.g., as due to an attack of the hydroxyl radicals derived from the hydrated manganese dioxide on the diphenylmethane radical (to give a diarylmethanol intermediate). This was explained by the fact that, when manganese dioxide was first dehydrated by being refluxed with toluene, and diphenylmethane was treated with this oxidant, the yield of benzophenone decreased from 74% to 2%.[59]

TABLE XV. Oxidation of Diarylmethanes[a]

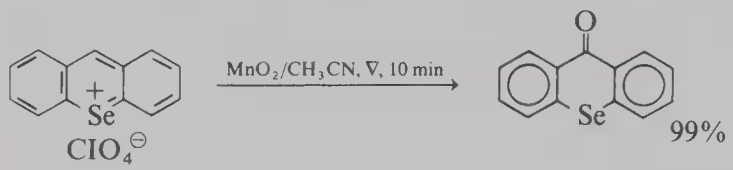


R^1	R^2	Reaction time[b] (min)	Yield (%) of tetra-arylethane[c]	Yield (%) of diaryl ketone[d]
		75	81	74
		40	92	26
		54	74	83
		215	25	0
		244	63	29
		350	17	73
		47	70	76
		63	70	71
		65	81	63
		395	10	0
		1310	3	29
		—	18[e]	—
		6	78	72
		280	0	49
		—	16[e]	80
		—	36[e]	—

[a] Reference 59.
[b] Time required to collect 50% of the water in a Dean-Stark water collector.
[c] Standard tetraarylethane conditions: 0.1 mol of diarylethane, 0.3 mol of MnO_2, 238 g of biphenyl, and 12 g of benzene are magnetically stirred, while distilling off the water at ~211°C.
[d] Standard diaryl ketone conditions: 1 g of diarylmethane and 10 g of MnO_2 are heated in the absence of any solvent at ~125°C for 6 h.
[e] Tetraarylethylene is formed as a side product in this reaction.

5.2.1. Oxidation of Heteroaromatic Rings. Loss of Aromaticity

An interesting oxygen insertion has been reported in the oxidation of certain heterocyclic salts. When selenoxanthylium perchlorate (**469**) was briefly refluxed with active manganese dioxide in acetonitrile, selenoxanthone (**470**) was obtained in quantitative yield.[543]

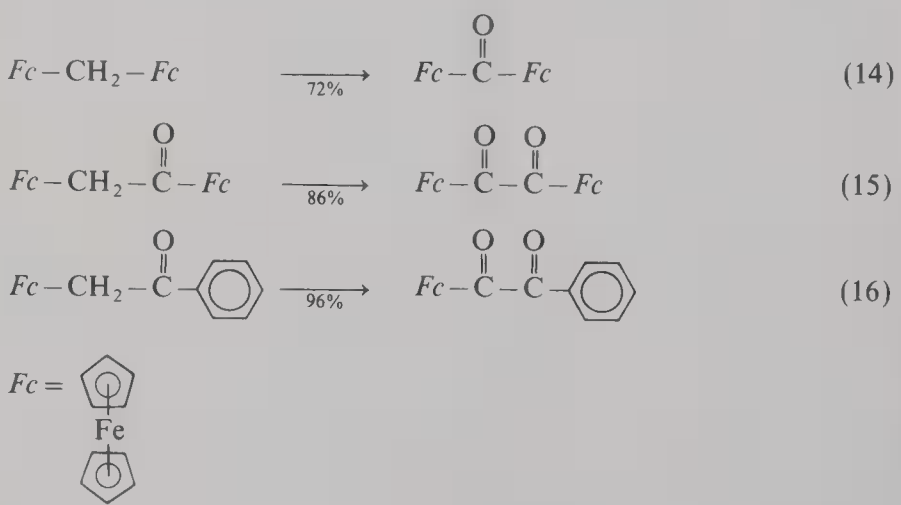


469 **470**

Many other heterocyclic salts were converted into carbonyl compounds in this way [e.g., chromylium perchlorate to coumarin (93%), xanthylium perchlorate to xanthane (90%), thiaxanthylium to thiaxanthone (96%)[543]]. Direct oxidation by active manganese dioxide of alkyl groups attached to heterocyclic ring-systems, for example, in quinaldine, lepidine, α- and γ-picoline, and 1-methylisoquinoline to the corresponding carboxylic acid, has been described.[480]

5.2.2. Oxidation of Alkyl Ferrocenes and Bridged Ferrocenes

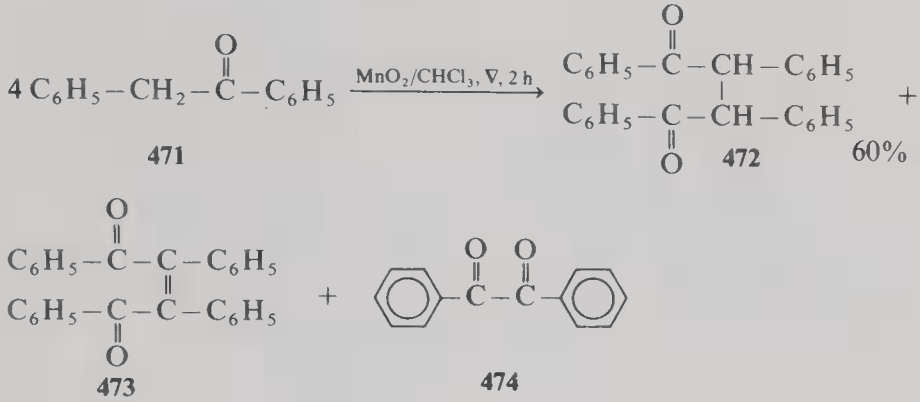
Alkyl ferrocenes are more labile toward manganese dioxide as compared to their aromatic alkyl analogs. A methylene group in diferrocenes, for example, undergoes facile oxidation with manganese dioxide under mild conditions to give carbonyl derivatives[544] [Eqs. (14)–(16)].



Oxidation of the aromatic analogs with manganese dioxide generally requires a higher temperature. In a new example,[318] treatment of deoxybenzoin (**471**) with manganese dioxide in refluxing chloroform (or methylcyclohexane) for 3 h gave dibenzoyldiphenylethane (**472**) in 60% yield, m.p. 254–255°C, lit.[545] m.p. 255°C, ^{1}H-NMR (DMSO-d_6): $\delta = 6$ ppm (C – H).

Some elimination by-product, yellow dibenzoyldiphenylethylene (**473**), 5%–15% yield) and a trace of benzil (**474**) separated on a fluorisil column with 3:2 (v/v) chloroform/hexane. Formation of the coupling products (**472**) and (**473**) can be explained by invoking a free-radical intermediate. Thus, little formation of benzil has been observed following treatment of deoxybenzoin with manganese dioxide, and, in contrast, no coupling product has been reported from a similar oxidation of diferrocenylmethane.

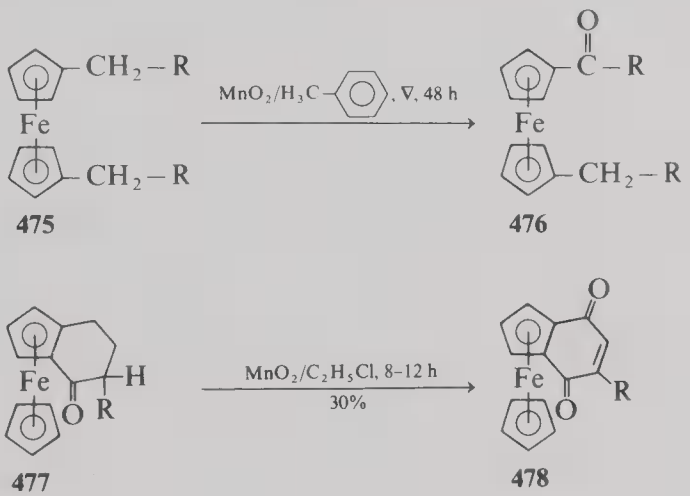
In another example[313] treatment of 1,3-dioxoindane with manganese dioxide in refluxing acetonitrile for 3–4 h followed by concentration of the resultant red solution, gave a mixture



471 472 473 474

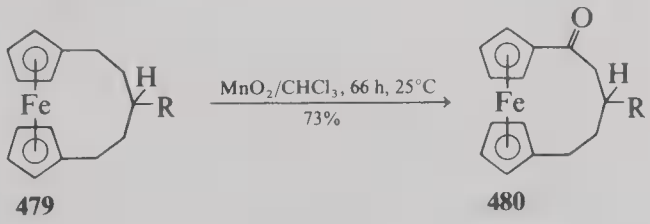
from which at least two high melting components were isolated after chromatography [mass spectrum, $M^{\oplus}m/e = 275$ (100%); $M^{\oplus}m/e = 360$ (100%); m/e 404 (10%)]. The formation of the expected trioxoindane was not observed. Extension of this oxidative coupling procedure to other systems containing labile (activated) methylene groups could constitute a useful synthetic method.

An unusual activation of a methylene group in certain alkyl ferrocenes was observed in earlier studies on ferrocenes; this included oxidation of (**475**) (R = H, CH_3) to **476** (R = H, CH_3)[546] and conversion (with elimination) of **477** (R = H, CH_3) into **478** (R = H, CH_3).[544,546]



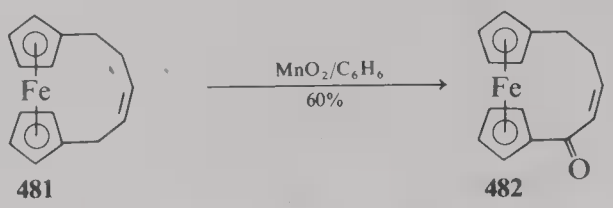
475 476 477 478

Activation of the methylene group by the ferrocene ring[547] is further shown in oxidation by manganese dioxide of a series of interesting methylene-bridged ferrocenes. A direct conversion of methylene group, for example, in ferrocenophane (**479**; R = H, C_6H_5) into ferrocenophan-1-one (**480**; R = H, C_6H_5) in 73% yield, following treatment with manganese dioxide, was suggested[548,549] to involve a free-radical pathway having a ferrocenophan-1-ol as the reaction intermediate.



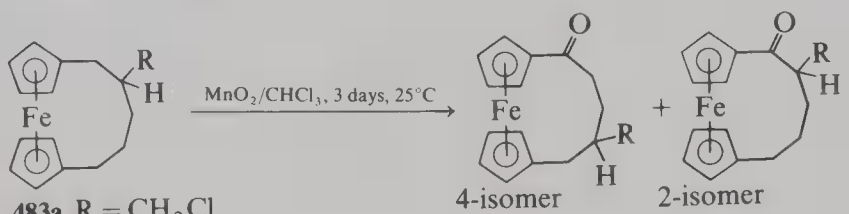
479 480

Similarly, ferrocenophane (**481**) was oxidized to a keto derivative (**482**) in 60% yield.[549] However, when the methylene bridge in ferrocenophanes contained a substituent, oxidation with manganese dioxide usually gave a mixture of isomeric products. Thus, treatment of



481 482

2-(chloromethyl)-ferrocenophane (**483**; $R = CH_2Cl$) with the oxidant produced an isomeric mixture of 2-(chloromethyl)-ferrocenophan-1-ones(4-isomer **484** and 2-isomer **485** in 24% and 44% yield, respectively).[549] Similar oxidation of ferrocenophane having an ether group substituent **483** ($R = CH_2OC_2H_5$) gave a mixture of **484** ($R = CH_2OC_2H_5$) and **485** ($R = CH_2OC_2H_5$) in 6% and 37% yield, respectively.[550]



483a $R = CH_2Cl$
b $R = CH_2OC_2H_5$

4-isomer **484a,b** 2-isomer **485a,b**

Thus far, examples have been cited on the direct attack by manganese dioxide on $-CH_3$, $-CH_2-$, and $=CH-$ groups. However, oxidation of an isolated acetylenic methine group ($\equiv C-H$) by the reagent in a neutral medium is rare, although it is known that the acetylenic hydrogen atom (e.g., in $RC\equiv CH$, R = alkyl) is acidic and susceptible to oxidation [e.g., monoalkyl acetylenes react with oxygen in the presence of base and copper(I) salts to give conjugated diacetylenes (1,3-diynes)]; for the thermodynamic reasons for the above oxidation by manganese dioxide, see more in Ref. 551. Note also that $-CH_2-$ or $=CH-$ groups are most reactive toward manganese dioxide oxidation (usually by a radical mechanism), and these groups, in regard to their acidity and electronegativity, are in the middle of the series $-CH_3 \rightarrow =CH_2 \rightarrow =CH_2 \rightarrow \equiv CH$ (where acidity arises from the increasing electronegativity of carbon as its hybridization changes from $sp^3 \rightarrow sp^2 \rightarrow sp^1$). A partial analogy can be envisaged in the oxidation (e.g., an oxygen transfer) of aromatic hydrocarbons to quinones by manganese dioxide with the metabolic hydroxylation of polycylic aromatic hydrocarbons, probably catalyzed by trace metals present in the biological systems (to give arene oxides and hydroxy aromatics).[552]

6. AMINES AND HYDRAZINES

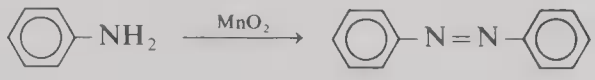
6.1. Amines

In a series of reagents used in the oxidation of amines, e.g., alkyl-substituted amines and various derivatives of amines [e.g., hydroxylamines, hydrazones, and bis(hydrazones)], active manganese dioxide has achieved a prominent place, followed by silver oxide, mercuric oxide, nickel peroxide, and other solid oxidants. The general oxidation of organic nitrogen compounds has recently been reviewed by Boyer.[553]

The manganese dioxide oxidation of nitrogen-containing compounds has been reviewed,[17,18,20] and mechanistic aspects[554] in relation to wet oxidants[554–556] have been discussed.

The susceptibility of an amine to oxidation is attributable to the availability of the unshared pair of electrons on the nitrogen atom. Oxidation of a primary amine with manganese dioxide may initially involve the transfer of one or both electrons to the oxidant,

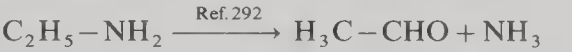
followed by elimination of a proton, e.g., oxidative coupling of aniline to azobenzene [Eq. (17)]. Assuming that the oxidation consists of two consecutive, one-electron-transfer processes, a free-radical, chain mechanism can be applied.[557] However, on the basis of recent kinetic[33] and other[558,570] studies, in the oxidation of substituted amines with manganese dioxide, the first step is apparently the removal of the α-hydrogen, instead of the imino hydrogen atom (N–H).[60] The formation of free radicals[57,60] and hydroxylamines[49,57] as intermediate products in the oxidation of amines with manganese dioxide was suggested in early studies. Oxidation of amines (e.g., *N*-alkylanilines) with manganese dioxide may involve oxidation of alkyl groups, cleavage of carbon–carbon bonds, and dehydrogenation of carbon–carbon or carbon–nitrogen bonds; consequently, the process may be either uni- or bimolecular.



(17)

6.1.1. Primary and Secondary Amines Including Anilines

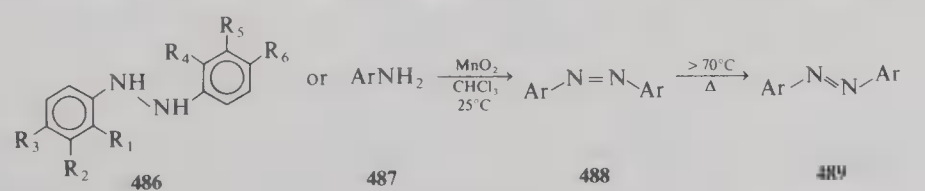
An early application of manganese dioxide for the oxidation of amines was in either acidic[559] or aqueous[292] media; it involved conversion of an aromatic primary amine (e.g., pyridoxamine)[559,560] or an aliphatic amine[292] into an aldehyde [Eq. (18)]. An early study of



(18)

the action of manganese dioxide in neutral media revealed that many aromatic primary amines (e.g., aniline) can be oxidized to the azo compounds in high yield (87%).[60,561] However, as subsequently showed by Hyatt,[562] the room-temperature oxidation by active manganese dioxide of substituted anilines (e.g., **487**), or more conveniently, hydrazobenzenes (e.g., **486**), produces the corresponding *cis*-azobenzenes (e.g., **488**) in excellent yield (89%–98%) and high purity. Thermal isomerization to the *trans* isomer (e.g., **489**) would account for the published results[60,292,563] (Scheme 17). The method[562] is thus stereospecific for synthesis of *cis*-azobenzenes from hydrozobenzenes or substituted anilines. In addition to the previous work,[60,292] the oxidative coupling of ring-substituted anilines to azo compounds in the presence of manganese dioxide in benzene solution has been thoroughly studied by Wheeler and Gonzalez.[563] The authors[563] found that substituted anilines, such as *p*-fluoro-, *p*-chloro-, *p*-bromo-, *p*-iodo-, *p*-methoxy-, *m*-chloro-, *o*-fluoro-, *o*-iodo-, *o*-methoxy-, and *o*-ethoxyanilines, were rapidly oxidized to the symmetrically substituted azobenzenes in 90% yield; normal oxidation was also observed with 3,5-dichloro-, 2,6-dimethoxy-, and 3-chloro-4,6-dimethoxyanilines. In agreement with the previous observation,[292] several substituted nitroanilines, e.g., 2-iodo-4-nitro-, 2,6-diiodo-4-nitro-, and 2-methyl-5-nitroanilines did not react with manganese dioxide,[563] although corresponding azo compounds were obtained from *o*- and *p*-nitroanilines.[60] The authors[563] found that *para*-substituted anilines react somewhat faster than other isomers; in general, electron-donating substituents on the ring (e.g., halogen or methoxy groups) favor the oxidation, whereas electron-withdrawing groups

SCHEME 17

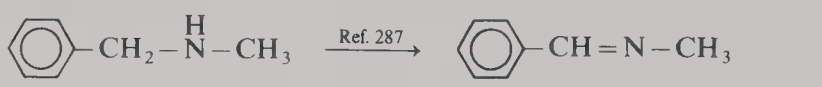


486 **487** **488** **489**

(e.g., nitro and carboxyl) inhibit it; the authors[563] speculated that the nitro group itself may be adsorbed on the surface of manganese dioxide and thereby prevent oxidation of the amino group. Anthranilic and *p*-aminobenzoic acids also gave no azo compound,[563] although a small yield (5%) of phenazine-1,6-dicarboxylic acid from the oxidation of the former has been reported.[564] Since the oxidation reaction of substituted anilines with manganese dioxide was carried out at >80°C,[563] the coupling product, as pointed out[562] must be *trans*-azobenzene formed by thermal isomerization of initially formed *cis*-azobenzene.

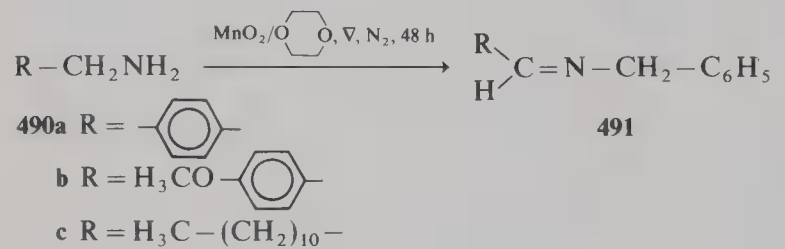
Conversion of anilines into the azo compounds apparently proceeds by a bimolecular process, and this speculation was supported by the results of a study of the reaction products obtained after treatment of a mixture of aniline and *p*-chloroaniline with manganese dioxide (to give azobenzene, *p*-chloroazobenzene, and *p,p'*-dichloroazobenzene).[565] Other primary amines[329,566,567] (e.g., 2-aminopyridine, but not polycyclic aromatic amines[563]) have been oxidized to the azo compounds with manganese dioxide. On oxidation with manganese dioxide, the aromatic primary diamines can either undergo a cyclization reaction or give an azo compound or a mixture containing an azo derivative and a quinone (via elimination of ammonia). For example, treatment of *o*-phenylenediamine in benzene with the reagent gave only the azo compound (50% yield), whereas *p*-phenylenediamine gave a mixture containing the corresponding azo compound and *p*-benzoquinone (via the quinone imine intermediate).[475,568]

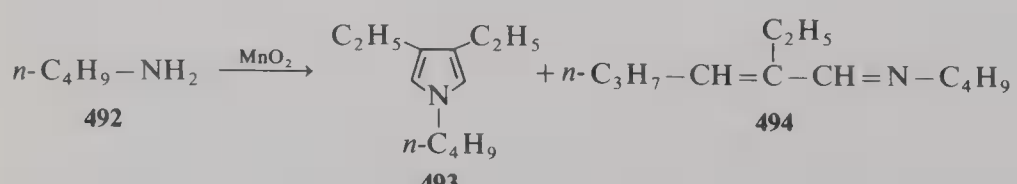
Highet and Wildman[287] accomplished the oxidation of benzylamine (also *N*-methylbenzylamine and *N*-methylpiperonylamine) in cold chloroform and confirmed the intermediate formation of an imine, e.g., Eq. (19). Later investigation[569] of this oxidation showed that

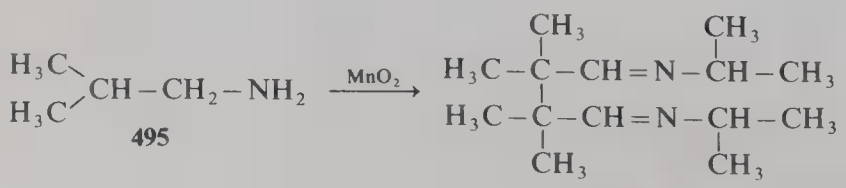


(19)

higher temperatures, an inert atmosphere, and the polarity of the solvent have a pronounced effect on the reaction path. Thus, on treatment with manganese dioxide in refluxing *p*-dioxan under nitrogen, benzylamines (**490a, b**) were converted into benzylidenebenzylamines (**491a, b**); butylamine (**492**) gave a mixture of 1-butyl-3,4-diethylpyrrole (**493**) and *N*-(2-ethyl-2-hexylidene)butylamine (**494**), whereas isobutylamine (**495**) gave a dimeric product (**496**).[569] Similarly, on treatment with manganese dioxide in refluxing benzene, a series of ring-substituted *N*-benzylanilines were converted into the corresponding



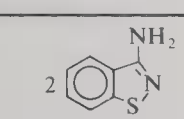
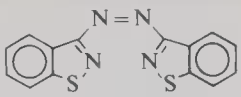
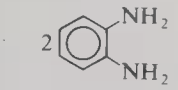
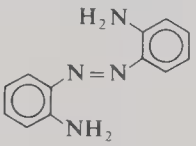
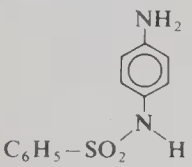
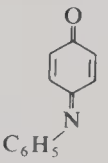
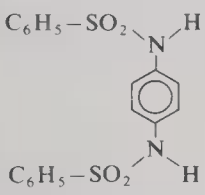
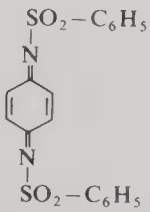
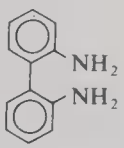
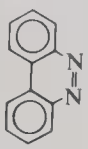
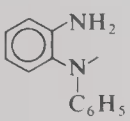
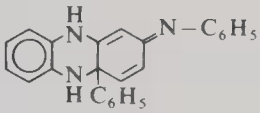
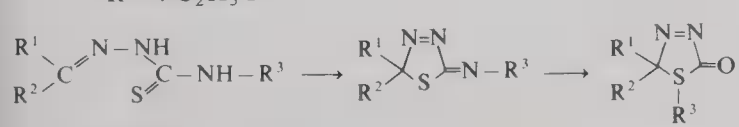




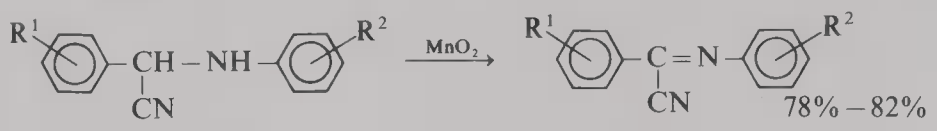
N-benzylideneanilines (Schiff bases) in excellent yields (70%–90%)[60]; a free-radical intermediate was probably involved in the formation of these[60] and the aforementioned products. (On manganese dioxide oxidation of allylic amines, e.g., cinnamylarylamines, see Ref. 570 and Table XVI.)

A series of secondary amines (aliphatic and aromatic) have been successfully oxidized with manganese dioxide. For example, α-phenyliminophenylacetonitriles (**498a,b,c**) were obtained in good yields by oxidation of α-anilinophenylacetonitriles (**497a,b,c**) with activated manganese dioxide in dry benzene at room temperatures[570]; similarly phenylacylaniles

TABLE XVI. Oxidation of Primary and Secondary Amines and Their Derivatives

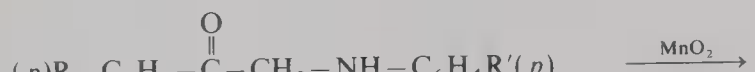
Substrate	Product	Reaction conditions	Yield (%)	Reference
		MnO_2/C_6H_6/ r.t.	12	567
		MnO_2/C_6H_6/ reflux/4 h	50	475, 568
		MnO_2/C_6H_6/ reflux/4 h	70	475, 568
		MnO_2/acetone/ 5 h/25°C	32	475, 568
		MnO_2/C_6H_6/ reflux/6 h	55	475, 568
		MnO_2/C_6H_6/ reflux/6 h	70	576
R = H			76	
R = 4-Br			75	
R = 4-Cl			75	
R = 3-O_2N			80	
R = 4-H_3CO			60	
R = 4-H_3C			65	
R = 4-C_2H_5O			60	
 $R^1 = R^2 = CH_3$, $R^3 = C_6H_5$		1. MnO_2/ benzene 2. $Mg(OAc)_7$	70	585

(**499a,b,c**) were converted into phenylglyoxalmonoaniles (**500a,b,c**) (70% yield),[571] and 2,3-di-*o*-toluidinoacrylonitrile (**501**) was oxidized by the reagent to give α-cyano-glyoxylidenedi-*o*-toluidine (**502**) (83% yield).[572]

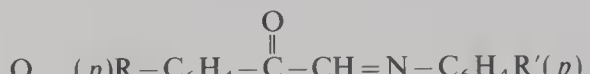


497a, R = R′ = H
b, R = H, R′ = CH_3
c, R = H, R′ = OCH_3

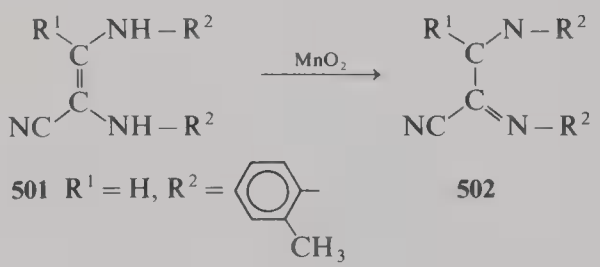
498 78%–82%



499a, R = R′ = H
b, R = H, R′ = CH_3
c, R = H, R′ = OCH_3



500



501 R^1 = H, R^2 =

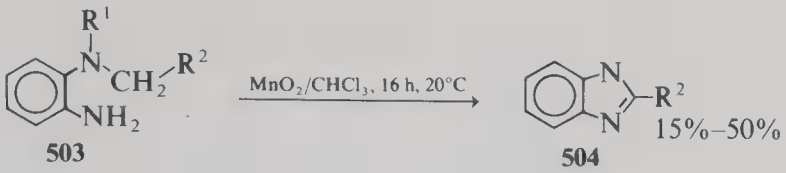
502

6.1.2. Oxidative Cyclization of Ortho-Substituted Anilines

Taking into consideration some systematic work by Henbest and co-workers[49,57,573,574] on the unique manganese doxide oxidation of dialkylaniines [e.g., facile oxidation of a methyl group alpha to the nitrogen atom (see Section 6.1.6)], Meth-Cohn, Suschitzky, and Sutton[575] found that, in the presence of a suitable *ortho*-substituent, disubstituted anilines on treatment with manganese dioxide (even in cold chloroform) undergo oxidative cyclization (compare Section 3.11) to give a variety of heterocyclic compounds. Thus, oxidation of *N*-*o*-aminophenylamines (**503a–503f**) gave benzimidazoles (**504a–504f**) to 50% yield.[575]

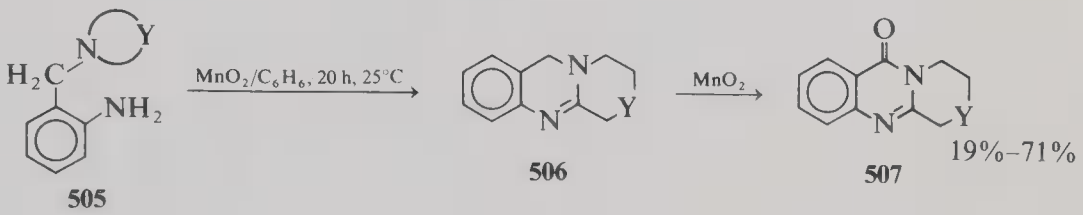
Oxidation of the homologs of *N*-*o*-aminobenzylamines (**505a–505e**) with manganese dioxide yielded quinazolones (**507a–507e**) in 19%–71% yield; the benzylic methylene group in the quinazoline intermediate (**506a–506e**) was specifically oxidized to a carbonyl group (compare Section 4.2) via a suggested hydroxyquinazoline intermediate.

Similar oxidation of *ortho*-carboxylic acids of *N*-alkylanilines produced benzoxazinones in 25%–65% yield and *o*-alkylbenzoic acids yielded phthalides. For example, oxidation of *N*-methylanthranilic acid (**508**) with manganese dioxide gave benzoxazinone (**509**) in 52% yield.[575] Surprisingly, no inhibition by the nitro group was found on cyclization of *p*-nitro derivatives of *N*-alkylanilinecarboxylic acids,[575] although this effect was observed in the similar oxidation of *N*,*N*-dialkylanilines.[49,57,573,574] Oxidation of 2-aminodiphenylamine with manganese dioxide in refluxing benzene yielded 2-amino-5-phenyl-3-(phenylimino)-3,5-dihydrophenazine in 70% yield[576] (Table XVI). Further examples of an intramolecular,



503 504

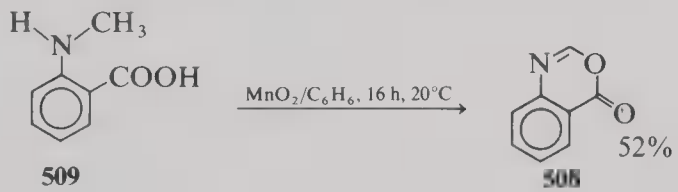
	R^1	R^2
a	CH_3	H
b	C_2H_5	CH_3
c	$-(CH_2)_3-$	
d	$-(CH_2)_4-$	
e	$-(CH_2)_5-$	
f	$-CH_2-CH_2-O-CH_2-$	



505 506 507

	Y in **505**	Y in **506**, **507**
a	$-(CH_2)_4-$	–
b	$-(CH_2)_5-$	$-CH_2-$
c	$-(CH_2)_2-O-(CH_2)_2-$	O
d	$-(CH_2)_6-$	$-(CH_2)_2-$
e	$-(CH_2)_2-N(CH_3)-(CH_2)_2-$	$-N(CH_3)-$

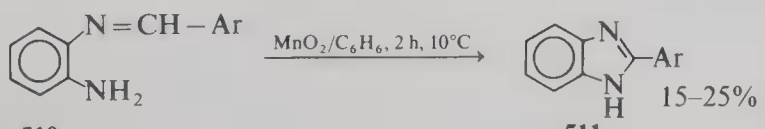
oxidative cyclization are provided by the oxidation of *o*-aminobenzilideneanils (**510a**, **510b**) and hydroxybenzilideneanils (**512a**, **512b**) (Schiff bases) with manganese dioxide, to give benzimidazoles (**511a**, **511b**) (compare **503** → **504**) and benzoxazoles (**513a**, **513b**), respectively.[475,476] No inhibition by the nitro group was reported in these cyclizations.



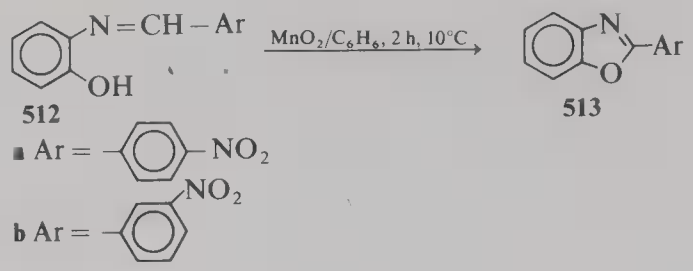
509 508

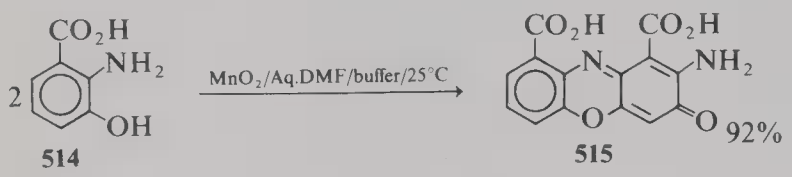
Similar intramolecular cyclization has been observed in nonenzymic synthesis of cinnabarinic acid (**515**, 2-amino-3-oxo-3H-phenoxazine-1,9-dicarboxylic acid) following oxidation of **514** (3-hydroxyanthranilic acid) with manganese dioxide.[577]

An example in the secondary amine series is an intramolecular cyclization of 1,3-diamine **516** to pyrazolidine **517**.[578,579] Active manganese dioxide is added in one portion at −20°C to −10°C to a solution of *N*,*N*′-diphenyl-1,3-propanediamine (**516**) in tetrachloromethane and the mixture is stirred for 2–3 h at the same temperature; 1,2-diphenylpyrazolidine (**517**)

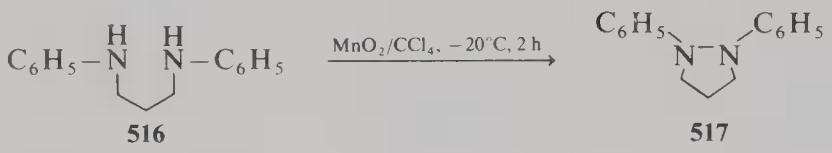


510 511

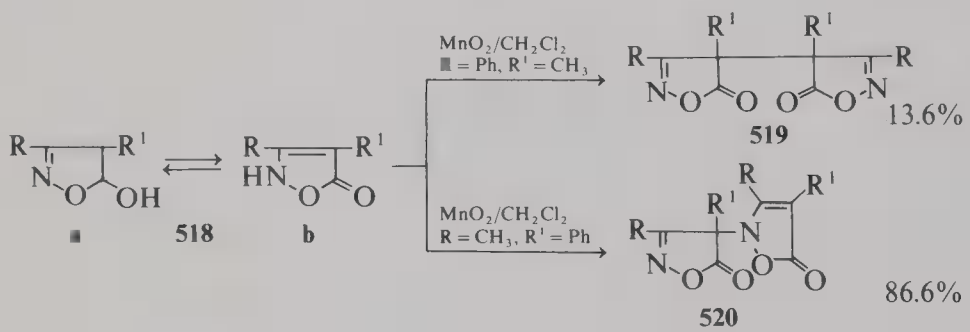




is isolated in 45% yield.[578] As has been pointed out,[578] cyclization of 1,3-diamines of type **516** (unsubstituted and substituted on a ring) to pyrazolidines **517** depends to a considerable extent on the type of active dioxide used. The oxidation of 3,4-disubstituted isoxazoline-5-



ones (**518**, existing as tautomers **518a** ⇌ **518b**) with manganese dioxide in dichloromethane leads to the formation of C−C or C−N-linked coupling products, depending on the nature of ring substituents in **518**. Thus, when **518** (R = Ph, R′ = CH_3) is oxidized, the product is the C−C dimer (**519**); however, when **518** (R = CH_3, R′ = Ph) is used, the C−N coupling product (**520**) is formed.[580]

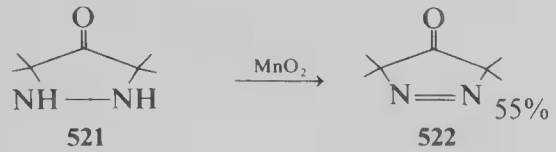


6.1.3. Dehydrogenation of Amines. Rearrangements

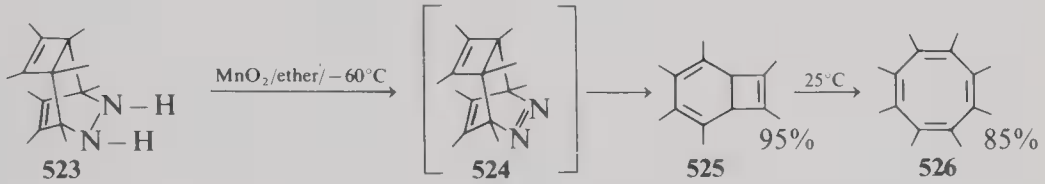
Previous work on intramolecular dehydrogenation of amines by manganese dioxide leading to C−C, C−N, or N−N-linked coupling products has been reviewed.[18] Dehydrogenation of 3,3,5,5-tetramethyl-4-pyrazolidone (**521**) to (**522**) (3,3,5,5-tetramethyl-1-pyrazoline-4-one) was accomplished with manganese dioxide in the pressure bottle (55% conversion yield).[581] Dehydrogenation of **523** (octamethyl-7,8-diazatricyclo[4.2.2.$0^{2,5}$] deca-3,9-diene) with manganese dioxide at −60 to −78°C, gave the rearranged product **525** (octamethylbicyclo[4.2.0]octa-2,4,7-triene) via the 7,8-diaza intermediate **520** (90%–95% yield); warming of the reaction mixture to room temperature (25%) yielded a new rearranged compound **526** (octamethylcyclooctatetraene) (85% yield).[582]

Similar reaction has been observed following treatment with manganese dioxide at −30°C (ether) of the cycloadduct **527**; the reaction product was a mixture of nitrogen

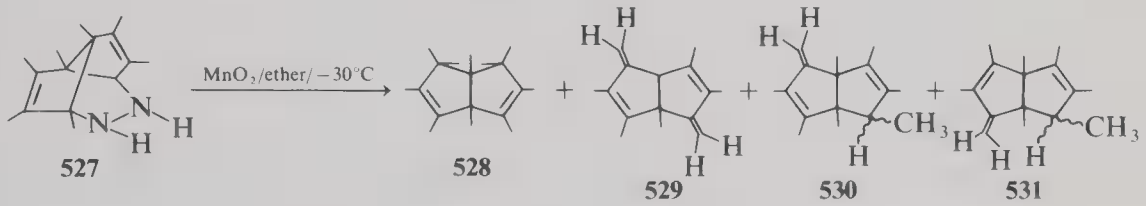
extrusion and rearranged compounds, e.g., octamethylsemibullvalene (**528**) along with **529**, **530**, and **531**.[582] Additional examples of selective oxidation by manganese dioxide of some primary and secondary amines and their derivatives are shown in Table XVI; some dehydrogenation and cyclization reactions are also included.



521 **522**



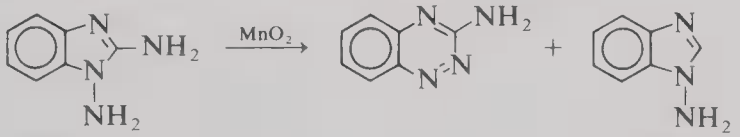
523 **524** **525** **526**



527 **528** **529** **530** **531**

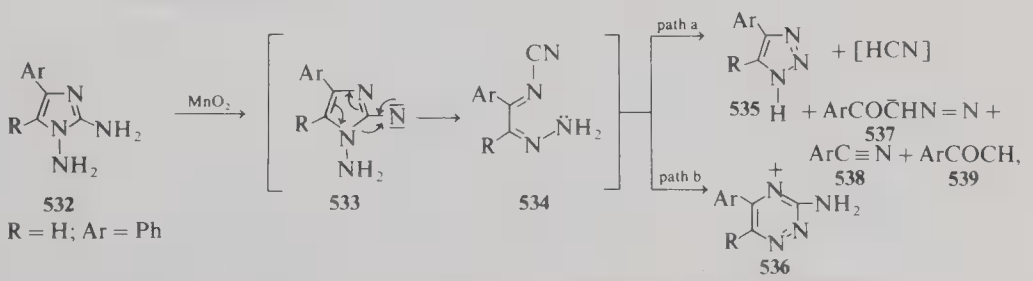
6.1.4. Ring Transformation of Aryl 1,2-Diaminoimidazole

Ring transformations of heterocycles have been a topic of current interest.[586,587] Anselme and co-workers[587,588] studied the oxidative fragmentation of 4-phenyl-1,2-diaminoimidazole (**532**) and related heterocyclic 1,2-diamines. Oxidation of **532** in benzene at reflux for 7 h with freshly prepared manganese dioxide gave 4-phenyl-1,2,3-triazole (**535**) and 5-phenyl-3-amino-1,2,4-triazine (**536**) in 20% and 22% yields, respectively; trace proportions of **537**, **538**, and **539** were also isolated. The formation of **535** and **536** was rationalized via formation of the C-nitrene (or nitrenoid) **533**, which could then undergo ring opening to the α-hydrazono-*N*-cyanoimine (**534**) followed by cyclization to either **535** (path a) or **536** (path b). The α-hydrazono-*N*-cyanoimine (**534**) can also account for the formation of **537** and **538**, while fragmentation of the *N*-nitrene would explain the presence of the acetophenone **539** (Scheme 18). Similar oxidation of 1,2-diaminobenzimidazole (**540**) yielded 3-aminobenztriazine (**541**) as the major product (33%) along with a trace of 1-aminobenzimidazole (**542**); no benzotriazole could be detected.[587]



540 **541** **542**

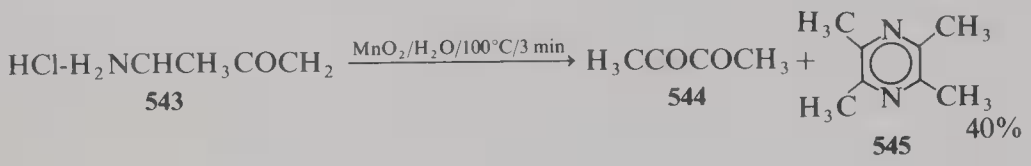
SCHEME 18



532 R = H; Ar = Ph **533** **534** **535** **536** **537** **538** **539**

6.1.5. Synthesis of α-Diketones and Pyrazine Derivatives from α-Aminoketones

Oxidation of 3-aminobutanone-2 hydrochloride (**543**) with manganese dioxide in water at 100°C gave biacetyl (2,3-butanedione) (**544**) (20% yield) (isolated as Ni-complex of dimethylglyoxime) and tetramethylpyrazine (**545**) (40% yield).[589]

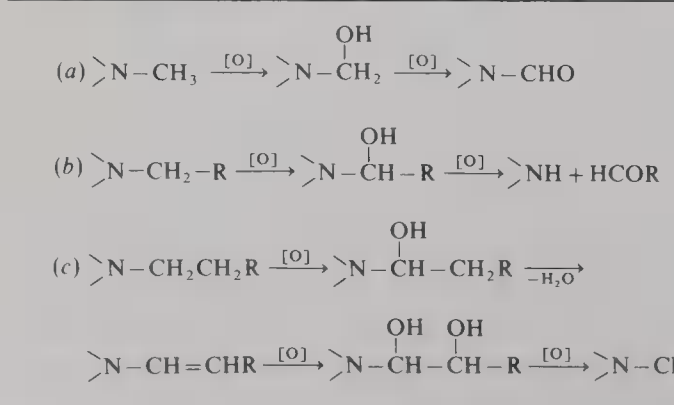


6.1.6. Tertiary Amines

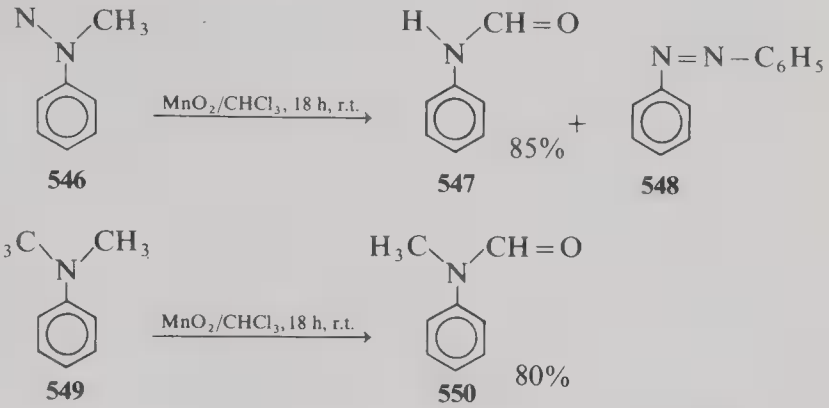
Tertiary amines are readily oxidized by a variety of reagents, the initial products usually being *N*-oxides, enamines, or carbinolamines. Depending on its structure and on the reaction conditions, a compound of the last type may be oxidized further, to an amide, or may be cleaved to a mixture of a secondary amine and a carbonyl compound. All of these reactions of tertiary amines have been observed by application of active manganese dioxide. Although Highet and Wildman[281] originally applied the reagent for conversion of the *N*-methyl group in the alkaloid dehydrotazzetine (see Table XII) into a *N*-formamido group, only a systematic and detailed study by Henbest and co-workers[49,57,573,574,590–592] led to differentiation of three main types of conversion in the oxidation of an amine (e.g., *N*-alkyl-, *N,N*-dialkylanilines, and aliphatic *N,N,N*-trialkylamines) (Scheme 19).

For all three paths of conversion, it is assumed that the first step involves the oxidation of the amine to a hydroxylamine.[49,57,590] In path (a), the hydroxylamine is oxidized further to give an *N*-acyl derivative. In path (b), the hydroxylamine rearranges to give a secondary amine and an aldehyde (or a ketone). In path (c), water is eliminated from the hydroxylamine, and the resultant enamine is oxidized further, to afford an *N*-acyl derivative and a carbonyl compound. The oxidation of an enamine most probably involves hydroxylation of the double bond, followed by oxidative cleavage of the resultant α-glycol. Thus, the three paths of conversion, (a), (b), and (c), involve the removal of two pairs, one pair, and three pairs of electrons, respectively, from the starting amine.[554] With several amines, the reaction takes essentially a single course; for example, *N*-methylaniline (**546**) gave formanilide (**547**) in 85% yield, and a little azobenzene (**548**; 2.5% yield); *N,N*-dimethylaniline (**549**) was oxidized to *N*-methylformamide (**550**) in 80% yield,[49] all according to route (a). Formation of some azobenzene (**548**) was attributed to the dealkylation of the starting material to aniline via the hydroxylamine intermediate; then, oxidation of *N,N*-dimethylaniline was facilitated by the

SCHEME 19

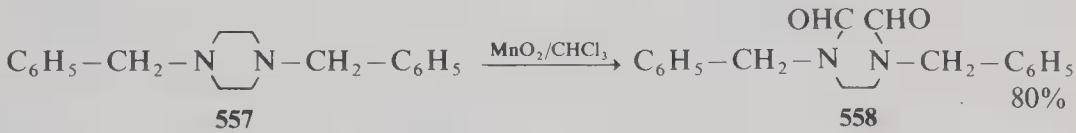


introduction of an electron-donating *p*-methyl group, but electron-withdrawing *p*-nitro substituents completely inhibited the reaction.



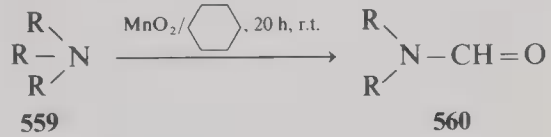
546 547 548 549 550

The oxidation of *N*,*N*-diethylaniline (**551**) proved to be more complex. The predominant reaction is by path (b) to give *N*-monoethylaniline (**552**) (via cleavage of the C–H bond of the α-carbon atom) and acetaldehyde (54% yield).[49,590] The *N*-monoethylaniline (**552**) thus formed then probably underwent further oxidation by path (c) to formanilide (**554**; 85% yield) via the enamine intermediate **553**. Small quantities of *N*-ethylformamide (**556**; 4%) (formed via enamine **555**) and azobenzene were also detected. Evidence of an enamine intermediate **555** was derived from a trapping experiment with chloranil (Scheme 20). As would be expected, *N*-ethyl-*N*-methylaniline gave both *N*-ethylformamide (16%) and formanilide (63%),[49] presumably through paths (a) and (b). A similar fragmentation reaction was observed with *N*,*N*-dibenzylstyrylamine to give dibenzylformamide (77%) and benzaldehyde; *N*,*N*-dimethyl- and *N*,*N*-diethylbenzylamine were cleaved to benzaldehyde in 50% and 86% yields, respectively[573] (cleavage of a tertiary C–H bond activated by an aromatic ring); however, dibenzylpiperazine (**557**) gave preponderantly the diformyl derivative **558** (80% yield).[573]



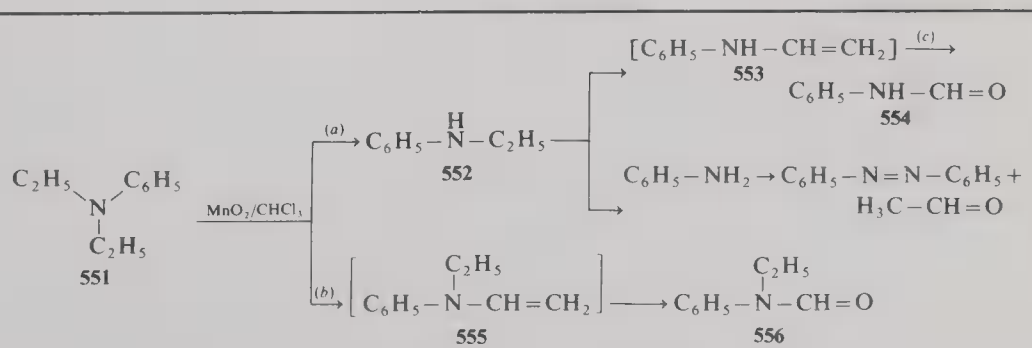
557 558

A similar path of oxidation has been observed with the aliphatic tertiary amines. Oxidation of trialkylamines of type **559** with manganese dioxide yields dialkylformamides of type **560**, apparently through paths (b) and (c) (via cleavage of the C–C bond adjacent to



559 560

SCHEME 20

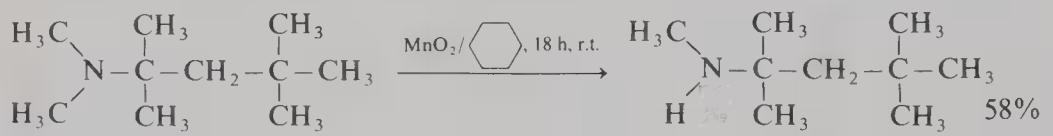


the tertiary nitrogen atom); the yield of the product usually increases with increase in the length of the carbon chain in the alkyl group (corresponding secondary amines and carbonyl compounds are also formed[49,57]; see Table XVII). However, the yield of the formamide is preponderant in the oxidation of trialkylamines of the type shown in Eq. (20).[57] The reac-

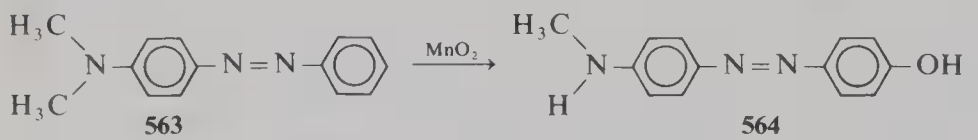
$$(R-CH_2)_3N \xrightarrow{MnO_2} (R-CH_2)_2N-CH=O \quad (20)$$

70%

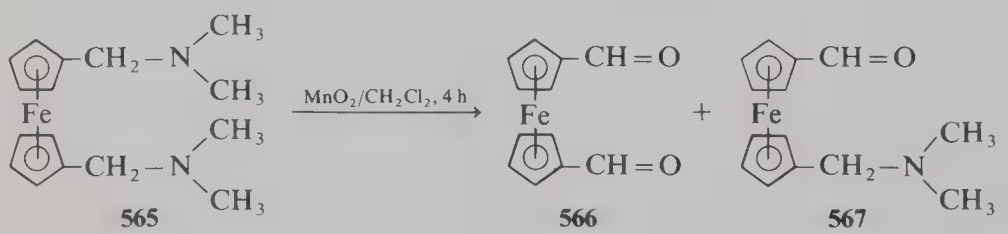
tivity of a C–H bond of the α-carbon atom in alkyl-substituted amines (e.g., aliphatic, alicyclic, and aromatic) plays an important role in the rate of oxidation of the amine; generally, reactivity of a C–H bond is in the order tertiary > secondary > primary. Since a tertiary C–H bond is most reactive it is not surprising that manganese dioxide oxidation of *N,N*-dimethyl- or *N,N*-diethylcyclohexylamine produces cyclohexanone in 85% and 51% yield, respectively.[573] Selective oxidations of some tertiary amines (e.g., Mannich bases) with manganese dioxide are shown in conversions of **561** into **562**,[574] **568** into **584** (a ring hydroxylation),[593] and **565** into **566** and **567**.[594]



561 **562**



563 **564**



565 **566** **567**

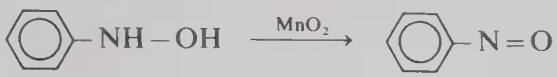
6.1.7. Hydroxylamines and Oximes

Hydroxylamines and oximes are sensitive to manganese dioxide; few of the examples described next show a typical mode of reaction. Oxidation of phenylhydroxylamine with manganese dioxide gave nitrosobenzene, e.g., Eq. (21),[329] whereas treatment of ethyl

TABLE XVII. Preparation of Formamides **560** from Tertiary Amines **559**[a]

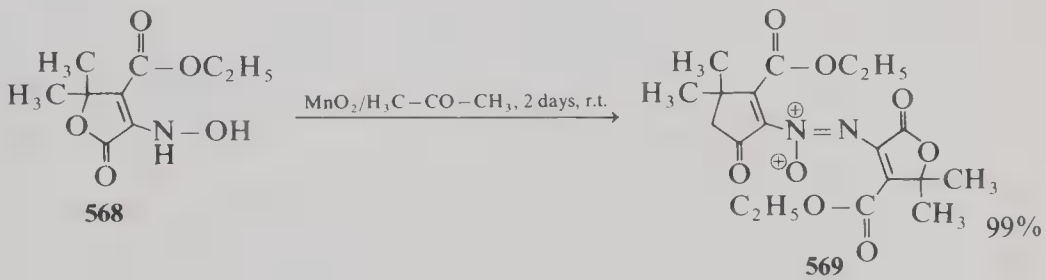
R	Yield (%) of **560**
C_2H_5	<1
n-C_3H_7	28
n-C_4H_9	40
n-C_5H_{11}	48
n-C_8H_{17}	54

[a] References 49, 57.



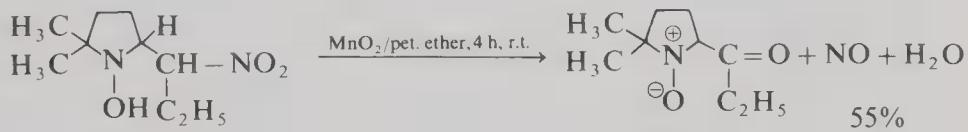
(21)

α-hydroxylamine-γ,γ-dimethyllactone (**568**) with the reagent gave an azoxy derivative, the dilactone dimer **569**, in quantitative yield[595] (coupling between unreacted hydroxylamine and a nitroso compound due to the slow reaction). A series of carcinogenic arylhydroxylamines were oxidized with active manganese dioxide (ACC) to nitroso derivatives in high yield (90%–98%).[596] The general experimental procedure is as follows.[596] To freshly prepared arylhydroxylamine in sufficient chloroform to effect complete solution at 0°C was added two equivalents of activated manganese dioxide (ACC) at once. The resulting suspension was stirred vigorously under nitrogen from 5 to 10 min (TLC spot test for complete oxidation). The manganese dioxide was removed by filtration through a bed of Celite and rinsed with a few milliliters of chloroform. The filtrate and washings were concentrated under reduced pressure and the compounds purified by column chromatography on either silica gel or aluminium oxide. The first bright emerald green band was collected and the solvent removed *in vacuo* to yield 90%–98% nitroso compounds homogeneous on thin layer chromatography. The following nitroso compounds were prepared: 1-naphthylhydroxylamine → 1-nitrosonaphthalene m.p. 84–85°C; 2-naphthylhydroxylamine → 2-nitrosonaphthalene m.p. 62–63°C; 4-biphenylhydroxylamine → 4-nitrosobiphenyl m.p. 74–75°C; 2-fluorenylhydroxylamine → 2-nitrosofluorene m.p. 77–78°C; 3-dibenzofuranylhydroxylamine → 3-nitrosodibenzofuran m.p. 111°C; and phenylhydroxylamine → nitrosobenzene m.p. 68°C.



568 **569**

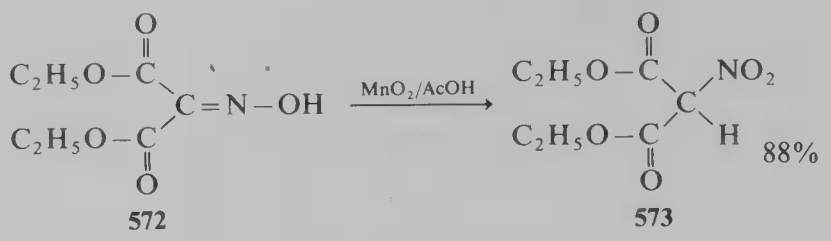
In an interesting example, treatment of β-nitrohydroxylamine with manganese dioxide under very mild conditions caused elimination of nitrogen monoxide to give an acylnitrone. Thus, manganese dioxide was added, in small portions with shaking, to a solution of 2,2-dimethyl-5-(1-nitropropyl)-pyrrolidin-1-ol (**570**) in petroleum ether, and the product **571** (5,5-dimethyl-2-propanoyl-Δ′-pyrrolidine *N*-oxide) was isolated after 4 h of shaking; yield was 55%.[597]



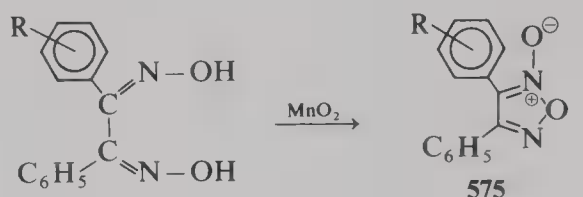
570 **571**

Under similar reaction conditions, certain oximes were oxidized to the nitro compounds; for example, on treatment with manganese dioxide, the malonic ester oxime **572** was converted into the nitro derivative **573**,[530] and oximes of diketones **574a**–**574c** were reportedly oxidized to oxadiazole *N*-oxides **575a**–**575c**.[598,599]

Stable free radical analogs of histidine containing a nitronyl nitroxide ring system in place of the imidazole ring have been generated by use of active manganese dioxide. Thus, the free radical **579** [*N*-(benzyloxycarbonyl-(1,3-dioxy-4,4,5,5-tetramethyldihydroimidazol-2-yl)-L-alanine, a red solution; uv (C_2H_5OH): $\lambda = 522(\varepsilon = 1370)$, 555 nm($\varepsilon = 1400$)] was prepared via an intermediate obtained by condensation of *N*-benzyloxycarbonyl-L-aspartic-β-semialdehyde (**576**) with *N*,*N*-dihydroxy-2,3-diamino-2,3-dimethylbutane monosulfonate



572 573

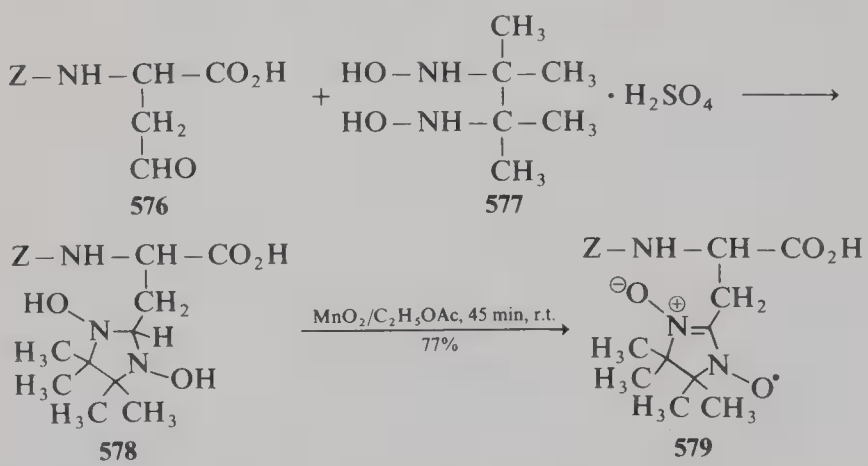


575

574a R = H
b R = 2-Cl
c R = 4-Cl

(**577**), followed by oxidation of the resulting adduct (**578**) with the reagent in ethyl acetate (to give **579** in 77% yield.[600]

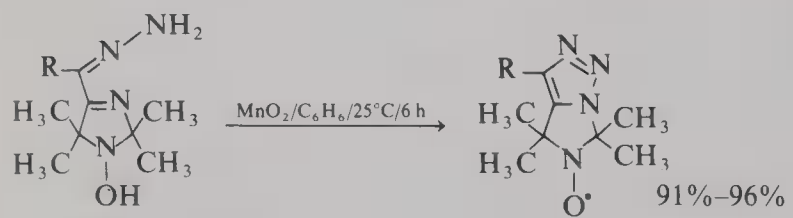
Similar stable free radicals were prepared in the imidazoline series. Thus, oxidation of hydrazones of 4-oxoalkyl-3-imidazoline (**580**, R = H, CH_3) with manganese dioxide in ben-



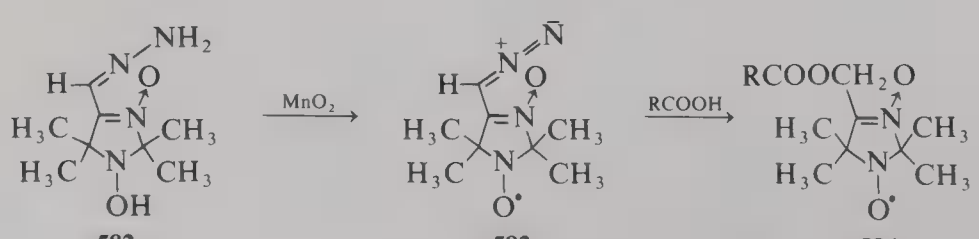
576 577

578 579

zene (25°C, 6 h) gave a nitroxyl free radical, e.g., imidazo[1,2,3]triazole (**581**, R = H, CH_3) in 96% and 91% yield. Similarly 3-imidazoline-3-oxide (**582**) was converted into a diazo compound (**583**) with nitroxyl radical center; the latter can be esterified on treatment with

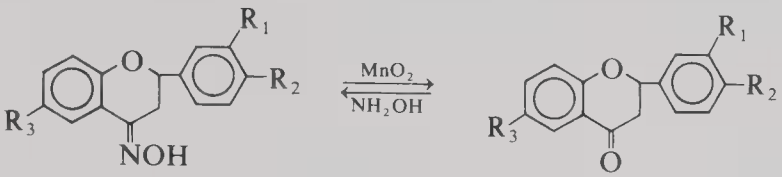


580 R = H, CH_3 581 91%–96%



582 583 584

acetic (or benzoic) acid in chloroform to give **584**.[601] The oxidation of 4-oximinoflavans (**585**) with active manganese dioxide in chloroform at room temperature affords the corresponding flavanones (**586**) in high yields (85%–92%). The authors[602] proposed a likely path for the oxidation of oximes, involving the iminoxy free radical intermediate. Some substituted benzaldoximes have been oxidized with manganese dioxide to heterocyclic derivatives.[603]

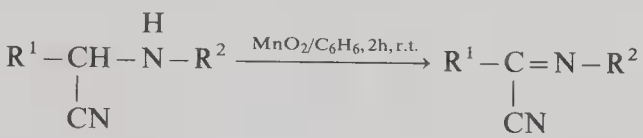


585 **586**

$R_1 = R_2 = R_3 = H$
$R_1 = R_3 = H,\ R_2 = OCH_3$
$R_1 = H,\ R_2 = OCH_3,\ R_3 = CH_3$
$R_1 = R_2 = OCH_3,\ R_3 = CH_3$
$R_1 = R_3 = OCH_3,\ R_3 = H$

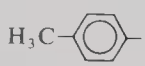
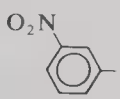
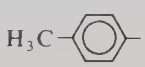
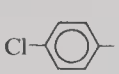
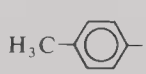
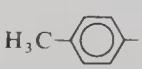
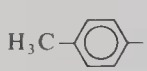
6.1.8. Cyano-anils from Aminonitriles

α-Aminonitriles of type **587** can be effectively oxidized with manganese dioxide in benzene to give good yields (74%–82%) of cyano-anils of type **588**[570]; see Table XVIII. The facile oxidation of **587** clearly suggests initial C–H proton removal [the cyano group in **587** apparently renders the C–H group acidic; however, this should be compared to the behavior of malononitrile towards manganese dioxide, see Section 7.1.



587 **588**

TABLE XVIII. Preparation of Cyano-anils **588** from Aminonitriles **587**[a]

R^1	R^2	Yield (%) of **588**
		80
		78
		82
		82
		74

[a] Reference 558.

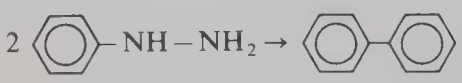
6.2. Hydrazines and Their Derivatives

6.2.1. Hydrazines

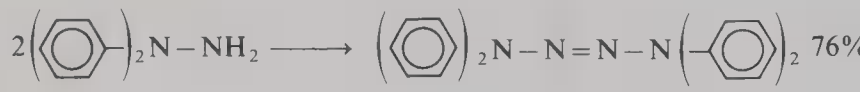
Hydrazines resemble amines in their sensitivity towards manganese dioxide. On treatment with manganese dioxide, 1,2-disubstituted (symmetrical) hydrazines are readily dehydrogenated to give a high yield of azo compounds, e.g., Eq. (22)[60]; the stereo-

(22)

specificity[562] of dehydrogenation of hydrazobenzenes has been discussed earlier in the text (Section 6.1.1). The mono- or 1,1-disubstituted (unsymmetrical) hydrazines, however, on dehydrogenation either produce hydrocarbons via C–C coupling and nitrogen elimination —e.g., Eq. (23)[475,568]—or form tetrazenes via N–N coupling—e.g., Eq. (24).[475,568] However,



(23)



(24)

on treatment with manganese dioxide in benzene solution, 2,4-dinitrophenylhydrazine lost its hydrazine moiety to give *m*-dinitrobenzene (50% yield).[292] The course of the reaction may depend on the nature of the solvent used; for example, treatment of *N*,*N*-dibenzylhydrazine (**589**) with manganese dioxide in benzene yields mainly tetrazene (**590**); in refluxing ethanol, however, the product is 1,2-diphenylethane (**591**)[475,568] (Scheme 21).

Following treatment with manganese dioxide, several hydrazine heterocyclic compounds (symmetrical and unsymmetrical) eliminate nitrogen, affording a novel synthesis of hydrocarbons, some of them via skeletal rearrangement; these include the conversions of **592** into **593**,[604] **594** into **595**,[605] and **596** into **597** and **598**.

6.2.2. Hydrazides

Kelly and co-workers[607,608] found that active manganese dioxide oxidizes phenylhydrazides in aqueous acetic acid at room temperature to give the corresponding acids in good yield; aromatic reaction products are benzene, phenol, and phenyl acetate. The reaction was applied to model dipeptides. In a typical procedure, a solution of *N*-benzyloxycarbonyl-α-L-glutam-1-oyl-glycine ethyl ester 3-phenylhydrazide (**599**) in 60% aqueous acetic acid was treated with active manganese dioxide and stirred for 30–45 min at room temperature to give *N*-benzyloxycarbonyl-α-L-glutam-1-oly-glycine ethyl ester (**600**) in 82% yield; similarly, other dipeptides were obtained in 62%–92% yield[375] (see Table XIX). The procedure avoids undesired alkaline hydrolysis, thus leaving the benzyloxycarbonyl and the ester protective

SCHEME 21

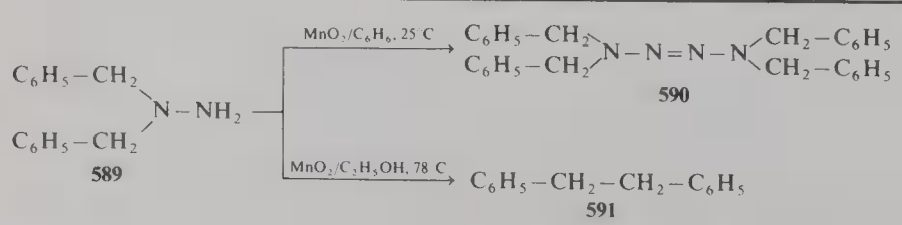
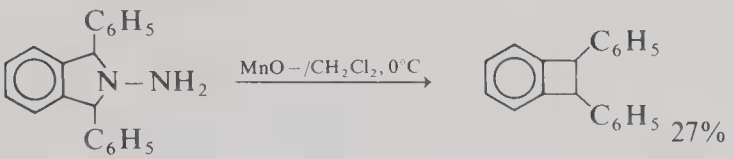


TABLE XIX. Oxidation of 3-Phenylhydrazides with Manganese Dioxide[a]

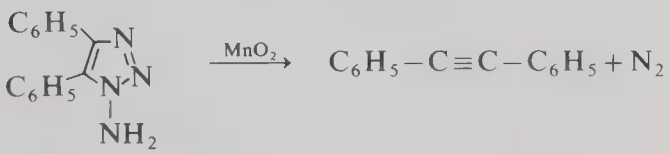
Product	Yield (%)
N-benzyloxycarbonyl-α-L-glutam-1-oyl-glycine ethyl ester	82
N-benzyloxycarbonyl-α-L-glutam-1-oyl-glycine methyl ester	92
N-benzyloxycarbonyl-α-L-glutam-1-oyl-L-valine methyl ester	62
N-benzyloxycarbonyl-α-Lglutam-1-oyl-L-leucine ethyl ester	78
N-benzyloxycarbonyl-L-glutamic acid	76

[a] Reference 607.

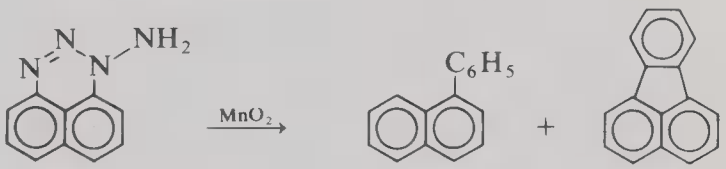
groups intact, and it generally proceeds without racemization. The results suggest use of the phenylhydrazide group for the protection of carboxyl groups in peptide synthesis. This method was successfully applied in a stereospecific synthesis of a dipeptide [*meso*-diaminopimelic acid-(L)-D-alanine][609] and other dipeptide syntheses.[610] Hydrazides of



592 **593**

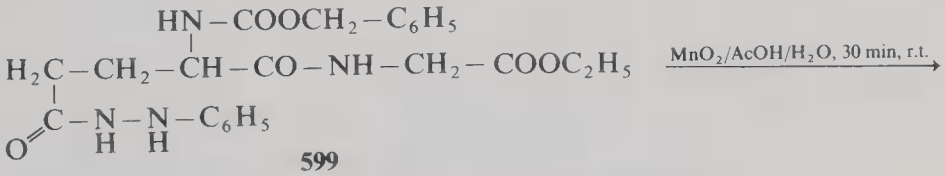


594 **595**

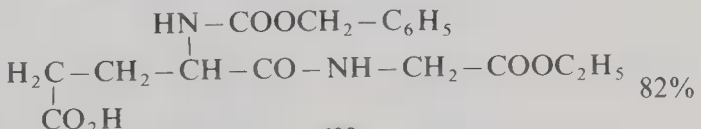


596 **597** **598**

salicylic or substituted salicylic acids,[69] benzoylhydrazides,[69] or dihydrazides, e.g., *N*-benzoylsalicylhydrazide ($_6H_5COHNNHCOC_6H_5$)[611] have been oxidized with active manganese dioxide in different solvents under different conditions. In all the cases the reaction products are the corresponding acids, e.g., salicylic or benzoic acids, benzophenone, etc. In the presence of ammonia[69,611] besides substituted benzoic acids, benzamides are formed, suggesting that free radical intermediates are involved in these oxidation reactions.



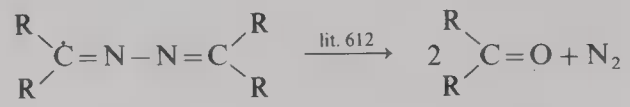
599



600

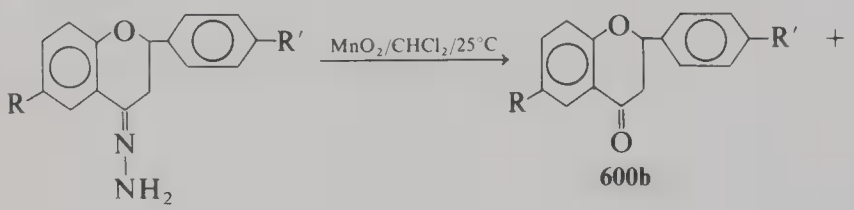
6.2.3. Azines

Azines are unstable in the presence of manganese dioxide, slowly undergoing cleavage to the corresponding carbonyl compounds with elimination of nitrogen, e.g., Eq. (25).[612] Interesting is a selective preparation of *cis*-1,2-dibenzoylpropane via manganese dioxide degradation of the heterocyclic ring in 2,5-diphenyl-3,4-diazanorcaradiene.[613] However, some azines can be prepared by oxidation of hydrazones with manganese dioxide. For example, when flavanone hydrazones **600a** are shaken with active manganese dioxide in chloroform at



(25)

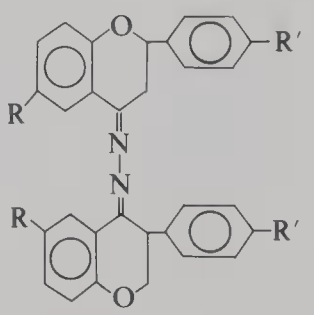
room temperature, a mixture of the parent ketone **600b** and the corresponding azine **601** results in each case.[614] The formation of flavanone azines, e.g., **601**, can be explained[612] if it is assumed that the intermediate diazo compounds dimerize followed by the loss of nitrogen. However, the conversion of the hydrazones into flavanones, e.g., **600b** can be explained by a free radical mechanism.[614]



600a

$R = R' = H$
$R = H, R' = OCH_3$
$R = CH_3, R' = H$
$R = CH_3, R' = OCH_3$

600b

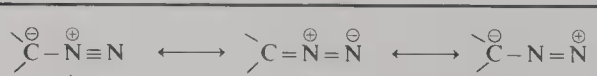


601

6.2.4. Hydrazones

Generally, mercury(II) oxide, silver oxide, and sometimes, nickel peroxide[615] have been used for oxidation of hydrazones; however, in many instances, manganese dioxide proved to be the best reagent for this purpose. Treatment of mono- or bis-hydrazones of carbonyl compounds with active manganese dioxide (a unimolecular dehydrogenation of the amino group) produces, respectively, diazo- or bis-diazo compounds, the structures of which are stabilized by resonance; the three forms of a diazo compound, $\diagdown C=N_2$, are shown in (Scheme 22, A↔B↔C), where structures A and B preponderate in the organic diazo compounds ($RC=N_2$, where R = an aromatic, heteroaromatic, or alicyclic group) and structure A is mainly present in the diazo salts, e.g., the diazomethane salts.[616] Thermodynamically, diazo compounds are unstable; the facile, photolytic, or thermal decomposition of diazo

SCHEME 22



compounds generates carbenes, whereas bis-diazo compounds produce acetylenes (e.g., acetylenic species, which can be trapped) (see Table XX). In early work, Barakat and co-workers[292] reported that treatment of benzophenone (and fluorenone) hydrazones with manganese dioxide in ether gives rise to the corresponding ketazines (52%–58% yield), presumably via the diazomethane intermediate. However, Schroeder[617] and, later, Reimlinger[618] demonstrated that manganese dioxide oxidation of benzophenone hydrazones (**602a–602e**) indeed gives diazoalkanes (**603a–603e**) indeed in high yield (70%–90%); by use of

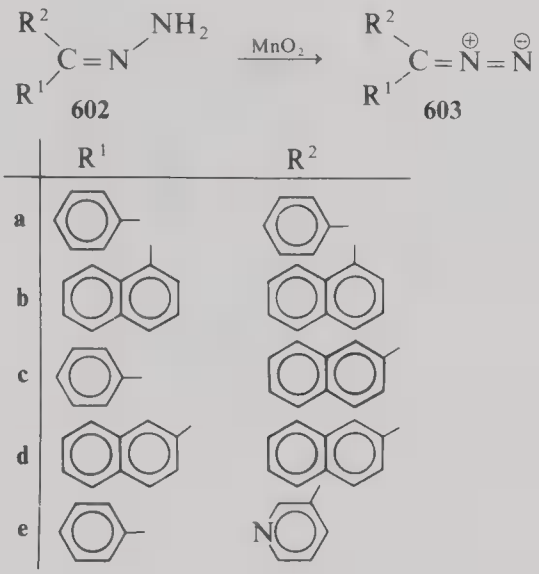
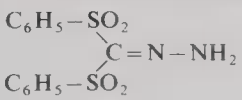
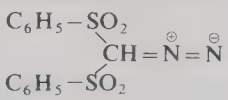
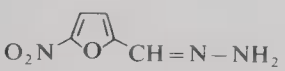
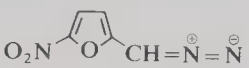
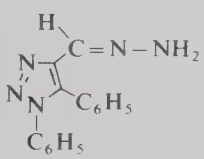
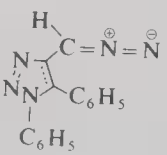
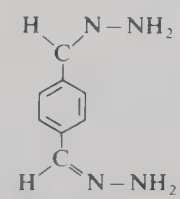
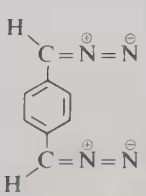
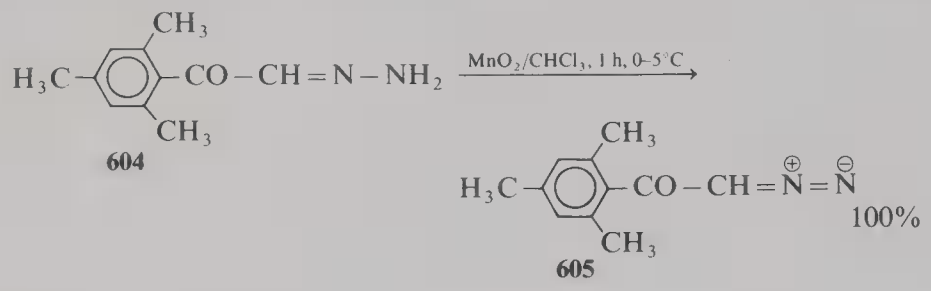


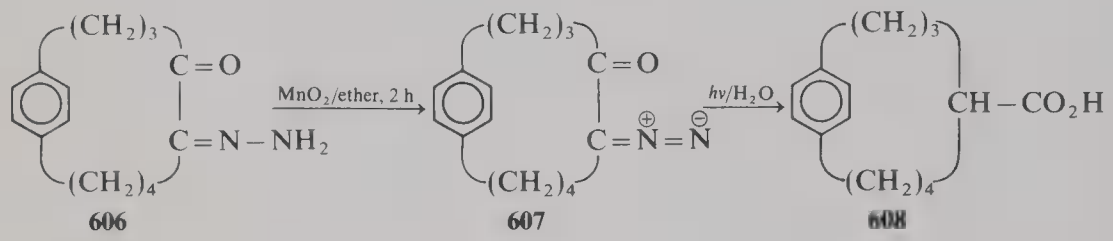
TABLE XX. Preparation and Degradations of Diazo Compounds by Manganese Dioxide

Substrate	Product	Reaction conditions	Yield (%)	References
		MnO_2/CH_2Cl_2/r.t.	55	625
		MnO_2/ether/Na_2SO_2/ 1 h/r.t.	82	626
		MnO_2/ether/ 15 min/r.t.	78	627
		MnO_2/ether/ 4 h/r.t.	99	622

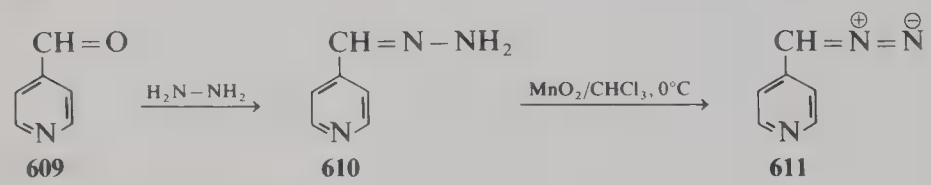
silver oxide, the yields were lower. Morrisson, Danishefsky, and Yates[605] found active manganese dioxide superior for oxidation of 1-mesitylglyoxal 2-hydrazone (**604**) to the α-diazo ketone (**605**) (100% yield); with mercury(II) oxide, the yield was only 75%. Allinger and co-workers[619] employed this procedure in the synthesis of 4-carboxy-8 paracyclophane (**608**) from 4,5-diketo-9-paracyclophane 4-monohydrazone (**606**) by way of the diazo intermediate **607**. Similarly,[620] 4-pyridyldiazomethane (**611**) was obtained in good yield from isonicotinaldehyde hydrazone **610** (prepared from aldehyde **609**) by treatment with manganese dioxide in chloroform solution at 0°C.



604 **605**

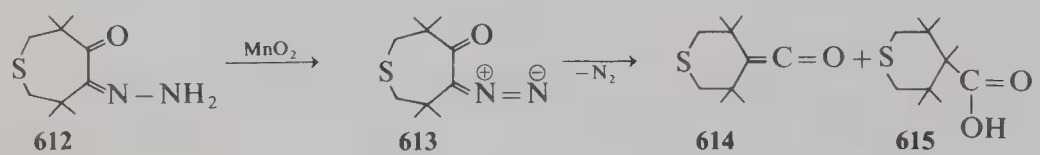


606 **607** **608**



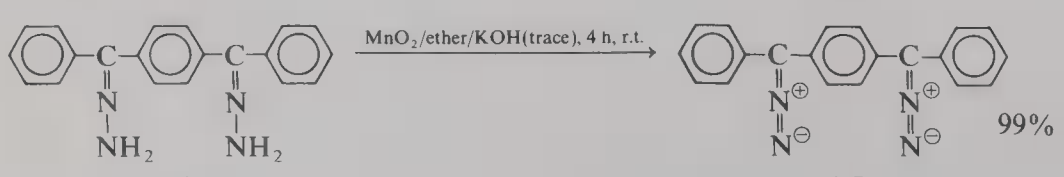
609 **610** **611**

Oxidation of hydrazone **612** with manganese dioxide gave the unstable α-diazoketone **613**, which is not stabilized by resonance; the conformation of the seven-membered ring in **613** is such that the diazo function and the carbonyl group are orthogonal to one another (a skew conformation). Compound **613** spontaneously decomposes (via a Wolf rearrangement) to give a ketene **614** (stable as the monomer) and an acid **615** (combined yield, 49%).[621]



612 **613** **614** **615**

Facile oxidations have also been observed with bis-[hydrazones]. For example, treatment of 1,3-dibenzoylbenzene-bis[hydrazone] (**616**) with manganese dioxide in ether solution gave purple 1,3-bis[α-diazobenzyl]benzene (**617**) in quantitative yield.[622,623]



616 **617**

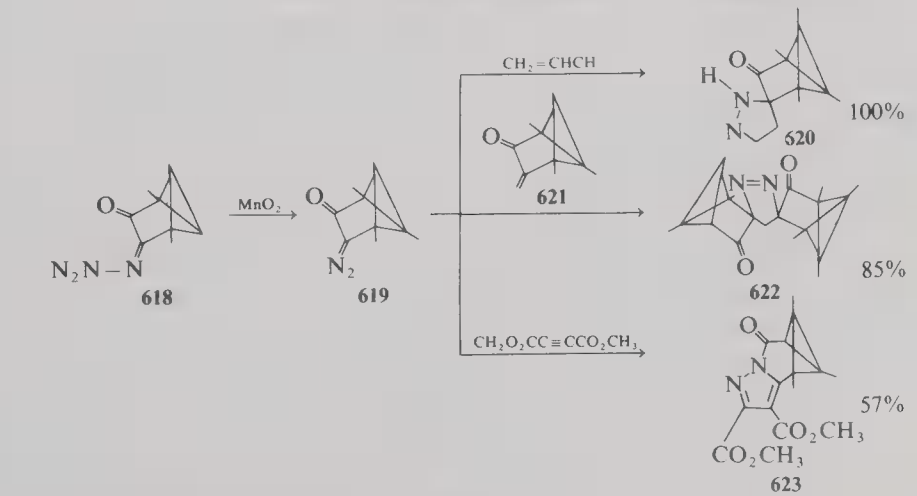
Preparation of a series of other diazo compounds has been reported,[605,624–628] and some of the fascinating degradations of diazo compounds with manganese dioxide that can be of synthetic value have been described[612,629–631]; some of these are summarized in Table XX. Wittig and Heyn[629] found that manganese dioxide is a more efficient oxidant for preparation of strained acetylene derivatives from diazo compounds.

6.2.5. α-Diazoketones. Useful Synthetic Intermediates

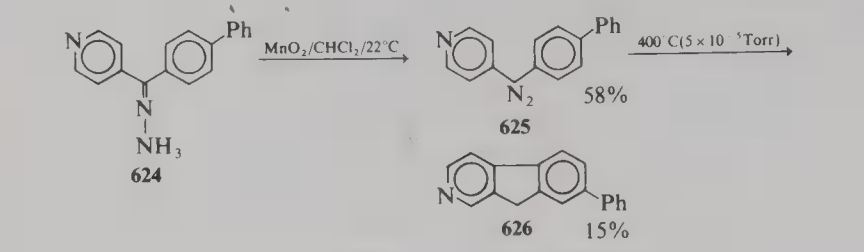
α-Diazoketones can be put to diverse uses in organic synthesis.[633] For example, the 1,3-dipolar addition to activated alkenes and alkynes affords pyrazolines and pyrazolenines, respectively. Loss of nitrogen from the diazoketone, either thermally, photochemically, or catalytically (transition metal), provides an α-keto carbene (or carbenoid) that may either display the well-known Wolf rearrangement[633a–633c,634,635] leading to ketenes or be trapped, for instance, by alkenes to yield α-ketocyclopropanes[633a] or dihydrofuran derivatives, the latter resulting from a (formal) 1,3-dipolar addition.[633a,633d] Upon treatment of diazoketones with acids, products are obtained that result from the intermediate α-keto carbonium ion, which is generated from the initially formed diazonium ion by loss of nitrogen.[633e,633f,636] Recently, Hogeveen and co-workers[637] examined the chemistry of bicyclobutane-bridged α-diazoketene (**619**) [prepared by oxidation of the hydrazone **618** with excess MnO_2 (ACC) in methylene chloride]. The reaction of the α-diazoketone (**619**) with excess acrylonitrile provided Δ^2-pyrazoline (**620**) in almost quantitative yield. The reaction of **619** with enone **621** (via the 1,3-dipolar addition of **619** to activated unsaturated carbon–carbon bond) afforded as the only product the *trans*-bis(bicyclobutyl ketone)-substituted pyrazoline (**622**) (85% yield), no *cis*-isomer being formed. Treatment of the diazoketone **619** with an activated alkyne, e.g., dimethyl acetylenedicarboxylate, gave an adduct which was identified as pyrazole (**623**) (57% yield) (Scheme 23). In contrast to the above-mentioned reactions with electron-deficient alkenes, no reaction occurs upon treatment of **619** with electron-rich alkenes such as vinyl acetate and 2,3-dimethyl-2-butene; also, no reaction occurs upon treatment with electron-rich alkynes such as 2-butyne.

In another example, hydrazone of 4-biphenyl-4-pyridyl ketone (**624**) was oxidized with manganese dioxide (ACC) in chloroform, to give (4-biphenylyl)-(4-pyridyl)-diazomethane (**625**) (58% yield); flash pyrolysis of (**625**) at 400°C (5×10^{-5} Torr) yielded 7-phenyl-2-azafluorene (7-phenylindeno[2,1-C]-pyridine) (**626**) (15% yield)[638] (Scheme 24).

SCHEME 23

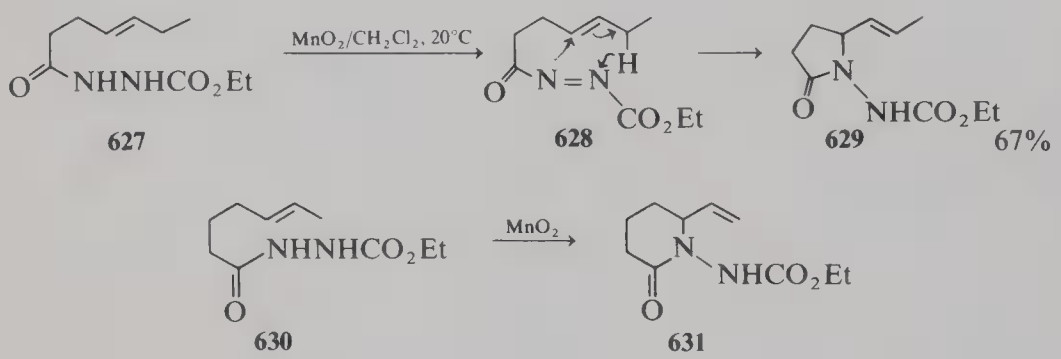


SCHEME 24



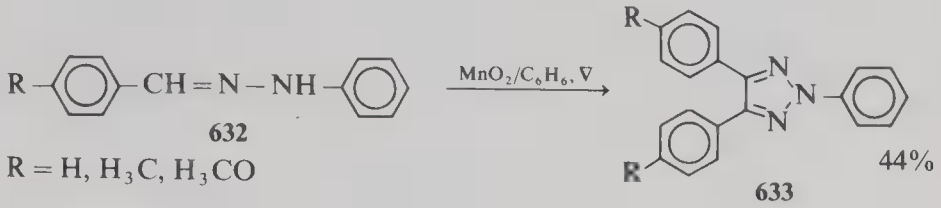
6.2.6. Lactams by Intramolecular Ene Insertion of Acylazocarboxylates

A method for lactam synthesis by intramolecular ene insertion of acylnitroso compound has been reported[639]; other synthetically pertinent ene reactions have been reviewed.[640,641] As reported by Vedejc and Meier,[642] γ, β or δ,ε-acylhydrazocarboxylates (**627**) (easily prepared from acid chlorides and ethoxycarbonylhydrazine) undergo intramolecular ene insertion reaction when oxidized with manganese dioxide. Among several oxidizing agents examined, active MnO_2 (ACC)[25] at 20°C gave the best results. Thus, when the hydrazide **627** was stirred with 25–30 mole excess of MnO_2 in methylene chloride, the crystalline lactam **629** was obtained in 67% yield. The intermediate azo compound **628** did not accumulate under these conditions, but the characteristic orange color attributed to **628** was observed using other oxidants at lower temperature. Similarly the hydrazide **630** was converted into the lactam **631** (~50% yield).



6.2.7. Phenylhydrazones

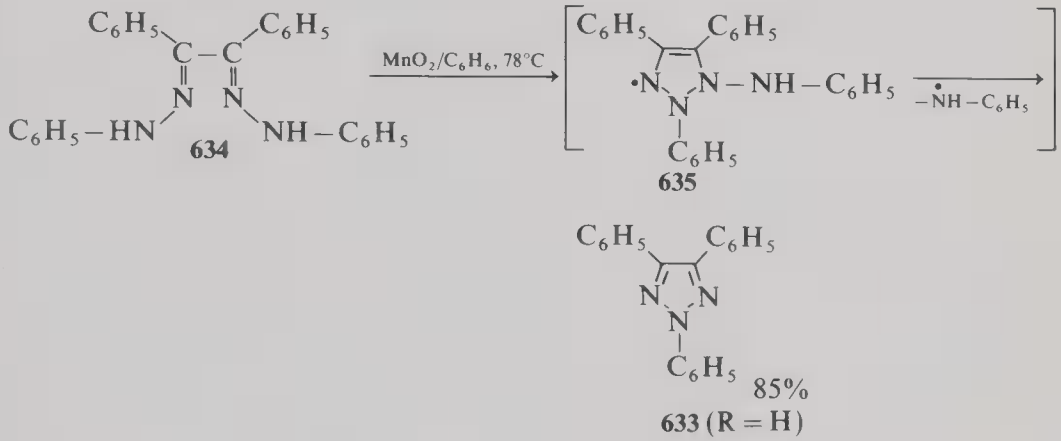
The oxidation of hydrazones with manganese has been studied by many workers.[292,475,476,478,605,612,614,619,625,628,631,643,644] Scrutiny of the literature shows that manganese dioxide oxidation of hydrazones gives different types of product depending upon the reaction conditions and the structure of the parent carbonyl compounds. On treatment with manganese dioxide, phenylhydrazones of ketones and aldehydes and bis[phenylhydrazones] (e.g., osazones) also produce an array of products. Bhatnager and George[16,476,644] showed that benzophenone phenylhydrazone undergoes oxidative fragmentation to give benzophenone and biphenyl (apparently via radical coupling) on treatment with manganese dioxide in benzene. In contrast, benzaldehyde phenylhydrazone (**632**), on similar treatment,[476,644] gives a mixture of various dimeric products formed through C–C, N–N, or C–N coupling of the intermediate radicals; this work supplemented an earlier study on oxidative dimers from benzaldehyde phenylhydrazones.[645] In addition, a small amount of 2,4,5-triphenyl-1,2,3-triazole (**633**) could be isolated from the reaction mixture; the formation of triazole (**633**) has been explained in terms of the oxidation of the benzil osazone (**634**) to give an 85% yield of **633** (R=H), possibly via the radical intermediate **635**.[644] On oxidation of benzaldehyde salicyloylhydrazone with active manganese dioxide, in



632
R = H, H_3C, H_3CO

633

addition to salicyclic acid (20%), 2-(*o*-hydroxylbenzyl)-4,5-diphenyl-1,2,3-triazole was isolated (40% yield)[643]; similar treatment of phenylhydrazone of 2,3-dioxobutyranilide 2-oxime also produced a triazole derivative.[646] Similarly, (*p*-bromophenyl)-glyoxal osazone was converted with manganese dioxide into (*p*-bromophenyl)-1,2,3-triazole.[647]

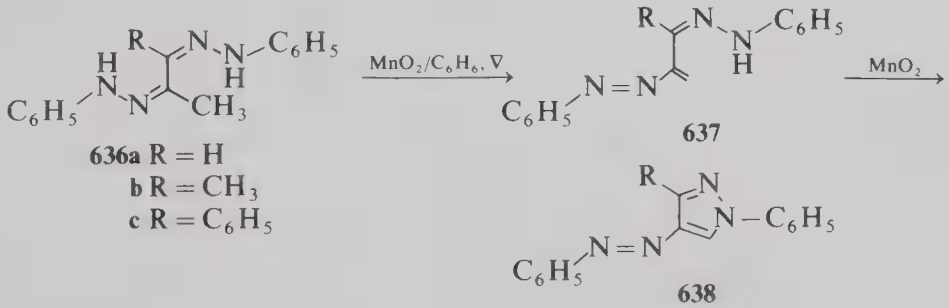


634

635

633 (R = H)

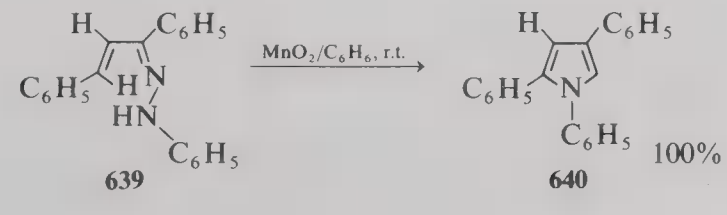
Glyoxal-osazone, pyruvaldehyde-(methylglyoxal)-osazone, and 2,3-butanedione-(biacetyl)-osazone gave excellent yields of *N*,*N*-diphenylbis[azoethenes] on an oxidation at room temperature with manganese dioxide in benzene solution[644]; however, ring-substituted glyoxal-osazones (e.g., *p*-Cl, *p*-Br, *p*-H_3C, COOH, and NO_2) were little affected by manganese dioxide at room temperature, but were readily oxidized with lead(IV) acetate in dichloromethane.[318] In refluxing benzene, however, methylglyoxalosazone (**636a**), bicetyl-osazone (**636b**), and methylphenylglyoxalosazone (**636c**) undergo cyclization, apparently via intermediates (**637a–637c**), to give good yields of the corresponding phenylazopyrazoles (**638a–638c**).[648] Similarly, an α,β-unsaturated phenylhydrazone (e.g., chalcone phenyl-hydrazone) was cyclized to 1,3,4-triphenylpyrazole in quantitative yield (conversion **639** → **640**).[475]



636a R = H
b R = CH_3
c R = C_6H_5

637

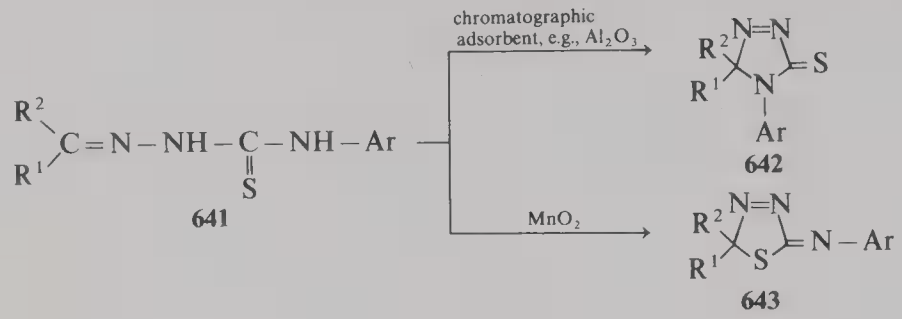
638



639

640

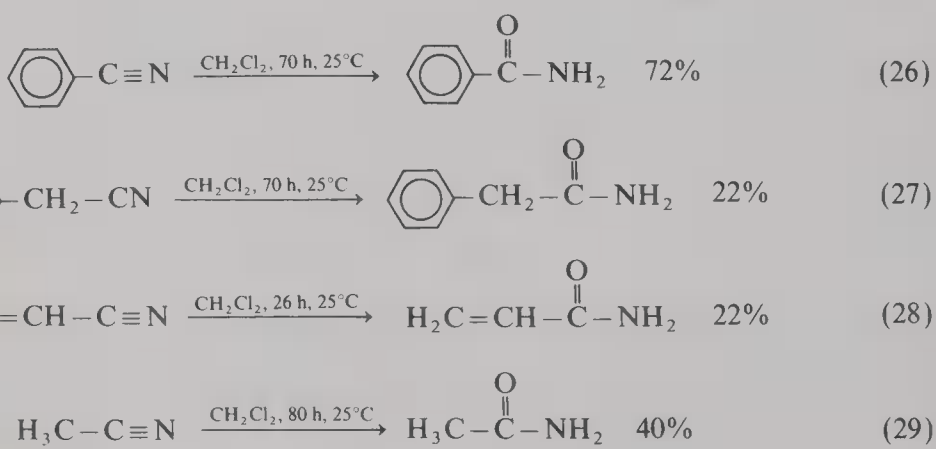
In a related reaction, a new method for cyclization of thiosemicarbazones has been reported. Thus, 4-arylthiosemicarbazones (**641**) have been cyclized either to 5-thio-Δ'-1,2,4-triazolines (**642**) with alumina[649] or to imino-1,3,4-thiadiazolines (**643**) with manganese dioxide.[650]



7. MISCELLANEOUS OXIDATIONS

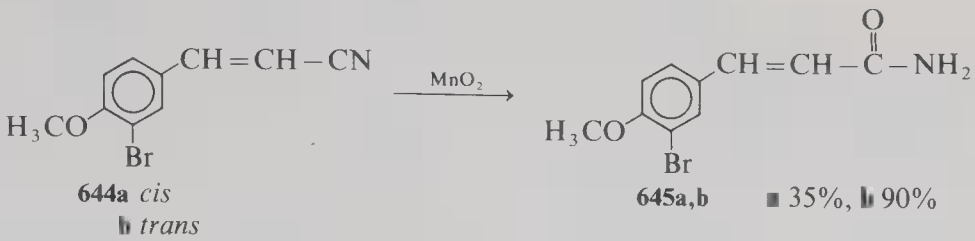
7.1. Nitriles

The hydrolysis of nitriles to amides generally requires rather drastic conditions involving strong acids or alkali, although hydrolysis may sometimes be effected at room temperature using hydrogen peroxide. Metal-catalyzed hydrolysis of nitriles to amides either involves the hydroxide ion as a reactant[651,652] or requires refluxing conditions.[653,654] In a new procedure,[655] aromatic and aliphatic mononitriles were readily hydrolyzed with manganese dioxide in neutral media (in dichloromethane) at room temperature to give good yields of amides with no other products (e.g., acids). The reaction probably involves a solid-phase catalyzed hydrolysis using water on the surface of the solid. The examples in Eqs. (26)–(29)



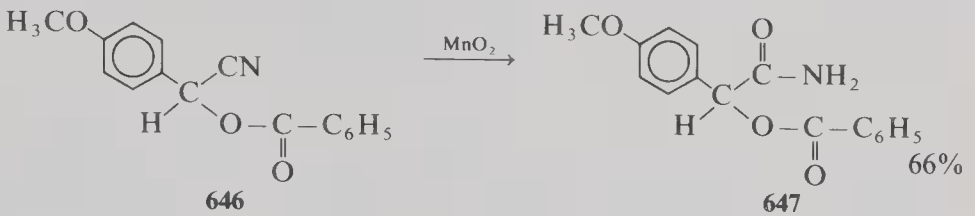
illustrate the scope.[655] Acetonitrile was also hydrolyzed with manganese dioxide in refluxing *p*-dioxan.[656] The relatively high formation of the amide **645** in the hydrolysis of *cis*- and *trans*-isomers of nitrile **644** (*cis*- and *trans*-3-bromo-4-methoxycinnamonitrile),[655] of the amide **647** from nitrile **646** (4-methoxymandelonitrile-*O*-benzoate),[655] and of 2-carboxamido-3-phenylquinoxaline (**649**) from 2-cyano-3-phenyl-1,2,3,4-tetrahydroquinoxaline (**648**) (via hydrolysis and dehydrogenation)[657] suggests that steric requirements for the manganese dioxide hydrolysis of nitriles are much less than those observed for normal hydrolysis.[651,653]

Recently[655a] the hydration of aqueous nitriles to amides has been examined over various preparations of active manganese dioxide. In most instances high yields of amides are obtained with complete freedom from coproducts or side reactions. For example, a suspen-

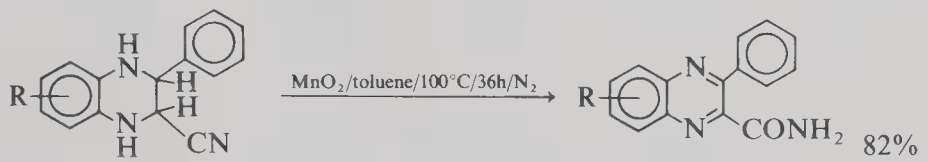


644a *cis*
b *trans*

645a,b ■ 35%, ■ 90%



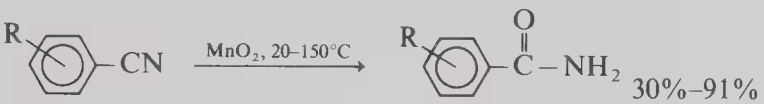
646 **647**



648 **649**

sion of manganese dioxide (ACC) (1 g), pyridine-3-carbonitrile (5 g) in water (35 ml) is refluxed for 5 h; concentration of the filtrate and washings gives pyridine-3-carboxamide (nicotinamide); yield: 5.5 g (>97%). The yield of the product varied with different preparations of the catalyst. The infrared spectra of manganese dioxide catalysts are observed and related to the catalytic activity. The possible reaction mechanism is discussed.

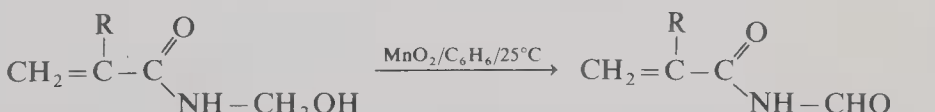
Another recent study[658] in this area reported hydrolysis of a series of aromatic nitriles, e.g., Eq. (30). Similar treatment of methylacrylonitrile ($H_2C=C(CH_3)CN$) gave a polymer



(30)

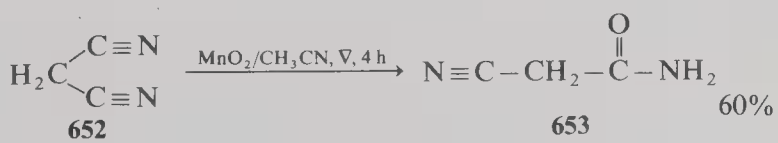
R = H, 4-H_3CO, 2-O_2N, 3-O_2N, 4-O_2N, 2-Br, 4-H_3C,

(amidonitrile copolymer) in 21%–31% yield[658] and *N*-methylolacrylic amide (**650**) was oxidized with active manganese dioxide in organic solvents, to yield *N*-formylacrylic amide (**651**) (75%–80% yield), a useful monomer for vinyl polymerization, including polymer cross-linking reactions.[659] However, the literature contains little information on manganese dioxide oxidation (e.g., hydrolysis) of aromatic or aliphatic dinitriles. A preliminary study made in this laboratory showed that, in the aliphatic series, only a most reactive dinitrile [e.g., malononitrile (**652**)] on treatment with manganese dioxide in refluxing acetonitrile was hydrolyzed to give cyanoacetamide (**653**, m.p. 119–120°C) in 55%–60% yield.[318] Higher



650 R = H
R = CH_3

651



652 **653**

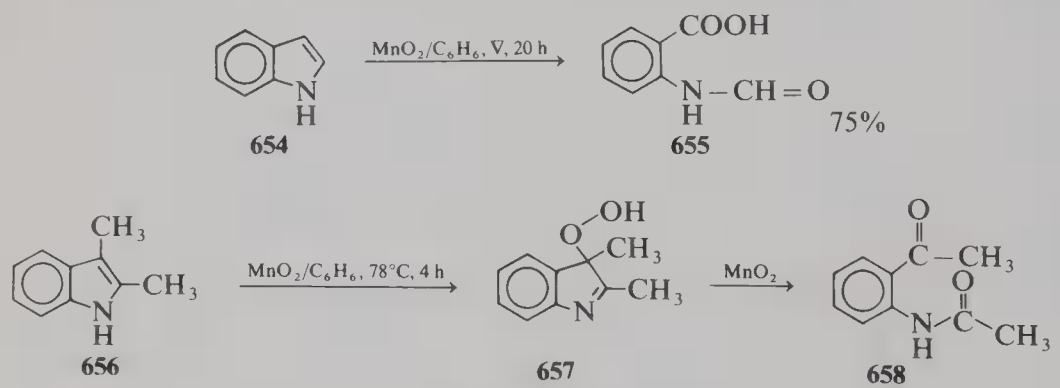
aliphatic dinitriles (e.g., glutaronitrile, adiponitrile) were recovered practically unchanged following similar treatment (e.g., refluxing acetonitrile; however, *p*-dioxan as the solvent was not tested). Treatment of 1,2-, 1,3-, and 1,4-dicyanobenzenes with manganese dioxide in refluxing acetonitrile (4–12 h) produces mixtures containing mono- and dicyanobenzamides; on prolonged heating some cyanobenzoic acids are also formed; mixtures can be separated by TLC or column chromatography [silica Gel HF 254 and 366, solvent 1:1 (V/V) chloroform/acetone or 1:1 (V/V) cyclohexane/ethyl acetate]; e.g., 1-cyano-3-benzamide (m.p. 225–226°C), 1-cyano-4-benzamide (m.p. 182–184°C).[318]

In contrast, considerable stability of the cyano group in 2-cyano-, 3-cyano-, and 4-cyanopyridines toward manganese dioxide has been observed; for example, 4-cyanopyridine was recovered practically unchanged following treatment with the reagent in refluxing acetonitrile for four hours[318]; see, however, Ref. 655a.

7.2. Indoles and Carbazoles

Opening of the heterocyclic ring in indole and 2,3-alkylindoles by manganese dioxide is partially due to the sensitive nature of the indole α,β-bond.[660] Manganese dioxide oxidation of indole (**654**) is reported to give mainly *N*-formylanthranilic acid (**655**)[480]; similar oxidation of 2,3-dimethylindole (**656**) also proceeds with the cleavage of the indole α,β-bond, to give **658** via a suggested indole hydroperoxide intermediate (**657**)[661]; involvement of a hydroperoxy-indolenine intermediate in the *in vitro* and *in vivo* cleavage of the indole α,β-bond of isovincoside lactam has recently been suggested[662]; however, an initial hydroxylation of the indole α,β-unsaturated bond (to give a 2,3-diol intermediate) is a real possibility.

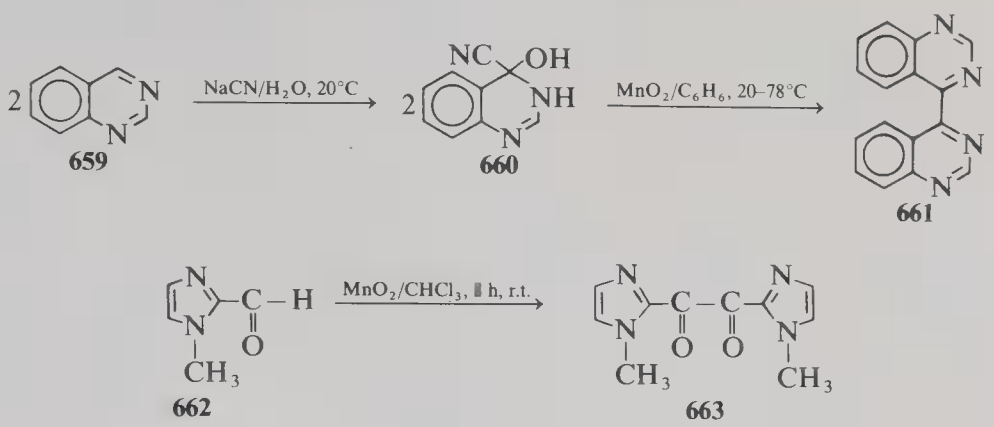
Study of the action of manganese dioxide on related tryptophans and their derivatives would be of considerable interest.



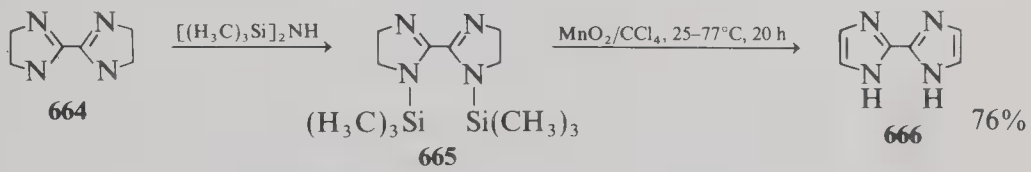
Manganese dioxide oxidation of tetrahydrocarbazole in refluxing benzene under nitrogen gives a mixture of carbazole and tetrahydrocarbazole-1(2H)-one; however, oxidation in the presence of air gives a complex mixture of products (e.g., spiroindoxyl and cyclopentanoquinol)[480] (see also Table XIV).

7.3. Oxidative Dimerization of Heterocyclic Compounds

An interesting case of oxidative dimerization has been observed with quinazoline (**659**), which was converted into 4,4′-biquinazolinyl (**661**) via a possible cyano-adduct (**660**), on treatment with aqueous sodium cyanide, followed by oxidation with manganese dioxide in benzene. Similar dimerization has also been observed with 2-methylquinazoline, but not with the 4-methyl isomer.[663] Treatment of 1-methyl-2-formylimidazole (**662**) with manganese dioxide in chloroform supposedly produces dimer **663** in moderate yield.[664] A new synthetic



route[665] to 2,2′-biimidazole (glycosine, **666**) is based on the oxidation under mild conditions of the easily available 2,2′-bi[2-imidazoline] (**664**). Compound **664** was made soluble in organic solvents by conversion into its bis[trimethylsilyl] derivative **665** with hexamethyldisilazane and then oxidized with activated manganese dioxide in tetrachloromethane (76% yield).



7.4. Nucleic Acid Derivatives

Oxidative fragmentation has been observed following treatment of nucleic acid derivatives with manganese dioxide in hot aqueous solution. For example, adenine and guanine[666] gave degradation products of the purine ring, e.g., urea, guanidine and biuret; thymidine 5′-phoshate (but not thymidine) was degraded to thymine[667] with manganese dioxide in hot water. Similarly, purine (but not pyrimidine) nucleosides[666] have been oxidized to the corresponding bases and their oxidation products; similar degradation has been observed with oligodeoxyribonucleotide and deoxyribonucleic acid.[666]

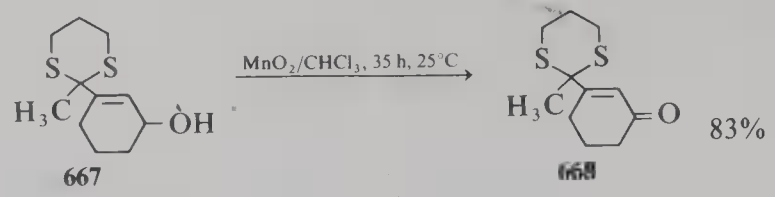
7.5. Organic Sulfides

Treatment of saturated alkyl or aryl sulfides (e.g., di-*n*-butyl- or phenyl dibenzyl sulfide) with manganese dioxide in light petroleum yielded corresponding sulfoxides in 71%–74% yield; no formation of sulfone has been observed[668]; similarly diallyl sulfide was oxidized to diallyl sulfoxide in 49% yield, e.g., Eq. (31).[481] Although some oxidation of organic thiols[669]

(31)

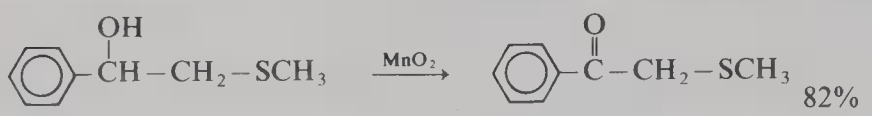
and disulfides with manganese dioxide has been observed, the reagent failed to attack 1,2-dithianes[670]; similarly, a sensitive 1,3-dithiane ring in the presence of manganese dioxide remained intact, for example, in oxidation of the unsaturated alcohol **667** [2-methyl-2-(1-cyclohexene-3-ol)-1,3-dithiane] to a ketone **668** [2-methyl-2-(1-cyclohexene-3-one)-1,3-dithiane].[185]

Similarly, *β*-hydroxy sulfides, sulfones, and sulfoxides having benzylic groups were suc-



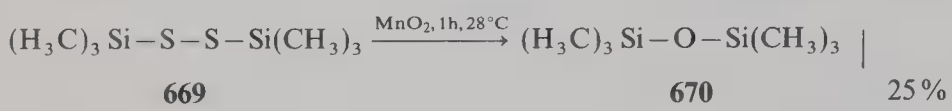
667 668

cessfully oxidized with active manganese dioxide to give high yields (80%–90%) of the corresponding β-keto sulfides, sulfones, and sulfoxides; note that the sulfide group, for example, in 2-methylmercapto-1-phenylethane-1-ol (β-hydroxy-β-phenethyl methyl sulfide) was not attacked by the reagent, e.g., Eq. (32).[671] An interesting decomposition of a disulfide



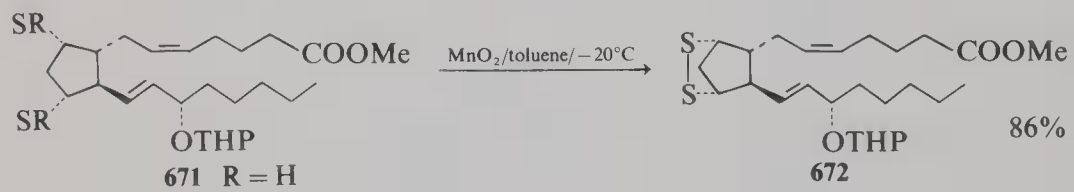
(32)

bridge by manganese dioxide has been described. Thus, slight warming of bis[trimethylsilyl] disulfide (**669**) with the reagent at 28°C yielded hexamethyldisiloxane (**670**) in 25% yield.[672]



669 670

The synthesis of the rigid endodisulfide ring of structure **672** (required as a stable prostaglandin analog) was possible only by use of manganese dioxide as oxidant. Thus, upon treatment of (**671**) with 1.5 equiv. of active manganese dioxide in degassed toluene at −20°C for 40 min under argon, **672** [methyl (5Z, 9α, 11α, 13E, 15S)-9,11-epidithio-15-hydroxyprosta-5,13-dienoate, endodisulfide analog of PGH_2] was obtained in 86% yield.[673] Other

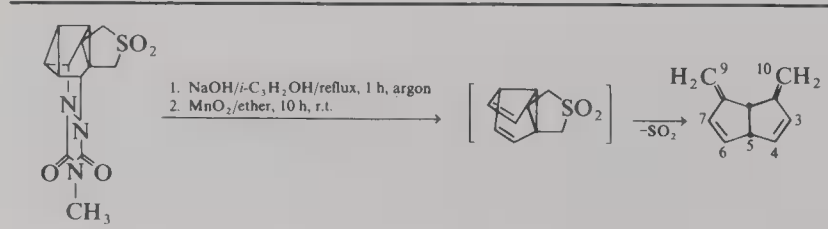


671 R = H 672

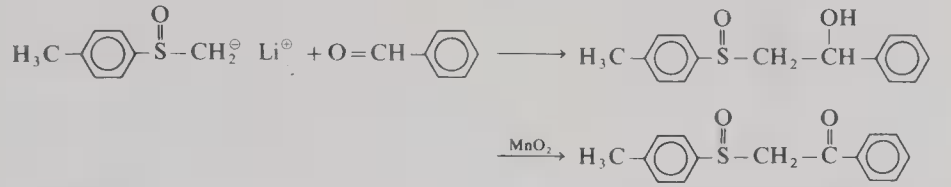
oxidation methods were unsuccessful. Paquette and co-workers[674] in their study of bullvalene derivatives observed a novel isomerization (shown below), following oxidation with manganese dioxide, and presumably arising by cheletropic extrusion of sulfur dioxide (Scheme 25).

Synthesis of ω-(*p*-tolysulfinyl)-acetophenone involved a manganese dioxide oxidation of 2-hydroxy-2-phenylethyl *p*-tolyl sulfoxide, which was obtained by condensation of *p*-tolylsulfinyl carbanion with benzaldehyde[675] (Scheme 26). Manganese dioxide oxidation of thioureas in chloroform at room temperature gave the corresponding ureas. A probable mechanism for this reaction may involve the initial formation of a carbodiimide intermediate which reacts with water, under experimental conditions, to afford the corresponding urea.[676]

SCHEME 25

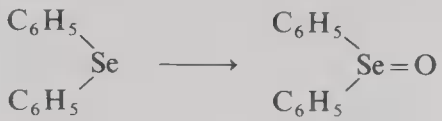


SCHEME 26



Dehydrogenation of 2,2′-bi(1,3-dithiolyl) to tetrathiofulvalene was performed with active manganese dioxide in refluxing acetonitrile (26% yield).[677] Active mangane dioxide has been applied as vulcanizing agent (e.g., cross-linking agent for polysulfide polymers).[678]

Treatment of diphenyl selenide with manganese dioxide (in CH_2Cl_2 or CH_3CN/25°C) gave diphenyl selenoxide in 85% yield [Eq. (33)]. Oxidation of other selenides (e.g., benzyl phenyl selenide) with the reagent to the corresponding selenoxides has also been observed.[318]



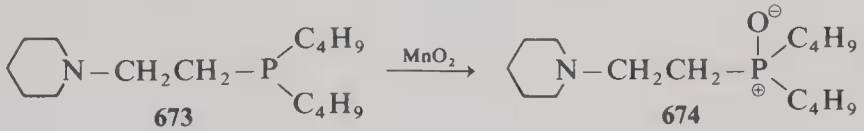
(33)

7.6. Phosphorous Compounds

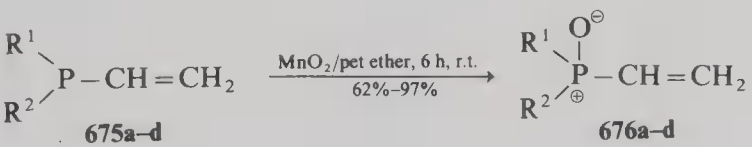
On treatment with manganese dioxide in neutral media, trivalent organophosphorous compounds are readily oxidized to pentavalent phosphine oxides (via accommodation of ten electrons in their empty 3d orbitals); an early report is a conversion of triphenylphosphine in light petroleum to triphenylphosphine oxide in 75% yield[292] [where the phosphine oxide group (P → O) has a hybrid structure comprising a dipolar form and a double bond character, e.g., Eq. (34)]. Kabachnik and co-workers[679–681] have oxidized with manganese dioxide

(34)

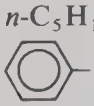
a series of tertiary saturated (e.g., conversion of **673** → **674**)[680] and vinylphoshines [e.g., conversions of **675a–675d** → **676a–676d**][679] and similarly vinyl-, allyl-, and vinylphenylphosphorous esters (e.g., conversion of **677** → **678**) to the corresponding oxides in high yields and without formation of side-products.

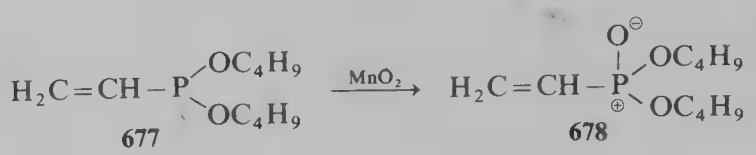


673 **674**



675a–d **676a–d**

	R^1	R^2	Yield
a	n-C_3H_7	*n*-C_3H_7	97
b	*n*-C_4H_9	*n*-C_4H_9	62
c	*n*-C_5H_{11}	*n*-C_5H_{11}	95
d	CH_3		88

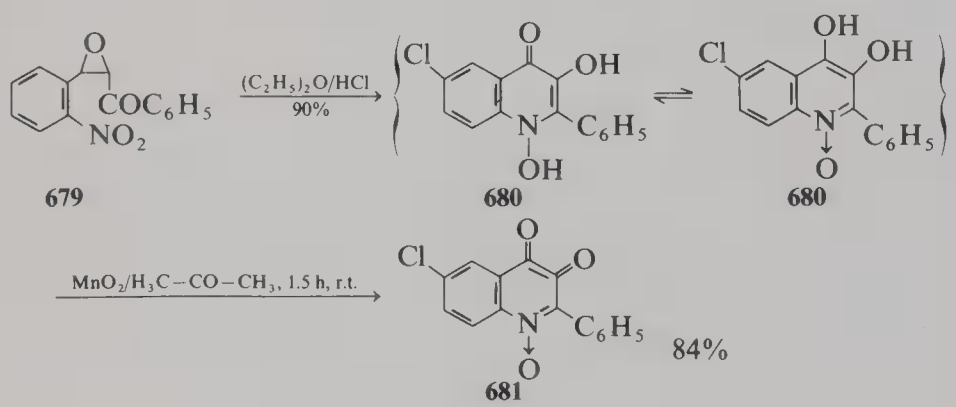


677 678

Manganese dioxide oxidation of phenyltrimethylene phosphite gave the corresponding phosphate in good yield[682]; similar treatment of diphenylferrocenylphosphinecarbinol gave a mixture of the corresponding phosphine and phosphine oxide aldehydes.[683]

7.7. Other Applications

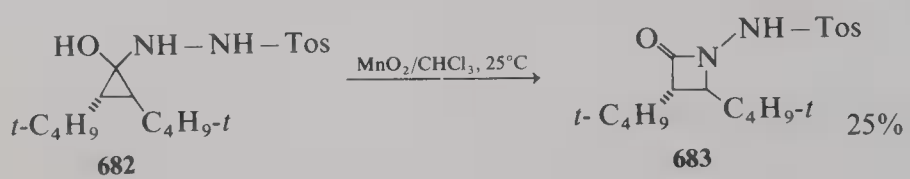
Quinoline-3,4-dione-1-oxides can be conveniently prepared via manganese dioxide oxidation of 1,3-dihydroxy-4(H)-quinolones. Thus, *cis*-1-benzoyl-2-(*o*-nitrophenyl)-oxirane (**679**) treated 24 h at room temperature with ethereal hydrogen chloride gave in 90% yield (**680**) [6-chloro-1,3-dihydroxy-2-phenylquinoline-4(1H)-one], believed to exist in equilibrium with its tautomer **680** ↔ **680a**; the latter in acetone was stirred with manganese dioxide (15 h) to yield dione (**681**) (6-chloro-2-phenylquinoline-3,4-dione-1-oxide) in 84% yield.[684]



679 680 680

681 84%

A novel oxidative ring expansion has been reported; thus, oxidation of the adduct of tosylhydrazine with *trans*-2,3-di-*t*-butylcyclopropanone (e.g., **682**) with active manganese dioxide gives the new *β*-lactam (**683**) in 25% yield (confirmed by an unequivocal synthesis).[685]



682 683 25%

In a recent study of nonphenol oxidative coupling of benzylisoquinolines (required for a synthesis of alkaloids dibenzazonine and appophine), Kuchan and co-workers[686,687] have oxidized with active manganese dioxide a series of *N*-bridged dienol intermediates, e.g., conversion of *N*-methyldienol into *O*-methylflavinantine (29% yield)[686] and conversion of a mixture of the epimeric (±)-*O*-methylsalutaridinols into (±)-*O*-methylsalutaridine (MnO_2, $CHCl_3$, 60% yield)[687]. (Compare phenol oxidative coupling, Section 3.11; compare also oxidation of the alkaloid tazzetine Refs. 281–283.) Treatment of 4-anilino-5-hydroxy-Δ^3-pyrrolin-2-one with active manganese dioxide (CH_2Cl_2, 1 h, 25°C) yielded a yellow fluorescent maleimide in unspecified yield.[688]

The tritium labeled alcohol, [γ-$^{14}C^3H_2OH$] coniferin was oxidized with manganese dioxide to the corresponding coniferyl aldehyde; the same aldehyde was also obtained by the enzymatic oxidation with cinnamyl alcohol dehydrogenase [NADP].[689]

Hulupone, useful as the bitter principle for beer, was prepared by active manganese dioxide catalyzed air oxidation of lupulone β-acid.[690] Pregnadienoates (e.g., alkyl 3,20-dioxopregnan-1,4-dien-21-oates, useful as intiinflammatory agents) have been prepared by manganese dioxide oxidation of the corresponding alcohols.[691] In addition to work described in Ref. 44, oxidation of pyrene with manganese dioxide in aqueous sulfuric acid ($\geqslant 50\%$ H_2SO_4 at 60°C) gave a mixture containing 1,6- and 1,8-pyrenediones, a coupling compound 1,1′-bipyrene (via, apparently, a free-radical intermediate), some pyrenic acid and other ring-degradation products.[692]

Active manganese dioxide was the reagent of choice for the oxidation of the isomeric adducts, following the condensation of 1,2,3,4- and 1,2,3,8-tetramethylcyclooctatetraenes with *N*-phenyltriazolinedione[693]; similar isomeric adducts of the dimethylcyclooctatetraene derivatives were also oxidized with manganese dioxide.[694]

A synthesis of the natural product eburnamonine involves a manganese dioxide oxidation.[695] Characterization of a Mn(IV) oxide-reductase system in a marine bacillus has been attempted.[696] Kinetic relations in the oxidation of acetylene microimpurities on hydrated manganese dioxide (e.g., β-MnO_2, H_2O) have been studied.[54,697] Kinetic study of cyclohexane oxidation by manganese dioxide has been reported.[698]

New active manganese oxide reagent [Eq. (35)] (MnO_{164}) was used in oxidation of

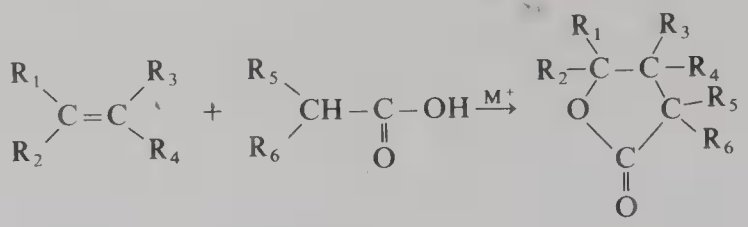
$$MnSO_4 + \text{aq. } NH_3/O_2 \text{ (1 atm)} \longrightarrow MnO_{164} \tag{35}$$

aniline (in aq. H_2SO_4) to benzoquinone.[699] Recent industrial applications of manganese dioxide include the following topics: (a) industrial methods for production of manganese dioxide (a review),[700] (b) unique and interesting properties of manganese dioxide as a tyical one-phase solid redox system (a review),[701] and (c) modern processes of industrial chemistry: manganese dioxide (a review).[702] Active manganese dioxide has been applied for sorption of waste gases (e.g., methane, carbon monoxide, phenol, etc.),[703,704] for sorption of aliphatic hydrocarbons (e.g., propene, acetylene, and propane),[705] for studies of effects of seawater cations and temperature on manganese dioxide–reductase activity in a marine bacillus[706]; also in formaldehyde removal,[707] in a kinetic study of oxidation of a benzene microimpurity in air,[54,708] benzoyl perioxide decomposition[709]; also in the oxidation of ethanol (by γ-MnO_2 voltametry),[710] and in the liquid-phase oxidation of hydrocarbons.[711,712] The kinetic study of the exhaustive oxidation of benzene by a pulsed microcatalytic method has recently been reported. The study showed[713] that the oxidation of benzene on active manganese dioxide (e.g., $MnO_2 \cdot H_2O$) involved interaction of adsorbed benzene and oxygen to form a species which was further oxidized in the rate-determining step. Additional applications of active manganese dioxide (e.g., analytical, physical, inorganic) have been surveyed.[19]

7.8. Miscellaneous Recent Results

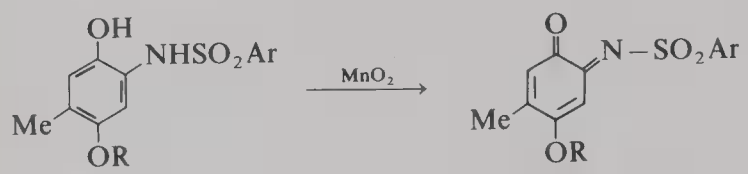
Diazo-ketones (see Section 6.2.4) may lead to a variety of products[714] arising either through the reactions of nucleophiles with the protonated diazocarbonyl function (diazonium or oxo-carbonium intermediates) or by loss of nitrogen resulting in an oxo-carbenoid species. Intramolecular carbon–carbon bond formation of the oxo-carbenoids with an appropriately situated olefinic group has been thoroughly investigated and is of great synthetic utility.[715]

The lactone synthesis involves the preparation of γ-butyrolactones from readily available olefins and carboxylic acids in a simple one-step process.[716] The general reaction which is depicted below [Eq. (36)] consists of the addition of a carboxylic acid having an α-hydrogen atom across the double bond of olefin in the presence of stoichiometric amounts (2 equiv/mol of lactone) of various metal oxidants, including active manganese dioxide. Higher valent metal salts of manganese, cerium, and vanadium have been used successfully in the lactone synthesis. Thus, γ-lactone from octene-1 and active MnO_2 in acetic acid was isolated



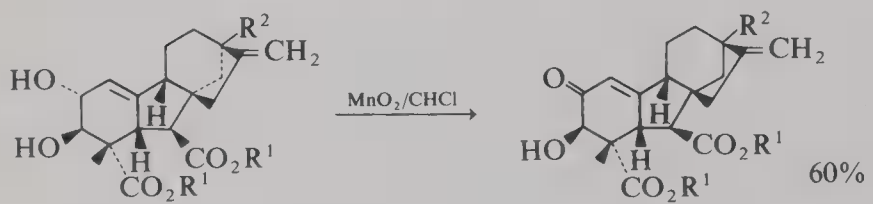
$M^+ = Mn(III), Ce(IV), V(V), Mn(IV)$ (36)

in 46%–67% yield.[716] *p*-Quinone monoacetals are useful synthetic intermediates.[717] The methoxy- and hexadecycloxy-quinone imines (**685**) were synthesized by oxidation of the corresponding phenols **684a** and **684b** with manganese dioxide[718] (see Section 3.11.2). Active manganese dioxide was a reagent of choice in the synthesis of Gibberellin A_{29} from

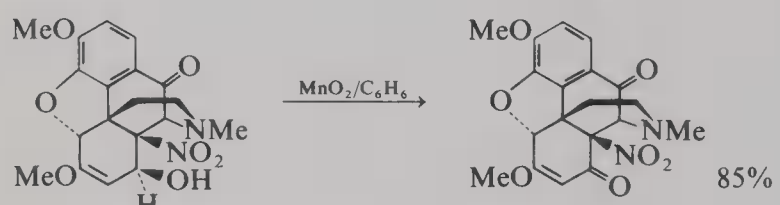


684a ; R = Me
b ; R = $[CH_2]_{15}Me$ **685**

Gibberellin$_3$. Thus, the specific oxidation of the triol dimethyl ester (**686**) with manganese dioxide gave the ketol **687** (60% yield) as the only product[719] (see Section 3.1.4). The presence of a secondary, allylic hydroxyl group in the alkaloid **688** (8,14-dihydro-8β-hydroxy-14β-nitro-10-oxothebaine) was established by oxidation with manganese dioxide (ACC) to form the diketone **689**[720] (see also Section 3.6).

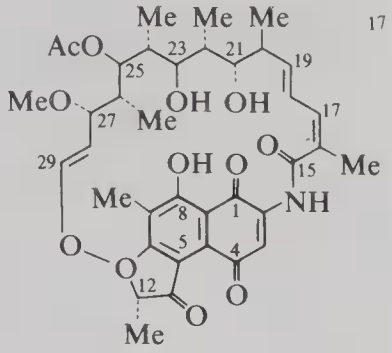


686 $R^1 = Me, R^2 = OH$ **687** 60%

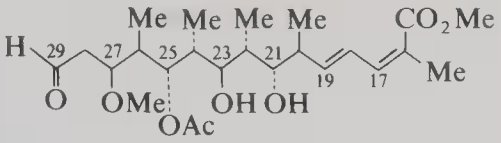


688 **689** 85%

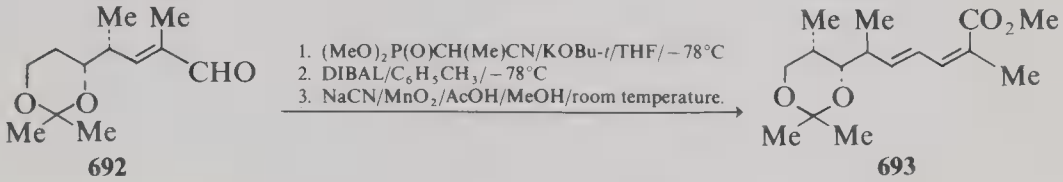
When heated in the presence of MnO_2 α-phenylsuccinimide gave α-phenylmaleimide as a major product and *dl*- and *meso*-2,3-diphenylbutane-1,2:3,4-bis(*N*-methyldicarboximide) as oxidative coupling dimers. Several *N*-substituted β-phenylmaleimides were obtained in 60%–73% yields by this procedure. The oxidation of phenylsuccinimido groups attached to polymers was attempted.[721] The esterification procedure of Corey[190] has been successfully applied by Kishi and co-workers[722] for the synthesis of antibiotic Rifamycin S (**690**), particularly its aliphatic segment (**691**), e.g., a conversion of the aldehyde **692** into the methyl ester **693** (see Section 3.10.2). Almost all oxidizing agents cyclize benzylidene-1-1′-bis-(2-naphthol) (**694**) to the stereoisomers **695** and **696** of phenylnaphtho[2,1-b]-furan-2(1H)-spiro′(2H)-naphthalene-2-one. A few are stereospecific. For example, active manganese dioxide in chloroform gives **695** and **696** (71% yield, the isomer ratio 53:47), whereas potassium permanganate in acetone is stereospecific for the spiran **696** (48% yield, the isomer ratio 99%)[723] (see Section 3.11). The sulfur-containing intermediates, e.g., thiocar-



690: Rifamycin S



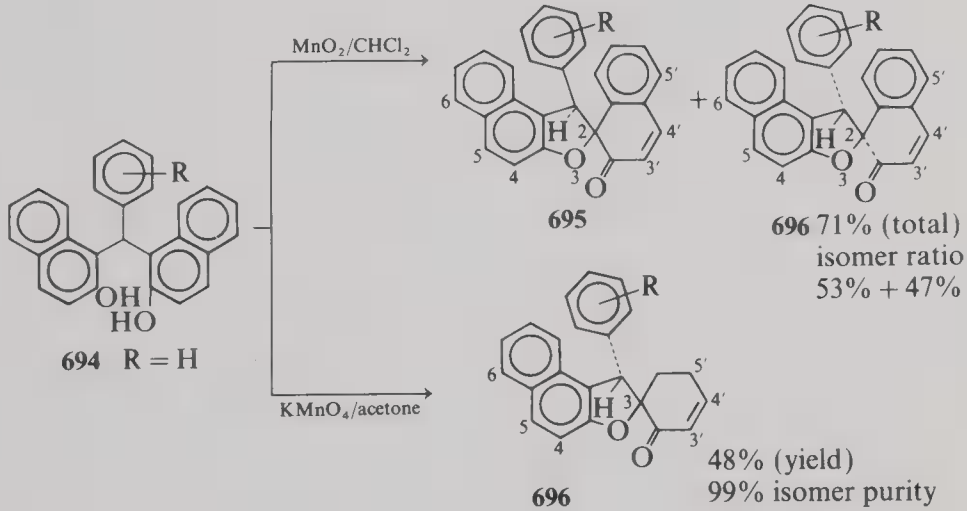
691



692 693

DIBAL = diisonutylaluminium hydride

bonyl yields are important synthetic intermediates.[724,725] A recent study[726] describes the oxidation of the dehydrazone (**697**) with a series of oxidants. In the case of manganese dioxide, the bis (diazo) compound **698** is assumed to be formed, and this should be a precursor to the synthesis of the labile thiacyclopentyne **699**. Although the formation of **699** is supported by isolation of the cycloadduct **700** the competing pathway of cleavage of **697** with MnO_2 perhaps through bis (diazo) compound **698** to dinitrile **701** accounts for all or nearly all the isolated product[726] (see also Section 6.2.4).

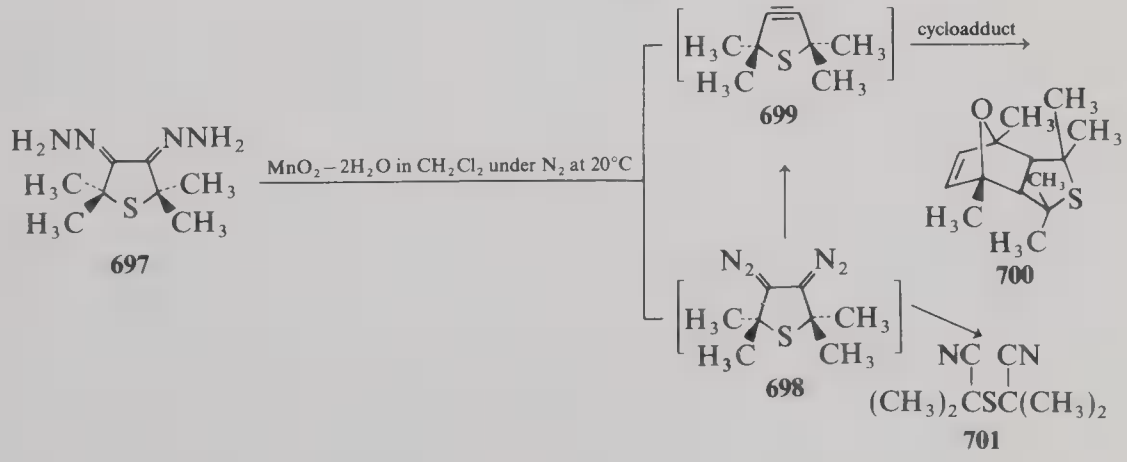


694 R = H

695

696 71% (total) isomer ratio 53% + 47%

696 48% (yield) 99% isomer purity



697

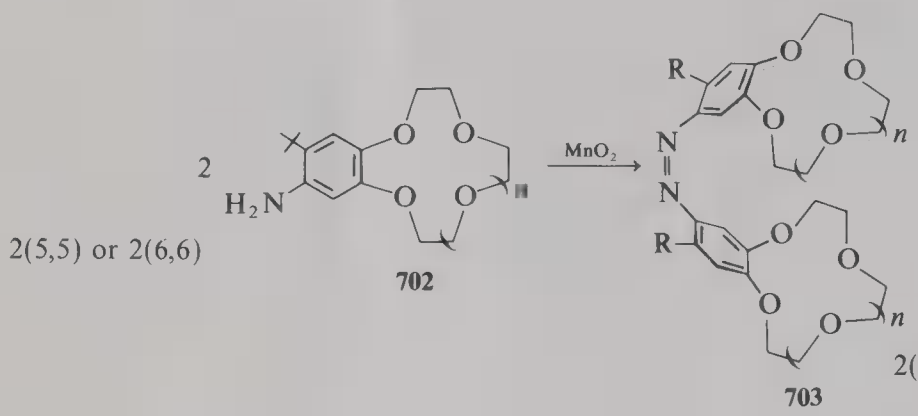
699

700

698

701

Recently a novel oxidative coupling of the amine (**702**) (4′-amino-5′-*tert*-butylbenzo-18-crown-6, $n = 3$) by manganese dioxide to give the azobis (benzocrown ether) (**703**) (5,5) has been reported.[753]



2(5,5) or 2(6,6)

702

2(5,5), R = *t*-Bu; $n = 2$

703

8. EXPERIMENTAL PROCEDURES

8.1. Preparation of 2-Formylchromone (**19**)[111]

A mixture of 2-(hydroxymethyl)chromone (**18**, 2 g, 11.4 mmol) suspended in chloroform (200 ml) is refluxed with stirring for 24 h. After 12 h, an additional 2 g of manganese dioxide is added. The mixture is cooled, filtered, and the filtrate evaporated. The residue is crystallized from ethyl acetate; yield: 1.1 g (56%).

8.2. Oxidation of Gibberellic Acid (**77**) with MnO_2[135]

To a solution of (**77**) (10 g) in 1.2 l of freshly distilled acetone was added active MnO_2[26] (90 g) and the suspension was shaken for 153 h at 20–23°C in a black-glass vessel. After filtration, the precipitate was thoroughly extracted with acetone, and the extracts were combined, evaporated, and the residue chromatographed on silica gel (400 ml) treated with 114 ml of phosphate buffer (pH 6.2). Elution with benzene–CH_2Cl_2 (3:2) gave enone (**78**) (14.5 mg). Elution with benzene–CH_2Cl_2 (1:4) gave lactone (**79**) (250 mg). Further elution with CH_2Cl_2–EtOAc (9:1) gave dilactone (**80**) (1.04 g).

8.3. Preparation of 2-Methyl-2(2′-methyl-1′-propenoxy)-propionaldehyde (**142**, $R^1 = R^2 = CH_3$) and Tetramethylsuccinaldehyde (**141**, $R^1 = R^2 = CH_3$) from Isobutyraldehyde (**140**; $R^1 = R^2 = CH_3$)[192]

A solution of (**140**; $R^1 = R^2 = CH_3$; 18 g) in tetrahydrofuran (150 ml) was passed at reflux (~100°C) under nitrogen through a bed of active manganese dioxide (50 g) in such a manner that the unreacted aldehyde was continuously recycled while the reaction products were concentrated in the reflux pot. After 48 h of reflux and recycling, the solvent and unreacted isobutyraldehyde were removed by distillation leaving a viscous oil (yield: 16.7 g), containing (G.L.C. analysis and separation) **142**; ($R^1 = R^2 = CH_3$) 50%, **141** ($R^1 = R^2 = CH_3$) 35%, and by-products (12%).

8.4. Conversion of Geraniol into Methyl Geranate[190]

A mixture of geraniol (50 mg) and manganese dioxide (575 mg) in hexane (8 ml) was stirred at 0°C for 30 min. Filtration, and removal of solvent, afforded geranial; yield: 48 mg (98%). The geranial so obtained was stirred with a mixture of sodium cyanide (82 mg), acetic acid (30 ml), and manganese dioxide (575 mg) in methanol for 12 h at 20–25°C, to give (after removal of the methanol partitioning between ether and water, and concentration of the ether extract) methyl geranate; yield: 51 mg (85–95%).

This procedure[190] was successfully applied in the conversion of a *trans,trans cis*-triene alcohol (a homolog of farnesol) into an ester (used in the synthesis of a juvenile hormone)[217], and also in conversions of a biologically important aldehyde[218], an annulene aldehyde[190], an cycloheptane ether aldehyde[191], and an unsaturated sugar (an unsaturated hexose)[219] into their corresponding esters, and conversion of the alcohol **138** in to the ester **139**.[191]

8.5. Preparation of 1-(4-Acetoxy-2,6,6-trimethyl-2-cyclohexen-1-yl) 2(E)-buten-1-one (**207**)[228]

To a suspension of activated MnO_2 (Attenburrow) (793 mg, 9.1 mmol) in CH_2Cl_2 (3 ml) was added a solution of (**206**) (78 mg, 0.31 mmol) in CH_2Cl_2 (3 ml). The mixture was vigorously stirred at room temperature for 5 h, and diluted with hot acetone. The insoluble materials were separated by centrifugation, and the supernatant liquor was concentrated. The crude product was chromatographed (SiO_2, hexane–AcOEt 5:1) to give 67 mg (87%) of (**207**) as white crystals m.p. 82.0–83.5°C.

8.6. Manganese Dioxide Oxidation of Solacongestidine (**249**)[263]

A solution of (**249**) (82 mg) in chloroform (8 ml) was stirred with active MnO_2 (0.8 g) at room temperature for 4 h until the starting material was no longer defectable by T.L.C. (benzene/ethyl acetate, 1:1). The inorganic material was filtered off and washed with chloroform. The combined chloroform solution yielded 87 mg of solid, which was adsorbed on Al_2O_3 (1 g) and placed on a column of Al_2O_3 (5 g grade 1). Elution with 1% methanol/ether furnished 75 mg of crude crystalline product. Recrystallization from methanol/acetone gave pale yellow needles of (**250**); m.p. 198–208°C, which were identical with 23-oxosolacongestidine.

8.7. Oxidation of Exo-allylic Alcohol (**274**) to the Ketone (**275**)[302]

The alcohol (**274**) (4.0 g, 20.3 mM) was added to a stirred suspension of active manganese dioxide (Attenburrow) (40.0 g, 406.2 mM) in benzene (200 ml). The mixture was refluxed for 4 days under a Dean–Stark water separator. The resulting mixture was filtered through Celite and the precipitate extracted with refluxing benzene (2 × 100 ml). The extracts were combined with the original filtrate and the solvent was removed. The residue was purified by chromatography on silica gel (chloroform–light petroleum 3:1) and recrystallized from light petroleum to yield the ketone (**275**) (2.5 g, 65%); m.p. 45–46°C.

8.8. Oxidation of DL-4-Hydroxy-3-methoxymandelic Acid (**309**) to Keto Acid (**310**)[318]

To a solution of (**309**)[319] (4 g) in chloroform (280 ml) at 55–65°C was added, with stirring, manganese dioxide (10 g) in two portions (about 5 g each) during 30 min. The slurry was stirred at ~60°C for 3 h, filtered, and the filtrate concentrated to give brown-orange crystals; yield: 1.4 g.

The crude keto acid was purified as follows: the product (300 mg) was dissolved in chloroform (10 ml), dried (Na_2SO_4), and concentrated to ~3 ml. The residue was mixed with benzene (6 ml) and carefully concentrated under nitrogen to beginning of crystallization; cooling in ice water gave slightly yellowish crystals: [$\lambda_{max}^{CHCl_3}$ 352 (sh) nm] of **310**; yield: 200 mg (65%); m.p. 81–82°C.

8.9. Preparation of 2′, 3′-*O*-Isopropylidene-5′-oxo-6,5′-cyclouridine (**342**)[388]

Activated manganese dioxide (5.5 g) was added to a solution of (**341**, 1.1 g) in methanol (165 ml), and the mixture was stirred vigorously at room temperature. After 22 h, TLC (EtOAc) indicated that the reaction was complete. The suspension was filtered, the residue was washed liberally with methanol, and the filtrate was passed through a short column (3 × 6 cm) of methanol-washed Dowex 50 (H^+). Removal of solvent afforded a colorless solid of (**342**) (1.01 g, 93%) which was sufficiently pure for the next step; (**342**) can be recrystallized from ethyl acetate.

8.10. General Procedure for Dehydrogenation of 4,5-Dihydro-1,2-oxazoles[38]

The 4,5-dihydro-1,2-oxazole (1 g) in dry benzene or 10:1 benzene–dioxane (50 ml) and active γ-manganese dioxide[37] (fivefold by weight) is heated under reflux for the required time (1–10 h), while the water formed is removed by means of a Dean–Stark trap. The end of the reaction is monitored by T.L.C. The solid is filtered through Celite and washed carefully with the same solvent. Evaporation of the filtrate leaves as a residue the pure 1,2-oxazole (98–100% yield); conversion of **406** into **407**.

8.11. Preparation of 7,7,8,8-Tetracyanoquinonedimethane, TCNQ (**414**)[318]

To a stirred suspension of the tetrahydro compound **413**[487] (10 g) in preheated toluene (200 ml 95°C) was added active manganese dioxide (20 g) during 5 min; the temperature was raised to 100–110°C and stirring was continued for an additional 10 to 15 min. The suspension was filtered while hot and the solid washed with warm toluene (75 ml; the yellow-orange product **414** was isolated on cooling (3.8–4.2 g); concentration gave an additional crop; total yield: 5.1–6.2 g.[489] The product was recrystallized from butyl (or ethyl) acetate, or acetonitrile, m.p. 295–296°C, lit.[487] m.p. 296°C.

8.12. Preparation of α-Cyanoglyoxylidenedi-o-toludine (**502**)[572]

Into a 250 ml round-bottomed flask equipped with a magnetic stirrer, Dean–Stark trap, and a reflux condenser was placed activated manganese dioxide (6.96 g, 0.08 mol) in benzene (150 ml). The mixture was refluxed for 12 h during which time 0.4 ml of water was collected. The reaction mixture was cooled and 2,3-di-*o*-toluidinoacrylonitrile (**501** 2.63 g, 0.01 mol) was added. The reaction mixture was refluxed for 12 h during which time 0.2 ml of water was collected. The hot solution was filtered through a Celite 545 bed to remove the manganese dioxide. The manganese dioxide was washed several times with dichloromethane. The resulting black solution was evaporated to a black oil. Several recrystallizations alternating between 2-propanol and 65–110 petroleum ether gave yellow-orange needles (**502**); yield: 2.18 g (83%).

8.13. Oxidation of m-Nitrobenzylidene-o-phenylenediamine

A mixture of **510b** (2 g, 8 mmol) and manganese dioxide (7 g) in benzene (150 ml) was

stirred at 10°C for 2 h, yielding a product which was chromatographed on alumina. Elution with petroleum ether/benzene gave[475] (**511b**); yield: 0.48 g (25%); m.p. 208°C.

8.14. Oxidation of o-(p-Nitrobenzylideneamino)-phenol (**512a**)

Treatment of a mixture of **512a** (2 g, 8 mmol) and MnO_2 (8 g) in benzene (150 ml) at 10°C for 2 h gave[475] **513a**; yield: 1.48 g (75%); m.p. 268°C.

8.15. Oxidation of 3-Hydroxyanthranilic Acid (**514**)[577]

3-Hydroxyanthranilic acid (**514**, 500 mg) is dissolved in aqueous N,N-dimethylformamide (16 ml DMF + 5 ml H_2O). To this solution are added, with stirring, $NaH_2PO_4 \cdot 2H_2O$ (2.4 g) and Na_2HPO_4 (0.7 g), followed by active (ACC) MnO_2 (1.5 g). The reaction mixture is stirred at room temperature for 90 min and then drowned in a solution of ferrous sulfate in 2 N HCl (100 ml).* The bright-red precipitate of cinnabarinic acid (**515**) is allowed to settle (preferably with cooling in a refrigerator). The product is removed by centrifugation,† washed with water and dried. Yield: 450 mg (92%). The product may be crystallized from a minimum volume of dimethylformamide. It does not melt below 350°C.

8.16. Preparation of 1,3-bis [α-diazobenzyl] Benzene (**617**)[623]

An Erlenmeyer flask was charged with 1,3-dibenzoylbenzene-bis-[hydrazone] (0.251 g, 0.8 mmol), (**616**) sodium sulfate (2 g), manganese dioxide (0.70 g, 8 mmol), anhydrous ether (125 ml), and a saturated solution of potassium hydroxide in ethanol (0.5 ml). Addition of the potassium hydroxide catalyst caused instantaneous formation of the red color of the bis-diazo compound. The reaction mixture, which was protected from light by an aluminum-foil wrapper, was stirred vigorously for 4 h and filtered; the ether was evaporated, to give a quantitative yield of red crystals of **617**; a sample recrystallized from cyclohexane had m.p. 125–126°C (dec.).

8.17. Synthesis of 4-Diazo-1,2,5,6-tetramethyltricyclo-[3.1.0.$0^{2,6}$] Hexan-3-one (**619**)[637]

To a solution of 180 mg of crude hydrazone **618** in 10 ml of CH_2Cl_2 was added 1 g of Na_2SO_4 and 300 mg of freshly activated MnO_2 (see note below) in 2 ml of CH_2Cl_2. The reaction mixture was stirred for 1 h at room temperature, subsequently 150 mg of MnO_2 in 2 ml of CH_2Cl_2 was introduced, and the mixture was again stirred for 1 h at room temperature. After filtration over Celite and evaporation of the solvent, about 170 mg of an orange oil was obtained that contained, according to a ^{1}HNMR integration, 60–80% diazo ketone (the yield varied, depending on the quality of MnO_2). Diazo ketone **619** is thermally unstable above 10°C; but when stored at −20°C in solution, it is fairly stable for several days. Attempts to purify **619** by preparative TLC and high-pressure LC resulted in decomposition; therefore, **619** was used without further purification; mass spectrum, found *m/e* 148.089, calcd *m/e* 148.090 ($M^+ - N_2$).

Activated MnO_2 was prepared according to the procedure of Attenburrow et al.[25] The quality of the MnO_2 used proved to be critical in order to obtain a good yield of **619**. The best results were obtained when the wet MnO_2 cake was partially dried at 50°C in vacuo (until it contained 20–30% moisture), stored as such, and activated for every experiment by being dried for 16–20 h at 50°C in vacuo with P_2O_5 as the drying agent.

* Due to the extreme fineness of the precipitate, the product does not filter well on conventional filter apparatus.

† The solution contains 15 g $FeSO_4 \cdot 7H_2O$ per 100 ml 2 N HCl. The function of the ferrous salt is to reduce the excess MnO_2 to a water-soluble Mn^{2+} salt.

8.18. Specific Oxidation of *myo*-Inosose Phenylhydrazone[318]

Treatment of *myo*-inosose phenylhydrazone (or any aldehydo- or keto-sugar phenylhydrazone) with manganese dioxide in dilute hydrochloric acid [e.g., stirring of phenylhydrazone (1 g), MnO_2 (1 g) in 2.5 N HCl (250 ml) at 0°–5°C in dark, almost neutral solution, pH 6.0–7.0 after 24 h] caused a complete destruction of the inositol moiety; the only product isolated was carbazole (90% yield, m.p. 247 C, M^+ $m/e = 167$). This procedure can be useful for a specific oxidative degradation (e.g. metal-catalyzed specific generation of hypochlorous ions) of a variety of acyclic, carbocyclic or heterocyclic systems (in aqueous or alcohol-aqueous media).

8.19. Dimethyl ent-3α,13-Dihydroxy-2-oxo-20-norgibberella-1(10), 16-diene-7,19-dioate (**687**)[719]

The triol (**686**) (609 mg) and activated manganese dioxide (ACC)[25] (6 g) in chloroform (30 ml) were stirred for 4 days. Filtration through a pad of "Celite," and evaporation of the filtrate and washings, gave a gum (577 mg) which was purified by p.l.c. using ethyl acetate-light peteroleum (9:1). Elution of the band at R_f 0.35–0.45 gave the ketol (**687**) (363 mg) 60% which was crystallized from methyl ethyl ketone-light petroleum as prisms, m.p. 98–101°C, *m/e* (Me_3Si ether) 534(M^+, 48%).

8.20. Preparation of Methyl(Z)-6-oxo-2-hepten-4-ynoate (**182**)[741]

A solution of methyl(Z)-6-hydroxy-2-hepten-4-ynoate (**181**, 450 mg in 10 ml of methylene chloride) was treated with 1.2 g of active manganese dioxide (ACC)[25] for 24 h at 25°C. After removal of MnO_2 and the CH_2Cl_2, unreacted starting material (100 mg) was separated from product (**182**) (260 mg, 74% based on unrecovered alcohol) by flash chromatography (silica gel/ether). The product, a yellow oil, exhibits UV (95% ethanol) λ_{max} 264 nm (ε 9800).

8.21. Preparation of 3-(2-Deoxy-3,5-di-O-p-toluol-β-*D*-erytropentofuranosyl)-6,7-dihydroimidazo[4,5-d][1,3]diazepin-8(3H)-one (**312**)[743]

A suspension of 500 mg (0.00 mmol) of **311a** and **311b** (84:16 8S/8R mixture), 2.5 g of activated MnO_2 and 20 ml of pyridine was stirred at room temperature for 19 h. The mixture was filtered over Celite, concentrated at 40°C (1 Torr), and then coevaporated twice with toluene. Purification of the residue by silica gel flash chromatography, with 3:97 MeOH–EtOAc and then by 5:95 MeOH–EtOAc as eluants, gave 80 mg (15%) of the recrystallized ketone (**312**) (m.p. 138–142°C).

8.22. Preparation of 6-Methoxy-4-methylbenzofuran-2-carbaldehyde (**300**)[747]

The alcohol (6-methoxy-4-methylbenzofuran)-2-ylmethanol (**299**) (13,0 g) was stirred and heated under reflux in benzene (1.1 l) with activated MnO_2 (110 g) in a Dean–Stark apparatus for 2 h. The oxide was then filtered off and was washed with boiling ethyl acetate. Work-up of the filtrate and washings gave the aldehyde (**300**) (9.4 g, 71%) as needles from methanol, m.p. 129–130°C.

8.23. Preparation of 8-Methoxy-3,4-dihydroisoquinoline (**417**)[750]

A mixture of 200 mg (1.23 mmol) of tetrahydroisoquinoline (**415**) and 500 mg (5.75 mmol) of manganese dioxide (ACC)[25] or γ-MnO_2[19] in 10 ml of CH_2Cl_2 was stirred at 23°C for 12 h, after which an additional 250 mg (2.87 mmol) of MnO_2 was added. After a

total of 40 h, the reaction mixture was filtered, and the filtrate was evaporated, affording 178 mg (1.10 mmol, 89%) of dihydroisoquinoline (**417**). The 8-methoxyisoquinoline (**416**) impurity was present by NMR < 10%.

8.24. Preparation of Azobis (Benzocrown Ether) **703** (5,5)[753]

To a solution of the amine (**702**) (300 mg) in 40 ml of dry benzene, freshly prepared MnO_2 (ACC)[25] (300 mg) was added and the mixture was stirred at 100°C for 3 h. About half of the benzene solvent was distilled off during this period. The hot mixture was filtered, the filtrate being evaporated to dryness in vacuo. The oily residue thus obtained was subjected to column purification (alumina–chloroform). The chloroform eluent was evaporated to dryness and the crystallization of the residue from diethyl ether gave orange crystals of **703** (5,5), m.p. 143.7–145.5°C: yield 40%.

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4

Reactions with Manganese (III) Acetate

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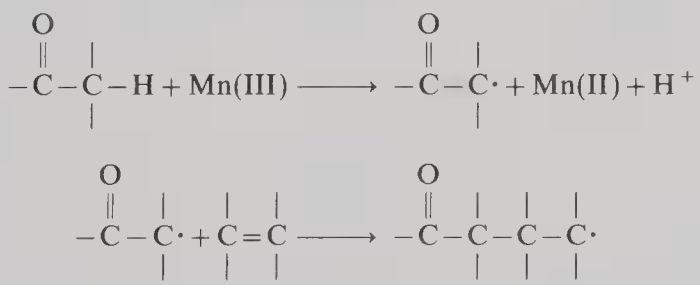
1. INTRODUCTION

Oxidations with manganese (III) acetate can be broadly divided into two classes:

1. Direct inner- or outer-sphere one-electron oxidation of the substrate after formation of an inner- or outer-sphere substrate–Mn(III) complex. Often subsequent oxidation of an intermediate radical is product determining. Numerous examples can be found in oxidations of alcohols, amino- and thio-compounds, carboxylic acids, and certain aromatics.
2. Indirect oxidation of the substrate after formation of an intermediate adduct free radical from interaction of manganese (III) acetate and an enolizable compound and subsequent addition or substitution of this radical to the substrate. Most examples here refer to aromatic substitution and oxidative addition of enolizable compounds to unsaturated systems.

Besides giving its synthesis and properties the first six paragraphs of this chapter on manganese (III) acetate deal with addition reactions of compounds, mostly bearing a hydrogen atom alpha to a carbonyl group, to olefinic and aromatic unsaturated systems. The essential sequence of such reactions is given by



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The fate of the primary adduct radical strongly depends on reaction conditions and the nature of the substrate. Substrates that are less reactive to common oxidants are more interesting since here the unique properties of manganese (III) acetate as a free radical generator can be more fully exploited.

The direct inner- or outer-sphere one-electron oxidations with manganese (III) acetate are presented according to functional group in Section 8. These oxidants bear many similarities with respect to a given substrate class with other one-electron oxidants like Co(III), Ce(IV), and some two-electron oxidants like Tl(III) and Pb(IV). It is often observed that owing to its lower reactivity, higher selectivities can be obtained with manganese (III) acetate as compared with other oxidizing agents. Many of these reactions proceed according to the simplified scheme

$$\text{Mn(III)} + \text{substrate} \longrightarrow \text{intermediate radical} + \text{Mn(II)}$$

$$\text{Mn(III)} + \text{intermediate R}\cdot \longrightarrow \text{product} + \text{Mn(II)}.$$

Complications may arise in the presence of water since water induces disproportionation of trivalent manganese into Mn(IV) and Mn(II) and alternative two-electron oxidations by Mn(IV) may take place.

2. SYNTHESIS AND PROPERTIES OF MANGANESE (III) ACETATE

Although a great amount of work has been done using manganese (III) acetate as an oxidizing agent, relatively little is known of the compound itself. Basically two forms are to be distinguished:

- The hydrated form, which conforms with a molecular formula Mn(III) $(OAc)_3 \cdot 2H_2O$, color cinnamon brown, easy to prepare reproducibly.
- The anhydrous form, color dark brown, difficult to prepare reproducibly, molecular formula variable.

Since many oxidations with manganese (III) species are known to be influenced by small amounts of water the latter form is preferred by many workers, especially for kinetic work. Moreover, small amounts of water cause disproportionation of Mn(III) acetate in glacial acetic acid.[1] Both the hydrated and anhydrous form have been made in various ways. Many workers introduced special modifications, which certainly have affected the chemical composition and reactivity of the anhydrous form. In Table I the most important routes to manganese (III) acetate are given.

The solubility of manganese (III) acetate in acetic acid depends on the synthetic procedure used and the water content of the acetic acid. The compound should be dissolved by gentle heating. Table II gives some pertinent results.

TABLE I. Routes to Manganese (III) Acetate

Reactants	Oxidizing agent	Product	Reference
$Mn(OAc)_2 \cdot 4aq$, HOAc	$KMnO_4$	Dihydrate	2, 3
$Mn(NO_3)_2 \cdot 6H_2O$, Ac_2O	HNO_3	Anhydrous	4, 5
$Mn(OAc)_2$, HOAc, Ac_2O	$KMnO_4$	Anhydrous	6, 7, 8
$Mn(OAc)_2$	O_3	Anhydrous	7
$Mn(OAc)_2 \cdot 4aq$	Anodic oxidation	Dihydrate	9
$Mn(OAc)_2 \cdot 4aq$	Cl_2	Dihydrate	10
$Mn(OAc)_2$, $(Et)_3$ N, HOAc	O_2	Dihydrate	11
$Mn(OAc)_2$, ketone	O_2	Anhydrous	12

TABLE II. Solubility of Manganese (III) Acetate in Acetic Acid–Water Mixtures

Manganese (III) acetate	HOAC	g/liter dissolved (°C)	Reference
Anhydrous	100%	10 (25)	6
Anhydrous	100%	3 (25)	7
Anhydrous	98%	150 (25)	7
Anhydrous	90%	Nil	7
Dihydrate	100%	160 (25)	7
Dihydrate	99%	Very low	7

Since the dihydrate dissolves poorly in water containing acetic acid, the anhydrous form is soluble in such systems only in a very limited range. Moreover, water causes disproportionation of manganese (III) species.

In acetic acid–water mixtures containing larger amounts of water, manganese (III) acetate hydrolyzes slowly to mixtures of $Mn(OH)_3$ and MnO_2.

In the following sections synthesis and properties of hydrated Mn(III) acetate and its anhydrous form will be treated separately.

2.1. Anhydrous Manganese (III) Acetate

Hessel[7] has studied the synthesis and chemical constitution of manganese (III) acetate in detail. He finds that the chemical constitution of anhydrous manganese (III) acetate conforms to the experimental formula $Mn_3(CH_3COO)_8OH$ or $[Mn_3O(CH_3COO)_6 \cdot CH_3COOH]^+ (CH_3COO)^-$. When the compound is properly washed and recrystallized this empirical formula is independent of the chemical route followed, viz., oxidation with $KMnO_4$, Pb(IV) acetate, or O_3 of manganese (II) acetate or treating $Mn(NO_3)_2 \cdot 6H_2O$ with acetic anhydride. In the literature treated by Hessel and also in later work the anhydrous form is usually indicated as $Mn(OAc)_3$. This is certainly erroneous and mostly due to improper analytical procedures. A disadvantage of Hessel's purification method is that the anhydrous manganese (III) acetate is treated with water. The route developed by Vaerman[12] and going back to earlier work of van Helden and den Hertog, although claiming the production of $Mn(OAc)_3$, in fact produces acetic acid–formic acid mixed complexes of Mn(III) when acetone is used as a ketone. Formic acid, formed by autoxidation from the ketone, is bound by both Mn(II) and Mn(III) acetate. These mixed acetate–formate complexes are less soluble in the medium used than manganese (III) acetate proper.

The crystal structure of anhydrous manganese (III) acetate was studied by Hessel and Romers.[7,13] These authors assume a linear polymer with empirical formula $[Mn_3O(OAc)_6 \cdot AcOH \cdot OAc]_n$. In the monomer unit three manganese atoms are connected by three pairs of acetate bridges and form an equilateral triangle with an oxygen atom in its center. Acetic acid molecules and acetate bridges between the monomer units complete the distorted octahedral coordination of the manganese atoms.

In solution a molecular weight of 640 ± 75 is found[7] and as best representation the following structure is proposed:

$$[Mn_3O(OAc)_6 \cdot 3\,AcOH]^+ [OAc]^-$$

Here the octahedral coordination of the manganese atoms in the trinuclear complex is completed by three acetic acid molecules.

Infrared spectra of anhydrous manganese (III) acetate prepared by a slightly different procedure are described by de Klein[1] and Hessel.[7] Both authors assume the presence of

acetic acid in the solid compound, although the absorption maxima assigned to acetic acid are at 1730[1] and 1710 cm^{-1},[7] respectively. At present infrared spectroscopy possibly offers the fastest technique to check the quality of anhydrous manganese (III) acetate.

The ultraviolet spectrum in glacial acetic acid is sensitive to the presence of water, manganese (II) acetate, and other acetates like sodium or potassium.[1,8] The effect of addition of manganese (II) acetate differs from that found of other metal acetates. This change in spectra of manganese (II) acetate is tentatively ascribed to formation of a Mn(III)–Mn(II) interaction complex of mixed valence. This rationale also explains the retarding influence of Mn(II) acetate (formed in reaction) upon the rate of Mn(III) acetate oxidations in acetic acid.

In Figs. 1 and 2 the spectral changes are given of manganese (III) acetate as found upon the addition of manganese (II) acetate and potassium acetate, respectively, in the region of 600–360 nm (16.6–27.7 kK). Further absorption maxima of manganese (III) acetate in glacial acetic acid are reported by de Klein[1] at 37.8 kK ($\varepsilon_{max} = 4 \times 10^3$), 34.2 kK ($\varepsilon_{max} = 3.5 \times 10^3$), and 21.6 kK ($\varepsilon_{max} = 310$), and by Szymanska-Buzar[14] at 34.5 kK ($\varepsilon_{max} = 8900$), 29.6 kK ($\varepsilon_{max} = 3650$), and 21.8 kK ($\varepsilon_{max} = 905$). The appreciable differences found by these authors can be ascribed to impurities such as manganese (II) acetate or differences in procedure of preparation of manganese (III) acetate.

The reflection spectra of solid anhydrous manganese (III) acetate, mixed with MgO, are given by Szymanska-Buzar.[14] The magnetic susceptibility of anhydrous manganese (III)

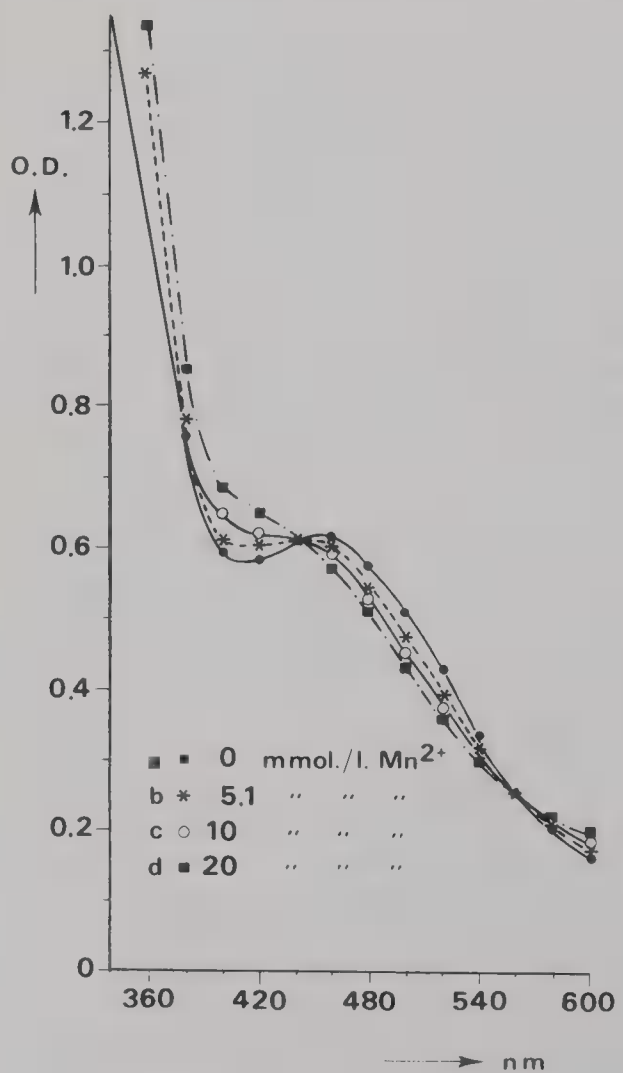


FIGURE 1. Influence of manganese (II) acetate on the absorption spectrum of manganese (III) acetate in acetic acid in the region of 600–360 nm [Mn(III) acetate] = 1.9 mmol $liter^{-1}$.

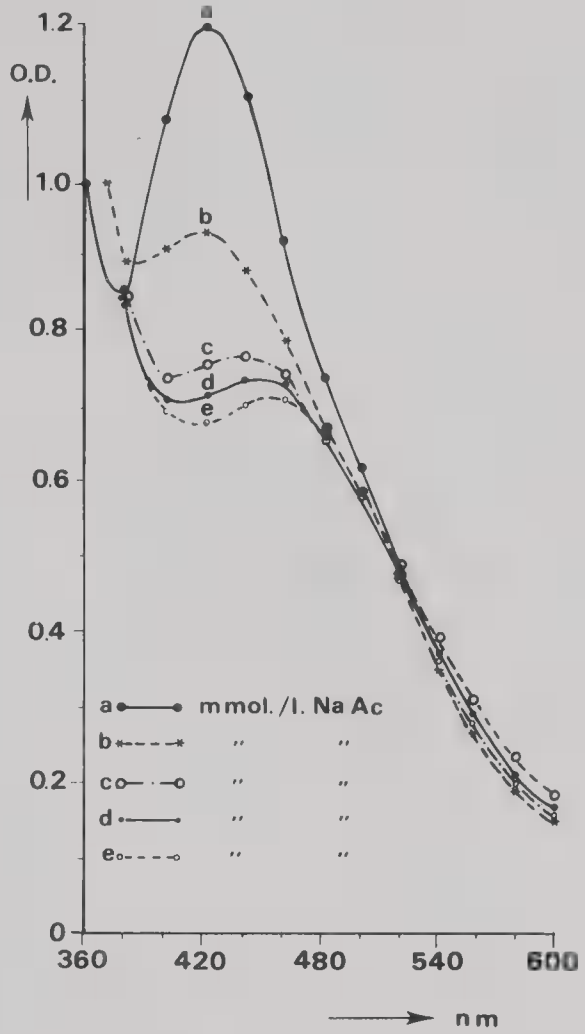


FIGURE 2. Influence of potassium acetate on the absorption spectrum of manganese (III) acetate in acetic acid in the region of 600–360 nm [Mn(III) acetate] = 2.25 mmol liter^{-1}.

acetate in the region of 77 K ($\mu_{eff} = 3.4\ \mu B$) to 294 K ($\mu_{eff} = 4.37\ \mu B$) is reported by Szymanska-Buzar.[14]

Using electron spin resonance de Klein[1] studied the disproportionation of manganese (III) acetate in acetic acid, assumed by many authors to explain their kinetics of oxidation. In glacial acetic acid at room temperature no evidence for disproportionation could be found. However, Kochi[8] using the same technique but a manganese (III) acetate quality that contained Mn(II), reports that essentially identical K_D values are found for anhydrous manganese (III) acetate and its dihydrate. At room temperature disproportionation of manganese (III) acetate is induced by water.[1] Table III gives some values of K_D obtained in this manner.

TABLE III. Influence of Water on the Disproportionation Constant K_D at Room Temperature in Acetic Acid–Water Mixtures
$K_D = [Mn(II)] \cdot [Mn(IV)]/[Mn(III)]^2$

Vol. % H_2O	K_D
1	7.6×10^{-6}
4.7	8×10^{-6}
9.1	3×10^{-5}
16	8×10^{-4}

Anhydrous manganese (III) acetate dissolves slowly in most solvents at room temperature. It can be dissolved in many solvents without appreciable reduction by gentle warming. Examples are ethanol, pyridine, and to some extent benzene and chloroform. It reacts at relatively low temperatures (70°C) with enolizable solvents such as acetone or methyl ethyl ketone, but is less reactive with simple esters like ethyl acetate. It is hardly soluble in acetonitrile and petroleum ether and decomposes in water. It exchanges acetate for carboxylic acid when dissolved in such acids.

2.2. Manganese (III) Acetate Dihydrate

The preparation of manganese (III) acetate dihydrate was first described by Christensen in 1883[2] and later elaborated in more detail.[3] It has been prepared by oxidation of manganese (II) acetate tetrahydrate by potassium permanganate,[2,3,15] chlorine,[10] and anodic oxidation.[9]

The chemical constitution of the dihydrate comes close to $Mn(OAc)_3 \cdot 2H_2O$.[15,7] Von Weinland[16] has proposed the structural formula $[Mn_3(OAc)_6(H_2O)_2](OAc)_3 \cdot 4H_2O$.

The magnetic susceptibility was studied by de Haas.[17] At low temperatures the material behaves anomalous magnetically, possibly due to mixed para- and ferromagnetism. The uv-spectrum of the dihydrate in acetic acid shows a broad absorption band with a maximum at 445 nm,[18] compared with 462 nm for the anhydrous form.[1] The solubility of the dihydrate in common solvents is similar to that of the anhydrous form.

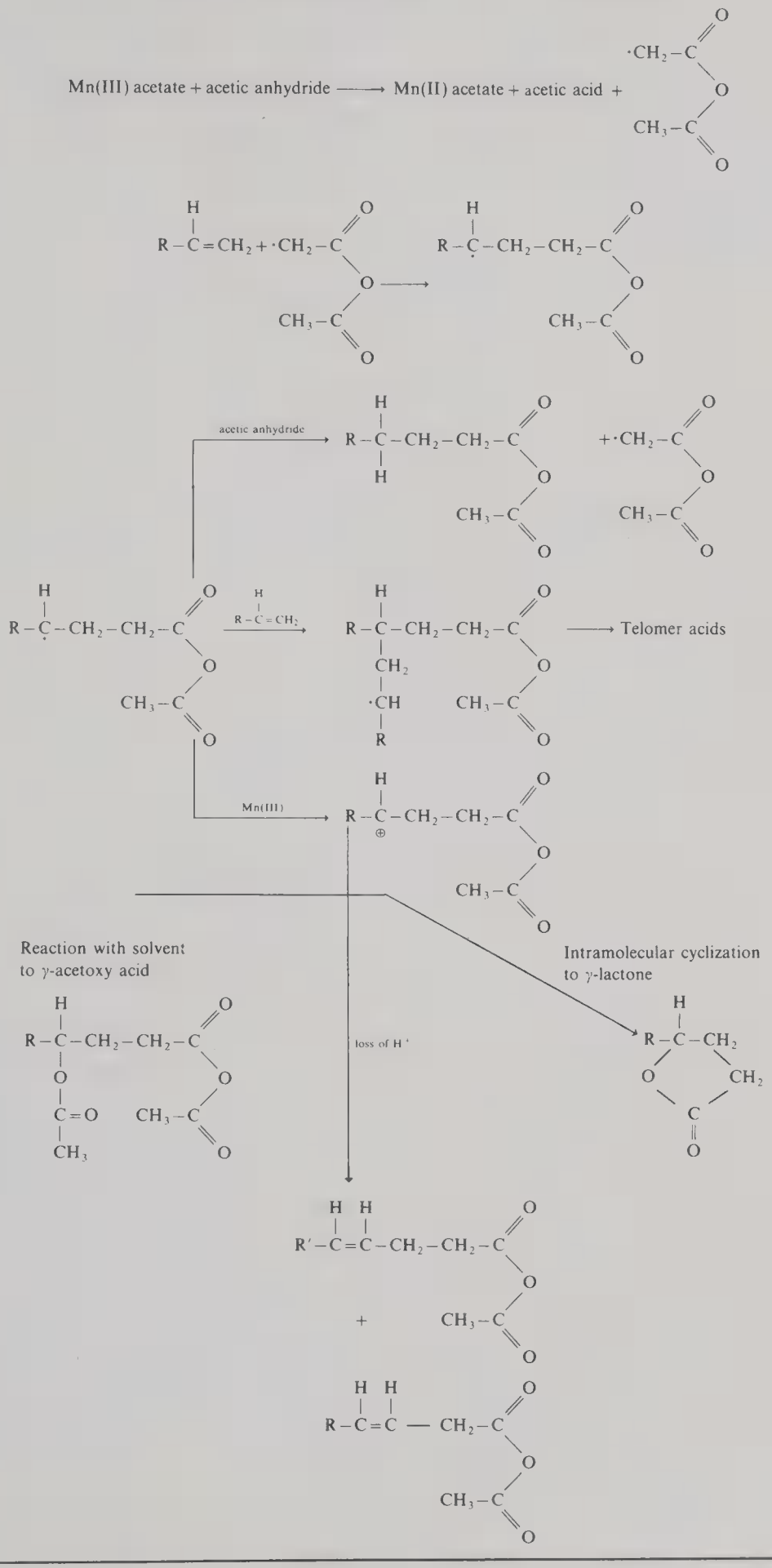
3. OXIDATIVE ADDITION REACTIONS OF ACIDS TO OLEFINIC UNSATURATED SYSTEMS

One of the more outstanding reactions initiated by manganese (III) acetate found by Bush and Finkbeiner[20] and Heiba and Dessau[21] is the oxidative addition of carboxylic acids to olefins leading to γ-butyrolactones. This reaction has been proven to be generally applicable, as exemplified by many workers, although lactones are not always major products.

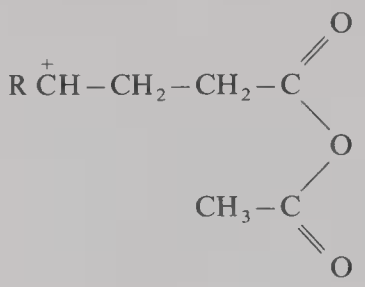
The course of the reaction and the formation of other major products depends largely on the nature of the substrate olefin, reacting acid, and on reaction conditions. There is now general agreement on the mechanism of this reaction together with its main side reactions. The major reactions involved in the Mn(III) acetate initiated addition of acetic acid to an α-olefin in acetic anhydride–acetic acid mixtures are given in Scheme 1.[22] From this mechanistic scheme the following basic requirements for oxidative addition can be drawn:

1. Direct generation of carboxyalkyl radicals. In the free acids this is largely limited to acetic, propionic and readily enolizable acids like cyanoacetic acid,[23] the major competing reaction being formation of carboxylradicals $RCOO^{\cdot}$. In the presence of excess anhydride, carboxyalkyl radical formation is favored and a larger variety of acids can be used.[22,24]
2. No oxidation of the primary formed carboxyalkyl radical. In this respect groups increasing the electron density on carbon α to the carbonyl group increase the propensity of carboxyalkyl oxidation by Mn(III).
3. Rapid addition of the carboxyalkyl radical to the olefin. The reactivity of various olefins towards the carboxymethyl radical was studied by Heiba[23] and is found to be governed by the stability of the intermediate adduct radical and steric considerations. Recently McQuillin and Wood[25] found evidence that some carboxyalkyl radicals may add reversibly to olefins. Slow addition may lead to competing reactions such as allylic hydrogen abstraction.

SCHEME 1


Mn(III) acetate + acetic anhydride ⟶ Mn(II) acetate + acetic acid +
acetic anhydride
Mn(III)
Telomer acids
Reaction with solvent to γ-acetoxy acid
Intramolecular cyclization to γ-lactone
loss of H⁺

4. Rapid oxidation of the intermediate adduct radical to carbenium ion. This is favored by a high Mn(III) concentration, high acid concentration, and high acetate concentration. The structure of the carbenium ion will determine whether lactonization or elimination of a proton to form a new unsaturated carboxylic acid will predominate. Moreover, with excess anhydride, formation of γ-acetoxyacid will compete strongly with ring-closure of the anhydride to a γ-lactone:



Also this step is sensitive to small amounts of Cu present,[26,27] which leads to mixtures of γ- and δ-unsaturated carboxylic acids. Low manganese (III) concentrations may lead to a chain transfer reaction of the intermediate adduct radical with the solvent[28,22] resulting in saturated carboxylic acids. When under these conditions high olefin concentrations are applied telomer or polymer products are formed.[22]

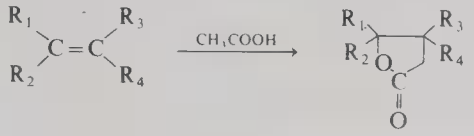
Since so many parameters control effective lactone production, a large variety of reaction conditions is known in the literature. Three main media are put into practice: acetic acid–potassium acetate or sodium acetate mixtures[21]; acetic anhydride–acetic acid mixtures[20]; acetic anhydride–acetic acid–potassium acetate or sodium acetate mixtures.[29] Each may be used in its own right, depending largely on structural constraints of the substrate olefin. As a result of a number of investigations there is a wealth of data concerning structural requirements for lactone formation. Since unfortunately reactions are rarely otimized and reaction conditions vary widely, interpretation of these data is rather speculative outside the general lines given above. Table IV covers the known examples of oxidative addition of acetic acid to more simple olefins. In Table V the results of oxidative addition of other acids, notably propionic and cyanoacetic, are summarized. Table VI treats the oxidative addition to cycloaliphatic systems. From cyclohexene and cyclopropene poor yields of lactone are obtained. However, the acetoxy or propionoxy acids obtained may readily be converted to γ-lactones by heating or alkaline hydrolysis followed by acid-catalyzed ring closure.

In this way yields of over 50% can easily be obtained. The side products in 1-methylcyclohexene are interesting in that exo-cyclic cyclohexene derivatives are formed in rather high yields.

Table VII shows that the scope of lactone formation is not limited to simple olefins and that the site of attack of the carboxyalkylradical may be rather specific, as exemplified in the indene derived and benzofuran system.

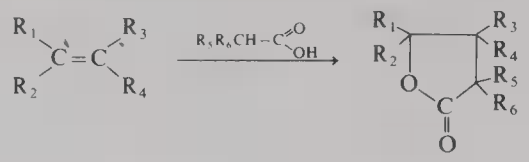
Typical results of reactions of terpenes and related compounds are shown in Table VIII. From the examples given it is clear that the reactivity of the double bonds in terpenes towards carboxylalkyl radicals differs widely. Reaction may lead to a relatively simple product, as in the case of norbornene,[30] or to a complicated mixture of γ-endo and spiro-lactones and δ-lactones as in the case of bornene,[31] reflecting extensive rearrangement of intermediate carbenium ions. The main products of oxidation of *p*-α,β,β-tetramethylstyrene[29] may be derived from α-isopropyl-*p*-methylstyrene arising from the first-mentioned compound by double bond isomerization.

TABLE IV. Oxidative Addition of Acetic Acid to Simple Olefins



R_1	R_2	R_3	R_4	% γ-lactone	Other main products	Reference
C_6H_5	CH_3	H	H	80, 30[a]		20
C_6H_5	H	H	H	75, 39		
C_6H_5	H	CH_3	H	21		
$C_6H_5CH_2$	H	H	H	16		
C_6H_5	H	H	C_6H_5	20		
$(CH_3)_3C$	H	H	H	12		
C_6H_5	C_6H_5	H	H	+		
C_4H_9	H	H	H	+		
C_2H_5	CH_3	H	H	+		
$(CH_3)_3C$	H	Cl	H	−		
H	H	H	H	73		32
C_6H_5	H	H	CH_3	79		21
C_6H_5	CH_3	H	H	74		
C_6H_{13}	H	H	H	74		
C_3H_7	H	H	C_3H_7	44		
C_6H_5	H	H	H	60		
C_6H_5	H	H	C_6H_5	16		
C_5H_{11}	H	H	H	18		33
H	H	H	H	38		34
CH_3	CH_3	H	H	30		23
$(CH_3)_3C$	H	H	H	48		
C_6H_5	H	H	CH_3 (trans)	79		
C_6H_5	H	H	$COOCH_3$	45		
$CH_2=CH(CH_2)_2$	H	H	H	24		
$CH_2=CH(CH_2)_4$	H	H	H	26		
$CH_2=CH$	H	H	H	30		
$CH_2=C(CH_3)$	H	H	H	13 + 37		
$CH_2=CH$	CH_3	H	H	37		
$CH_2C\equiv C(CH_2)_4CH_3$	H	H	H	50		
$CH_3C_6H_5$	CH_3	CH_3	CH_3	Minor		29
$CH_3C_6H_5$	$(CH_3)_2C$	H	H	Major		
C_4H_9	H	H	H	19	$CH_3(CH_2)_3CH(OAc)(CH_2)_2COOH$ 61%	35
C_2H_5	H	CH_3	CH_3	55	$CH_3-CH_2-C(CH_3)(CH_2COOH)-C=CH_2$ 22%	

TABLE V. Oxidative Addition of Some Carboxylic Acids to Simple Olefins



R_1	R_2	R_3	R_4	R_5	R_6	% γ-lactone	Other main products	Reference
C_6H_5	CH_3	H	H	CH_3	H	25		36
C_6H_5	CH_3	H	H	CN	H	57		36
C_6H_5	H	H	H	CH_3	H	50		21
$(CH_3)_3C$	H	H	H	CN	H	+		34
$(CH_3)_3C$	H	H	H	CH_3	COOEt	44		34
$(CH_3)_2CH$	CH_3	H	H	CH_3	COOEt	48		34
$(CH_3)_3C$	H	H	H	H	COOMe	15		34
C_6H_5	H	H	H	CN	H	41		23
C_6H_{13}	H	H	H	CN	H	60		23
C_6H_5	CH_3	H	H	CN	H	43		23
						57		36
C_3H_7	H	H	C_3H_7	CN	H	49		23
C_6H_5	H	H	CH_3	CN	H	51		23
$H_2C=C(CH_3)$	H	H	H	CN	H	5		33
$CH_2=CH$	CH_3	H	H	CN	H	39		
C_6H_{13}	H	H	H	CH_2COOH	H	25		23
C_4H_9	H	H	H	CH_3	H	15	40% 1-methyl-4-propionoxy-octanoic acid +37% 1-methyl-octanoic acid	37
CH_3	CH_3	C_2H_5	H	CH_3	H	28	$CH_3CH_2CH(CHCOOH)CH_3-C(CH_3)_2-O$ Prop (28)	37
							$CH_3CH_2CH(CHCOOH)CH_3$ —— $C(CH_3)=CH_2$ (30)	

4. Mn(III) ACETATE-INITIATED ADDITION OF ALDEHYDES TO OLEFINIC UNSATURATED SYSTEMS

Most free radical additions of aldehydes to olefins yield ketones as main products. Thus the peroxide,[51,52] γ-radiation,[51,53] and oxygen[54] initiated addition of aldehydes to 1-alkenes provide a convenient method for the synthesis of ketones. The acyl radical $R-\dot{C}=O$ is believed to be formed as an intermediate in these systems. In the presence of manganese (III) acetate a free radical addition of aldehydes to olefins is also observed. However, depending on reaction conditions, both the expected ketones and rather unexpected aldehydes can be formed. The primary intermediate from the interaction of manganese (III) acetate and the aldehyde is the formylalkyl radical[55]

$$R-\dot{C}H-CHO$$

Formation of acyl radicals $R-\dot{C}=O$ by chain transfer can be largely suppressed by working at high manganese (III) acetate concentrations and by addition of small amounts of Cu(II)

Table VI. Oxidative Addition of Carboxylic Acids to Cycloaliphatic Systems

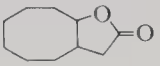
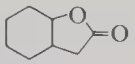
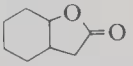
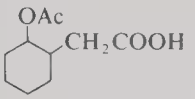
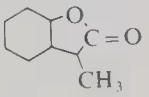
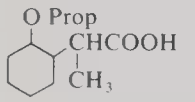
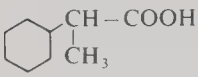
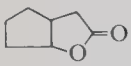
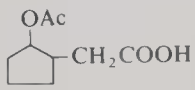
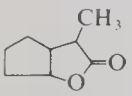
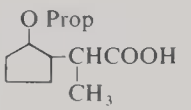
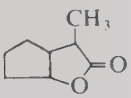
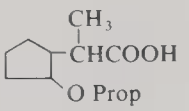
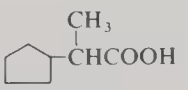
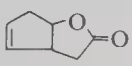
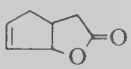
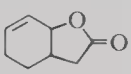
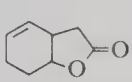
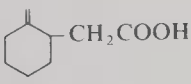
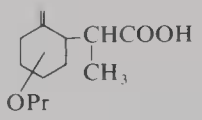
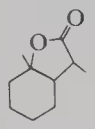
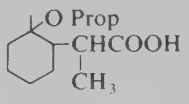
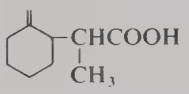
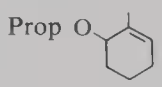
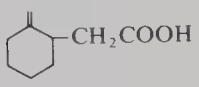
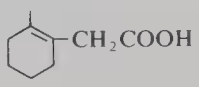
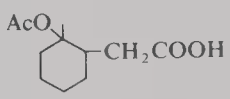
Olefin	γ-lactone (% yield)	Other main products	Reference
	 (62)		
	 (10)	 (22)	20
	 (12)	 (50)	39
	 (5)	 (27)	
		 (35)	
		 (33)	
	 (13)	 (69)	39
	 (12)	 (40)	39
	 (13)	 (40)	37
		 (35)	
			38
			
			38
			
	(33)	 (41)	39

Table continued

Table VI. *(Continued)*

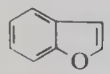
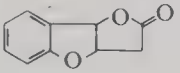
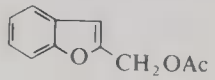
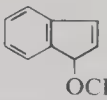
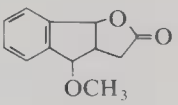
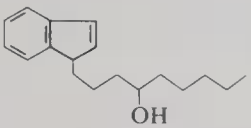
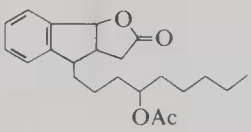
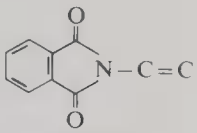
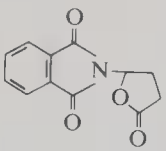
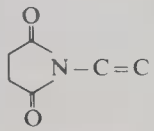
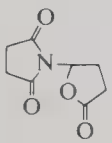
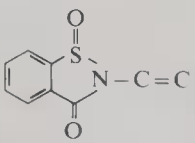
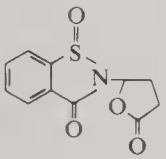
Olefin	γ-lactone (% yield)	Other main products	Reference
	(23)	 (36)	39
	 (28)	 (30)	37
		 (22)	
		 (20)	
	No lactone		40
			
			

acetate.[56] In the latter case unsaturated aldehydes are formed. In the absence of polar solvents like acetic acid, manganese (III) acetate concentration is low and ketones are formed in high yield.[57,58] With regard to the substrate olefins the yield of saturated versus unsaturated aldehydes and other products largely depends on the structure of the intermediate adduct radical: The ratio of oxidation to hydrogen abstraction by chain transfer increases from secondary radicals to tertiary radicals. Moreover, the rate of oxidation of bulky tertiary radicals increases as the radical is more sterically hindered, whereas hydrogen abstraction rate by chain transfer decreases.[56] Thus 1-alkenes yield primarily saturated aldehydes and acetoxy-aldehydes, whereas internal olefins and vinylidenes give mixtures of saturated and unsaturated aldehydes but no acetoxy-aldehydes. A complication of these reactions is the formation of extensive amounts of telomers. However, this can be suppressed by working at low olefin concentrations. Separation of products from telomers in most cases can be done quite easily by distillation.

The most important reaction sequences are given in Scheme 2. Since the formation of ketones is largely suppressed by addition of Cu(II) and at high Mn(III) concentrations, acyl radicals are most probably mainly formed via chain transfer of intermediate adduct radical (compound A in Scheme 2) with aldehyde rather than chain transfer of formyl alkylradicals with aldehyde.

Table IX gives some pertinent results. Yields in this table are given with respect to oxidant consumed per mole of product. They rather reflect selectivity of formation of the volatile reaction products but not absolute yields. When the corresponding olefins and aldehydes are available the present method forms an elegant synthetic route towards α-alkyl substituted aldehydes otherwise prepared by the Darzens glycidic ester condensation or dehydrogenation of alcohols.

TABLE VII. Oxidative Addition of Acetic Acid to Complex Olefins

Substrate	Lactone (% yield)	Other main products	Reference
 Benzofuran	 (21)		41
 1-Methoxy-methyl-indene	 (68)		42
 1-(3-Hydroxyoctyl)indene	 (52)		42
 *N*-Vinylphthalimide			43
 *N*-Vinylsuccinimide			
 *N*-Vinyl-o-sulfobenzimide			

5. Mn(III) ACETATE-INITIATED ADDITION OF KETONES TO OLEFINIC UNSATURATED SYSTEMS

Organic peroxides[62,63] and γ-radiation have been used to initiate the radical addition of ketones to olefins, although surprisingly little on such reactions is reported in the literature. The one-electron oxidation of enolizable ketones by manganese (III) acetate has offered a new and convenient method for the generation of α-oxo alkyl radicals[64,65] useful in a number of synthetic routes to saturated and unsaturated ketones, substituted dihydrofurans, tetralones, and diketones. Although yields in most cases are only moderate, this reaction may still be the method of choice when the substrate olefins and ketones are readily available. Reactions have been performed with a great variety of ketones and olefins. The reactions are generally accelerated by addition of acetic acid, although product patterns may change. In the presence of Cu(II) acetate unsaturated adducts are formed.

5.1. Formation of Higher Saturated, Unsaturated, and Acetoxy-Ketones

In the presence of manganese (III) acetate simple ketones like acetone, methyl-ethylketone, cyclic ketones, α- and β-diketones like pyruvic ester, and acetyl-acetone can be

TABLE VIII. Oxidative Addition of Acetic Acid to Terpenes

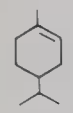
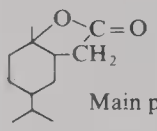
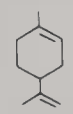
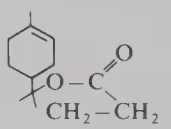
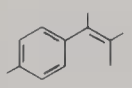
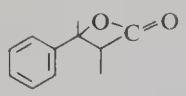
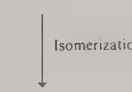
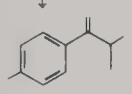
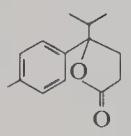
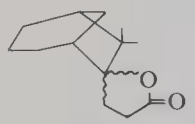
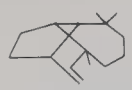
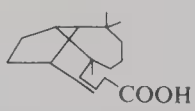
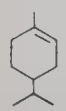
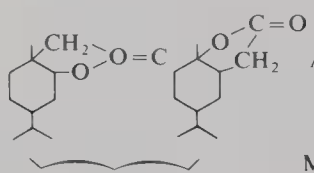
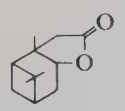
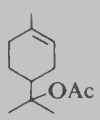
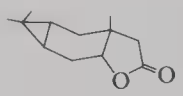
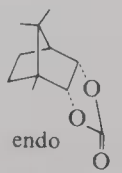
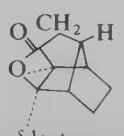
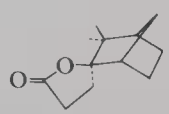
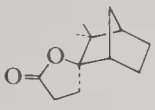
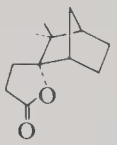
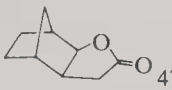
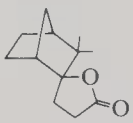
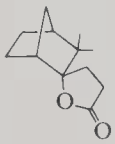
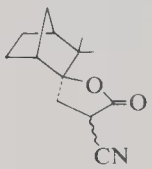
Substrate	Product	Reference
 *d*-Carvomenthene	 Main product 1-*p*-Menthanol-2-yl-acetic acid lactone	44
 *d*-Limonene	 1-*p*-Menthene-8-ol-9-yl-acetic acid lactone	45 44
  Minor		29
   Major		
 Camphene	 Major	46
 Longifolene		
 (+) *p*-Menth-1-ene (= *d*-carvomenthene)	 ~30% Mixture allyl acetates (major product with lactone)	47
 (+) α-Pinene	 Lactone = minor prod  Major acetate α-terpinel acetate Mixture unsaturated acetates = major product	48
 (+) Carene-3	 44%	49
 Bornene	 endo  δ lactone 	31

TABLE VIII. *(Continued)*

Substrate	Product	Reference
 Camphene	 exo 9  endo 1	30
 Norbornene	 47% *exo* 2-Oxo-4,7-methanobenzofuran	30
	 	
	 CN	50

SCHEME 2

$$RCH_2CHO \xrightarrow{Mn(III)} R\dot{C}HCHO \xrightarrow{RCH_2CHO} RCH_2\dot{C}O$$

$$RCH_2\dot{C}O + R_1CH_2CH=CH_2 \longrightarrow R_1CH_2\dot{C}HCH_2COCH_2R \xrightarrow{\text{Chain transfer}} \text{Saturated ketone}$$

$$R\dot{C}HCHO + R_1CH_2CH=CH_2 \longrightarrow R_1CH_2\dot{C}HCH_2\underset{\displaystyle R}{\underset{|}{C}}HCHO \xrightarrow{\text{Chain transfer}} \text{Saturated aldehyde}$$

(A)

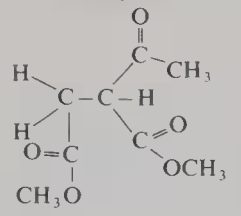
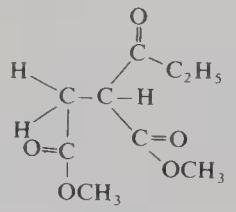
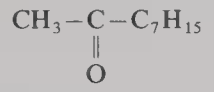
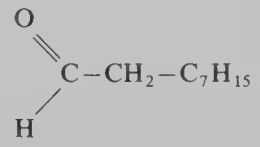
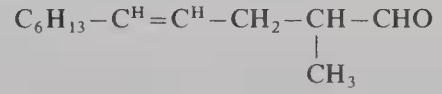
$$R_1CH_2\dot{C}HCH_2\underset{\displaystyle R}{\underset{|}{C}}HCHO \xrightarrow{Cu(II) \text{ or } Mn(III)} R_1CH=CHCH_2\underset{\displaystyle R}{\underset{|}{C}}HCHO$$

$$R_1CH_2CH=CH-\underset{\displaystyle R}{\underset{|}{C}}HCHO$$

$$R_1CH_2\dot{C}HCH_2\underset{\displaystyle R}{\underset{|}{C}}HCHO \xrightarrow{Mn(III)} R_1CH_2\underset{\displaystyle OAc}{\underset{|}{C}}HCH_2\underset{\displaystyle R}{\underset{|}{C}}HCHO$$

$$RCH_2\dot{C}HCH_2\underset{\displaystyle R}{\underset{|}{C}}HCHO \xrightarrow{RCH_2CHO} RCH_2\dot{C}O + \text{Saturated aldehyde}$$

TABLE IX. Addition of Aldehydes to Unsaturated Systems

Aldehyde	Olefin	Temperature (°C)	Solvent	Catalyst	Product (%)[a]		Reference
Acetaldehyde	—	80	—	—	Biacetyl	(18)	57
Acetaldehyde	Dimethylmaleate	80	—	—		(75)	
Propionaldehyde	Dimethylmaleate	80	—	—		(75)	
Acetaldehyde	1-Heptene	80	—	—		(45)	
Acetaldehyde	1-Heptene	60	HOAc	—		(32)	
						(34)	
Propionaldehyde	1-Nonene	60	HOAc	Cu(II)		(32)	

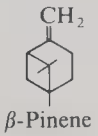
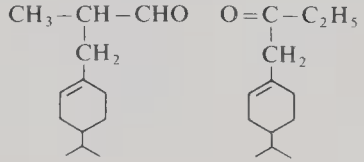
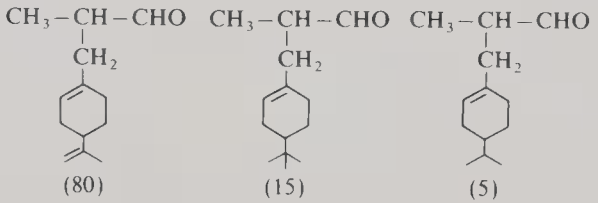
Butyraldehyde	1-Hexene	60	HOAc	Cu(II)	$C_3H_7-CH=CH-CH_2-\underset{\displaystyle C_2H_5}{\underset{\vert}{CH}}-CHO$	(40)	
Acetaldehyde	1-Heptene	50	—	—	$CH_3-\overset{\displaystyle O}{\overset{\Vert}{C}}-C_7H_{15}$	(73)	58
Acetaldehyde	1-Heptene	80	HOAc	—	$CH_3-\overset{\displaystyle O}{\overset{\Vert}{C}}-C_7H_{15}$	(9)	
					$\begin{matrix} O \\ \Vert \\ C-CH_2-C_7H_{15} \\ / \\ H \end{matrix}$	(54)	
					$\begin{matrix} O \\ \Vert \\ C-CH_2-CH_2-\underset{\displaystyle OAc}{\underset{\vert}{CH}}-C_5H_{11} \\ / \\ H \end{matrix}$	(37)	
Propionaldehyde	1-Nonene	20	HOAc	—	$C_9H_{19}-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CHO$	(74)	58
					$C_7H_{15}-\underset{\displaystyle OAc}{\underset{\vert}{CH}}-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CHO$	(17)	
					$CH_3-CH_2-\overset{\displaystyle O}{\overset{\Vert}{C}}-C_9H_{19}$	(9)	

[a] Where the sum of products given exceeds 50%, the percentages given are the percentages of volatile reaction products with respect to manganese (III) consumed on a stoechiometric basis. Total yield is usually $<50\%$.

Table continued

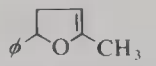
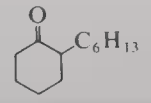
TABLE IX. *(Continued)*

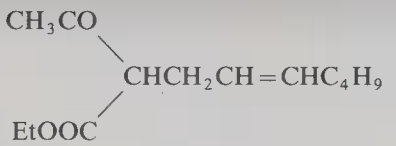
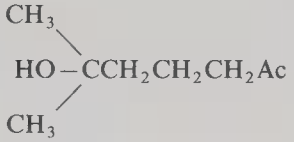
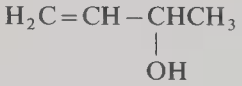
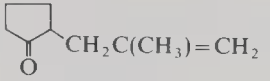
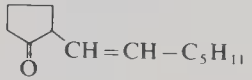
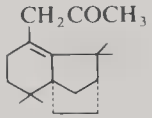
Aldehyde	Olefin	Temperature (°C)	Solvent	Catalyst	Product (%)[a]		Reference
Butyraldehyde	1-Nonene	70	HOAc	—	$C_9H_{19}-\underset{\displaystyle C_2H_5}{\underset{\vert}{CH}}-CHO$	(72)	
					$C_7H_{15}-\underset{\displaystyle OAc}{\underset{\vert}{C}}-CH_2-\underset{\displaystyle C_2H_5}{\underset{\vert}{CH}}-CHO$	(28)	
Propionaldehyde	1-Pentene	60	HOAc	—	$C_5H_{11}-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CHO$	(20)	60
Propionaldehyde	Isobutylene	60	HOAc	—	$\begin{matrix} CH_3 \\ \diagdown \\ C=CH-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CHO \\ \diagup \\ CH_3 \end{matrix}$	(70)	56
					$\begin{matrix} CH_2 \\ \diagdown\!\!\!= \\ C-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CHO \\ \diagup \\ CH_3 \end{matrix}$		
					$\begin{matrix} CH_3 \\ \diagdown \\ CH-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CHO \\ \diagup \\ CH_3 \end{matrix}$	(27)	

Propionaldehyde	2-Methyl-1-pentene	60	HOAc	—	Mixture of three isomeric unsaturated aldehydes (96) $CH_3-CH_2-CH_2-CH(CH_3)-CH_2-CH(CH_3)-CHO$ (4)		
Propionaldehyde	Isobutylene	50	HOAc	Cu	$(CH_3)_2C=CH-CH(CH_3)-CHO$ $CH_2=C(CH_3)-CH_2-CH(CH_3)-CHO$	(93)[b]	56
					Saturated aldehyde	(7)	
Propionaldehyde	 β-Pinene	60	HOAc	—	 (84) (16)		61
Propionaldehyde	β-Pinene	60	HOAc	Cu	 (80) (15) (5)		

[b] Ratio of β,γ- and γ,δ unsaturated aldehyde is 0.25.

TABLE X. Addition of Simple Ketones to Olefins

Ketone	Olefin	Solvent	Temperature	Cu(II) added	Product	(% Yield)	Reference
Acetone	Styrene				$\phi CHCH_2CH_2Ac$ | OAc	(27)	64
						(14)	
Acetone	1-Hexene		Reflux	—	$Ac(CH_2)_6CH_3$	(330)	28
Acetone	1-Octene	HOAc	85°C	—	$Ac(CH_2)_8CH_3$		65
					$AcCH_2CH_2CHC_6H_{13}$ | OAc		
					$AcCH_2CH=CHC_6H_{13}$		
Acetone	1-Heptene	–	80°C	—	$Ac(CH_2)_7CH_3$	(80)	66
Acetone	1-Heptene	Excess	65°C	—	$Ac(CH_2)_7CH_3$	(68)	
					5-Acetoxy-2-decanone	(19)	
Acetone	1-Heptene	Little		—	$Ac(CH_2)_7CH_3$	(38)	
					5-Acetoxy-2-decanone	(42)	
Acetone	1-Heptene	+	65°C	Cu	$CH_3(CH_2)_4CH=CHCH_2Ac$	(45)	
					$CH_3(CH_2)_3CH=CH(CH_2)_2Ac$	(25)	
Pyruvic ester	1-Heptene	+		Cu	$CH_3(CH_2)_3CH=CHCH_2CH_2COCO_2Et$	(23)	67
Acetone	1-Octyne	+		Cu	$AcCH_2CH=CHC_6H_{13}$	(13)	68
					$AcCH=CHCHC_6H_{13}$ | OAc		
Cyclohexanone	1-Hexene	HOAc				(53)	

Acetoacetic-ester	1-Heptene			Cu		(33)	69
Acetone	$(CH_3)_2C(OH)CH=CH_2$ 2-Methyl-3-buten-2-ol			—		(85)	70
					$Ac(CH_2)_3CHCH_3$ OH	(50)	
	Allylalcohol			—	$Ac(CH_2)_3CH_2OH$	(35)	
Acetylacetone	1-Heptene			—	3-Acetyl-2-decanone	(60)	71
Acetylacetone	1-Heptene	HOAc		Cu	$(CH_3CO)_2CHCH_2CH=CHC_4H_9$	(16)	
			40°C	—		(55)	72
			40°C	Cu		(44)	
Cyclopentanone	1-Heptyne			Cu			
Acetone	Ethylene			Telomers			73
Acetone	Ethylene	HOAc		Cu	ω-Unsaturated telomers		74
Acetone	Isolongifolene						75

added readily to a variety of olefins like α-olefins, styrene, isobutylene, hydroxy-functional olefins, and 1-alkynes (Table X). In the absence of added acetic acid the reaction is relatively slow and yields mainly saturated adducts. When acetic acid is added in low amounts and the reaction is performed at higher temperatures much of the manganese (III) acetate goes in solution and oxidizes the primary ketone-adduct radical. Thus under such conditions large amounts of acetoxyketones will be formed together with unsaturated ketones:

$$\mathrm{RCCH_2\cdot + R_1CH{=}CH_2 \longrightarrow R_1\dot{C}H{-}CH_2CH_2CR} \xrightarrow{\mathrm{Mn(III)}} \mathrm{R_1CH(OAc){-}CH_2CH_2CR}$$

When saturated adducts are the products of choice and a fast reaction is wanted, such reactions can best be performed by slowly adding both manganese (III) acetate, to obviate oxidation products, and olefin, to suppress telomerization,[28] to the ketone.

The effect of the structure of α-oxo-alkyl-radical on rate of addition to unsaturated systems was clearly demonstrated by Vinogradov,[68] primary radicals adding more readily on alkenes and alkynes than secondary and tertiary radicals:

$$\mathrm{\cdot CH_2C(=O){-} > R\dot{C}H(C(=O)){-} \gg (R)_2\dot{C}C(=O){-}}$$

The rate of recombination of secondary α-oxo-alkyl radicals with formation of 1,4-diketones approaches that of the addition to unsaturated systems and the tertiary α-oxo-alkyl radicals are further oxidized by excess manganese (III) acetate.

There is no uniformity in the major site of attack by manganese (III) acetate on simple asymmetric ketones like methyl-ethyl ketone. Vinogradov[68] claims preferential formation of the secondary radical

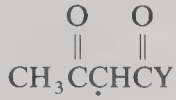
$$\mathrm{CH_3C(=O)\dot{C}HCH_3}$$

whereas Okano[76] finds more of 1-acetoxy-2-butanone than of 3-acetoxy-2-butanone upon oxidation of methyl-ethyl-ketone by manganese (III) acetate, which is more in line with similar unpublished results of the present author. Also Heiba[77] reports preferential formation of the least substituted α-ketoradical. This divergence of conclusions may partly come from the widely different reaction conditions used. Chain transfer from primary radicals to methylene groups such as

$$\mathrm{\cdot CH_2C(=O)CH_2CH_3 + CH_3C(=O)CH_2CH_3 \longrightarrow CH_3C(=O)\dot{C}HCH_3 + CH_3C(=O)CH_2CH_3}$$

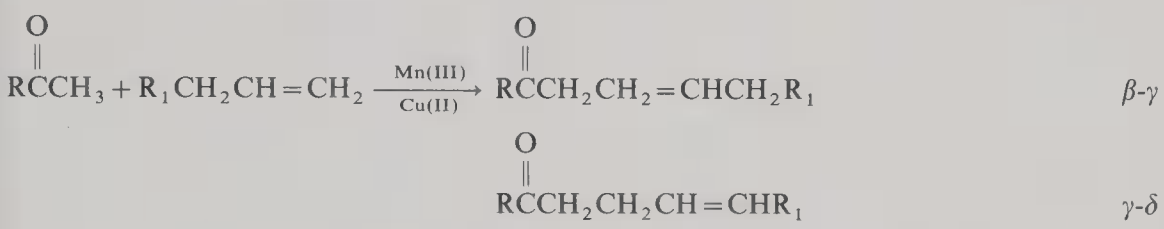
can occur to different degrees.

In activated β-diketo-systems like aceto acetic ester and acetyl-acetone exclusive formation of secondary radicals



takes place[69,71] with manganese (III) acetate whereas peroxides form both primary and secondary radicals. In γ-keto ester or γ- or δ-ketoacetoxy compounds,

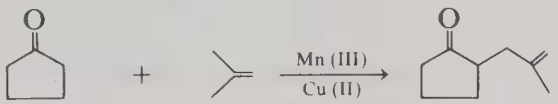
the ratio of primary to secondary radicals formed approaches unity. Addition of Cu(II) acetate results in formation of unsaturated ketones. The ratio of β–γ to γ–δ unsaturated ketones depends on a number of structural factors[69,72]:



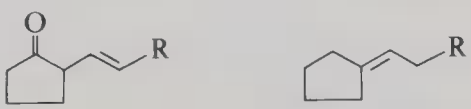
β-γ

γ-δ

In keto esters the amount of β–γ unsaturated adduct increases with the separation of keto and ester groups. Thus pyruvic and acetoacetic ester form exclusively γ–δ unsaturated adducts with 1-heptene, whereas methyllevulinate, $CH_3CO(CH_2)_2COOMe$, forms 40% β–γ and 60% γ–δ adduct with 1-heptene.[69] In acetoalkylacetates $CH_3CO(CH_2)_nOAc$ a similar observation was made,[69] the amount of β–γ adducts with 1-heptene increasing with the number of methylene groups separating acetoxy and carbonyl group. In the addition of cycloalkanones[72] cyclopentanone forms almost exclusive γ–δ unsaturated adduct, whereas cyclohexanone and cycloheptanone add to isobutylene in the presence of Cu(II) acetate with formation of equal amounts of β–γ and γ–δ adducts.



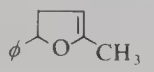
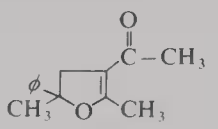
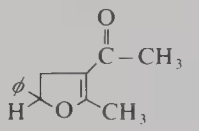
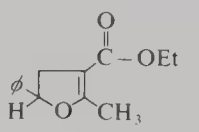
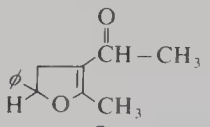
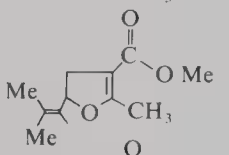
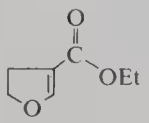
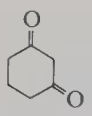
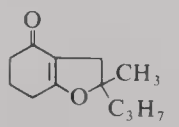
α-Oxo-alkylradicals add readily to acetylenic systems, as is exemplified by the addition of cyclopentanone to 1-heptyne.[72] The primary adduct radicals from this reaction are not oxidized by Mn(III) or Cu(II) but show chain transfer with the solvent instead. At temperatures below 80°C mainly β–γ unsaturated ketones are formed; at higher temperatures isomerization to α–β unsaturated ketones takes place as exemplified by the reaction of cyclopentanone and 1-alkyne.[72]



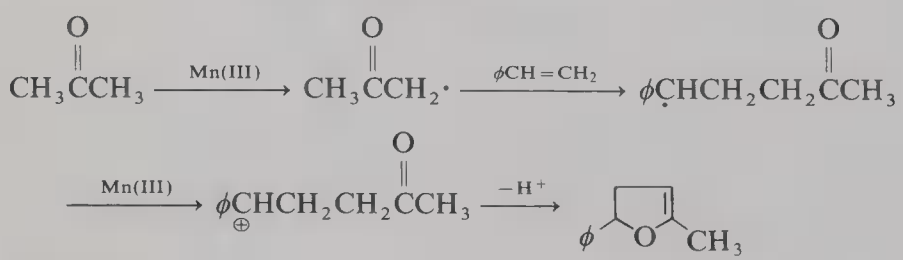
5.2. Formation of Dihydrofurans

In the presence of manganese (III) acetate, dihydrofurans may be formed in high yield from readily enolizable ketones and olefins (Table XI). The reaction proceeds via addition of

TABLE XI. Formation of Dihydrofuranes

Ketone	Olefin	Product	(% Yield)	Reference
Acetone	Styrene		(14)	64
Acetylacetone	α-Methylstyrene		(100)	78
Acetylacetone	Styrene		(30)	
Acetylacetic ester	Styrene		(57)	
Acetylacetone	Isobutylene		(60)	71
Acetylacetic ester	1,1-4,4-Tetramethyl-butadiene		(72)	79
Acetylacetic ester	Ethylene		(20)	80
	2-Methyl-pentene-1		(74)	78

α-oxoalkylradicals to the olefin, oxidation of the intermediate adduct radical to a carbenium ion, and subsequent cyclization of this carbenium ion to the dihydrofuran:



From this scheme it can be rationalized that higher yields can be obtained with

a. Readily oxidizable ketones like β-diketones.
b. Olefins with a vinylidene structure like α-methylstyrene and isobutylene.

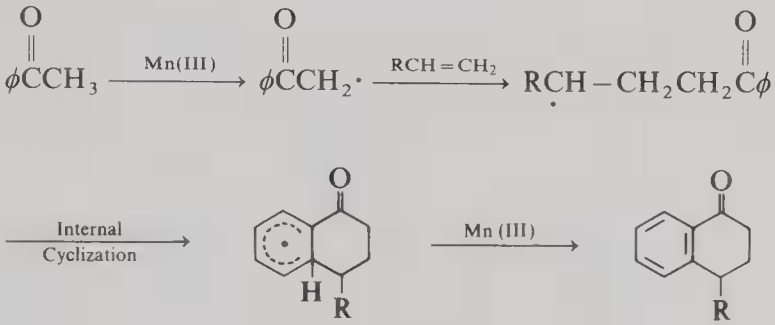
Side products to be expected from this reaction are

a. Saturated ketones, obtained by chain transfer from the intermediate adduct radical when this is less readily oxidized.
b. Unsaturated ketones and γ-acetoxy ketones, obtained from the intermediate carbenium ion when ring closure competes with H^+ elimination and acetoxylation by the solvent.

The reaction products with terminal olefins in all cases have consisted of only one isomer. The corresponding reactions of Tl(III) and Pb(IV) acetate have reportedly led to other isomers or mixtures of isomers[78] and probably proceed via ionic mechanisms.

5.3. Formation of Tetralones

When an aromatic ketone such as acetophenone is reacted with an olefin in the presence of manganese (III) acetate, α-tetralones can be formed according to the following scheme[81]:

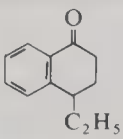
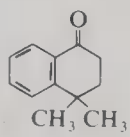
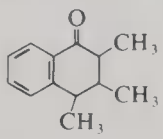
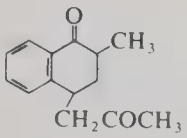


It follows from this reaction scheme that side products to be expected are

1. Saturated linear ketones derived from chain transfer of the intermediate adduct radical; these can be suppressed by working at low acetophenone concentrations.
2. Unsaturated linear ketones and linear keto acetates from oxidation of the intermediate adduct radical.

Despite these side reactions, reasonable yields of tetralones can be obtained as exemplified in Table XII.

TABLE XII. Formation of Tetralones

Ketone	Olefin	Tetralon	(Yield %)	Reference
$C_6H_5COCH_3$	1-Butene		(49)	81
$C_6H_5COCH_3$	Isobutylene		(43)	
$C_6H_5COCH_3$	2-Butene		(53)	
$C_6H_5COC_2H_5$	2-Keto-pentene-1		(10)	82

5.4. Formation of 1,4-Diketones

When a ketone is reacted with isopropenyl acetate in the presence of manganese (III) acetate the predominant nonpolymeric reaction product formed is a 1,4-diketone according to the following scheme[77]:

$$RCOCH_3 \xrightarrow{Mn(III)} RCOCH_2\cdot \xrightarrow{CH_2=\overset{OAc}{\overset{|}{C}}-CH_3} RCOCH_2CH_2\dot{C}(OAc)CH_3$$

$$\longrightarrow RCOCH_2CH_2COCH_3 + CH_3\dot{C}O$$

Although yields are only moderate, reportedly due to polymerization of isopropenylacetate, this route offers a single step preparation of 1,4-diketones from readily available reagents, and is much more selective than peroxide initiated reactions.[83]

Table XIII gives some pertinent results.

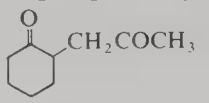
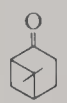
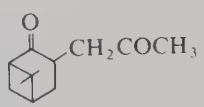
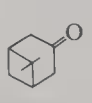
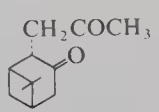
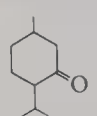
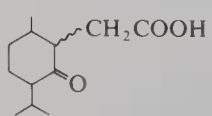
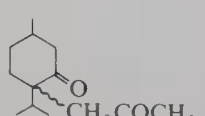
6. MANGANESE (III) ACETATE–ACETONE-INITIATED ADDITION OF HALOALKANES TO UNSATURATED SYSTEMS[84]

A mixture of manganese (III) acetate and acetone can be used as an initiating system for addition of haloalkanes to unsaturated systems.[84] Thus acetonyl radicals are readily formed from such systems and by chain transfer form halo alkyl radicals with the haloalkane when this is present in excess:

$$CH_3COCH_3 \xrightarrow{Mn(III)} CH_3COCH_2\cdot \xrightarrow{CCl_4} CH_3COCH_2Cl + CCl_3\cdot$$

$$CCl_3\cdot + RCH=CH_2 \longrightarrow R\dot{C}HCH_2CCl_3 \xrightarrow{CCl_4} RCH(Cl)CH_2CCl_3$$

TABLE XIII. Formation of 1,4-Diketones by Addition of a Ketone to Isopropenylacetate

Ketone	Product (Yield %)		Reference
$C_6H_5COCH_3$	$C_6H_5COCH_2CH_2COCH_3$	(20–35)	77
Cyclohexanone		(20–35)	
$CH_3(CH_2)_3CH(CH_3)COCH_3$	$CH_3(CH_2)_3CH(CH_3)COCH_2CH_2COCH_3$	(major product)	
 Dimethyl-6,6-norpinanone-2			83
 Dimethyl-6,6-norpinanone-3			
 *p*-Menthanone-3			

The reaction has the typical characteristics of a chain reaction with kinetic chain lengths of 8–10. Yields of 1,1,1-trichloro-3-chloroalkenes from α-olefins and carbon tetrachloride are usually 80%–90% on converted olefin.

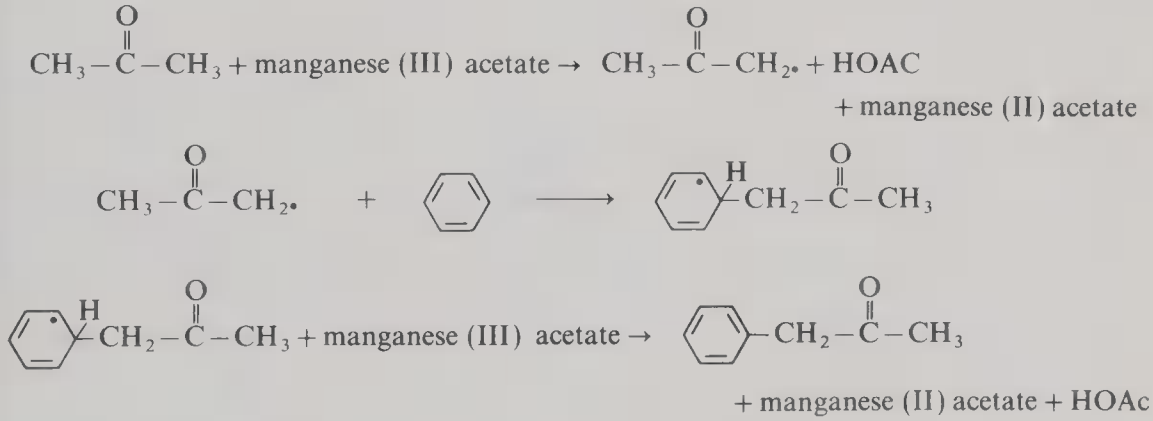
7. AROMATIC SUBSTITUTION REACTIONS

7.1. Introduction

A number of methods have been reported for aromatic substitution reactions by radicals generated by manganese (III) acetate. Thus carboxymethyl, acetonyl, and nitromethyl radicals readily substitute on the aromatic ring of suitable substrates.

Yields of these oxidative substitution reactions largely depend on reaction conditions, structure of intermediate radicals, substrate, and presence or absence of polar solvents like acetic acid. In many examples yields of pure compounds are differently extracted from the original work. However, even when yields are low, the products are obtained in one single step from simple compounds whereas alternative synthetic methods for many examples require multistep procedures.

The substitution reactions of this type require two equivalents of manganese (III) acetate as exemplified by the following reaction scheme for the substitution of acetone to benzene:



7.2. Oxidative Carboxymethylation

Oxidative carboxymethylation is characterized by the fact that the primary formed aryl-acetic acids in many examples are easily further oxidized by excess manganese (III) acetate to yield benzylacetates, benzylidene diacetates, and benzaldehydes. When the reaction is performed in acetic anhydride instead of acetic acid, arylacetic anhydride is the major product.[36] Table XIV gives some pertinent results. In monosubstituted benzene derivatives a free radical substitution pattern is closely followed.[87] In *p*-disubstituted benzenes a high selectivity of products can be obtained.

7.3. Oxidative Aromatic Substitution by Ketones

The reaction of acetone with benzene in acetic acid in the presence of manganese (III) acetate results in the formation of methyl-benzyl ketone.[89] In alkyl substituted benzenes such as toluene side chain oxidation to benzylacetate is a major side reaction, although the rate of

TABLE XIV. Oxidative Carboxymethylation of Aromatic Compounds

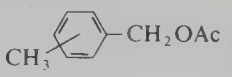
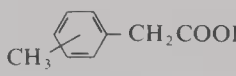
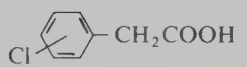
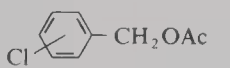
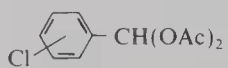
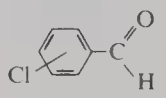
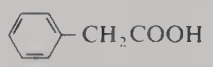
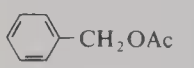
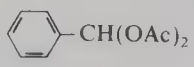
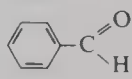
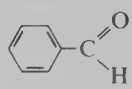
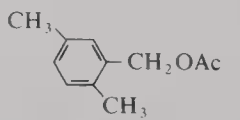
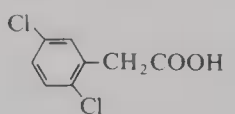
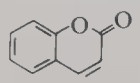
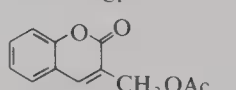
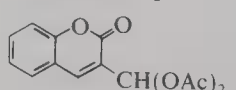
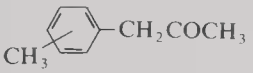
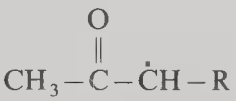
Substrate	Solvent	T (°C)	Product	(% Yield)	Reference
Toluene	HOAc	110		(74)	6
			o *m* *p* 40 20 17		
	$HOAc/Ac_2O$			(69)	36
	HOAc/KOAc			Major product	85
	Ac_2O			Sole product	36
Chlorobenzene	HOAc	110		(13)	86
				(30)	87
				(21)	87
				(17)	
				(11)	
Benzene	HOAc	100		(8) (19)	86, 87, 36
				(51) (26)	
				(9)	
				(18) (48)	
Benzene	Ac_2O			(48)	36
p-Xylene	Ac_2O			(61)	36
p-Dichlorobenzene	Ac_2O			(58)	36
	AcOH Ac_2O				88
					

TABLE XV. Oxidative Aromatic Substitution by Acetone

Substrate	Solvent	T (°C)	Product	(% Yield)	Reference
Benzene	HOAc	70		(36)	89
Toluene	HOAc	70		(30)	68 89
				(7)	

aromatic substitution is higher.[68] The aromatic substitution by ketones is largely confined to acetone since under the conditions used mainly

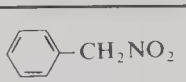
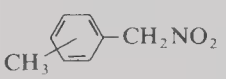
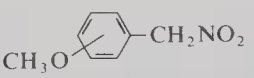
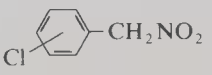


radicals are generated from methyl-alkyl ketones. These radicals do not substitute on the aromatic system but dimerize instead,[68] as do tertiary α-keto radicals. The reactions have to be performed in acetic acid,[90] probably because the oxidation of the intermediate acetonyl-cyclohexadienyl radical is a slow step and requires relatively high Mn(III) concentrations. Table XV gives some results.

7.4. Oxidative Nitromethylation

In acetic acid solution manganese (III) acetate promotes the substitution of nitromethyl-radicals onto aromatic rings.[91,92] The reaction is largely confined to nitromethane, since with nitroethane only small amounts and with 2-nitropropane no substitution products could be obtained. The electrophilic nitromethyl radical adds preferentially onto aromatics with electron-releasing substituents. No substitution products were found with nitrobenzene as a substrate. It is interesting to note that nitromethyl radicals preferentially attack the aromatic ring of alkylsubstituted aromatic systems rather than abstracting benzylic hydrogen. Although ortho substitution predominates, a drawback of this reaction is the formation of

TABLE XVI. Nitromethylation of Aromatic Hydrocarbons

Substrate	Product	(% Yield)	Reference
Benzene		(78)	91 92
Toluene		(77)	
Anisole		(77)	
Chlorobenzene		(20)	

ortho, meta, and para substituted products from simple aromatic compounds. An electrochemical variation of this reaction to regenerate manganese (III) acetate has been reported.[93] As with the other aromatic substitution reactions, two moles of manganese (III) acetate are consumed per mole of product. The reaction is certainly of synthetic utility since making aryl nitromethanes commonly involves rather lengthy procedures, whereas with the present method simple aromatic compounds may be utilized. Table XVI gives some results.

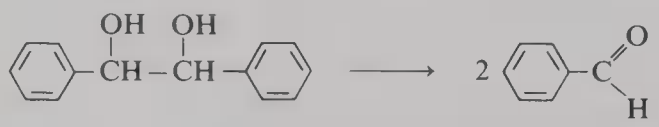
8. DIRECT OXIDATION REACTIONS WITH MANGANESE (III) ACETATE

8.1. Introduction

Apart from its use in oxidative addition and substitution reactions treated in the previous sections, manganese (III) acetate constitutes a mild one-electron oxidant. Direct inner- or outer-sphere one-electron oxidations with manganese (III) acetate in many cases proceed via the primary formation of an intermediate radical. The fate of this primary radical depends on the nature of the substrate and reaction conditions. Thus, with excess Mn(III) in many cases it is rapidly oxidized in a ligand transfer reaction to an acetate. However, the primary radical may dimerize, disproportionate, lose a proton, or enter in a sequence of transfer or addition reactions with other compounds present, in a one-step procedure from substrates to products which otherwise require a multistep sequence.

8.2. Alcohols

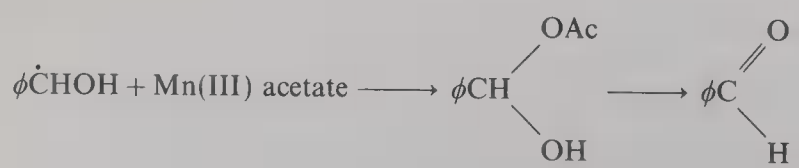
Simple alcohols like ethanol do not readily react with manganese (III) acetate in glacial acetic acid. Reactions of more complex alcohols like α-glycols and α-keto alcohols have been extensively studied.[94,95] The loss of a stable radical by C–C fission is sometimes easier than the removal of the H atom of a CH(OH) group, as exemplified by the oxidation of hydrobenzoin[94]:



The secondary α-keto alcohols are always oxidized with preservation of the carbon skeleton, giving diketones[94,95]:

The oxidation of benzylalcohol yields benzaldehyde.[96] The primary and rate determining step in this reaction, reportedly, is formation of the aromatic cation radical. This is followed by loss of a proton with concomitant formation of the benzyl radical, which is oxidized in a subsequent step to benzaldehyde, possibly in a ligand transfer oxidation via the benzalhemiacetate:

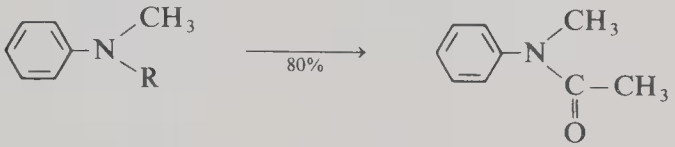
$$\phi CH_2OH \xrightarrow[60^\circ C]{Mn(III)} {}^{\cdot}\phi^{+} CH_2OH \longrightarrow \phi\dot{C}HOH + H^{+}$$



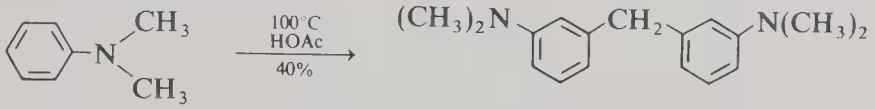
Clearly the oxidations of aliphatic alcohols follow a different mechanism. An interesting application of this one-electron oxidation of alcohols is its use as an initiating system for the graft polymerization of vinylacetate to *p*-vinylalcohol.[97]

8.3. Amino Compounds

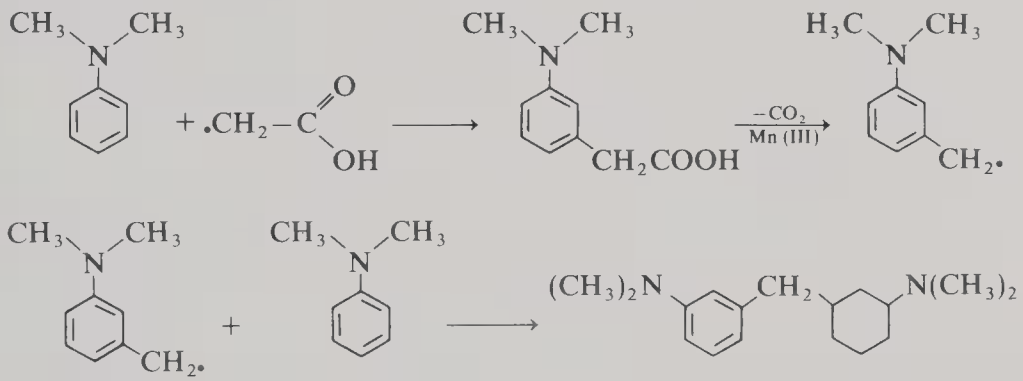
The oxidation of *N*-substituted anilines is well exemplified by Bronsdijk,[98] Dewar,[99] and Rindone.[100] At room temperature in acetic acid or chloroform–acetic anhydride mixtures the main product from *N*,*N*-dimethylaniline is *N*-methylacetamide, ϕNMeAc.[98,100] In a comparative study with Pb(IV) acetate, Co(III) acetate, Tl(III) acetate, and Mn(III) acetate it was shown[100] that the latter oxidant gives cleaner reactions and highest yields of amides. With mixed *N*-methyl–*N*-alkyl amines the higher alkyl is preferentially eliminated:



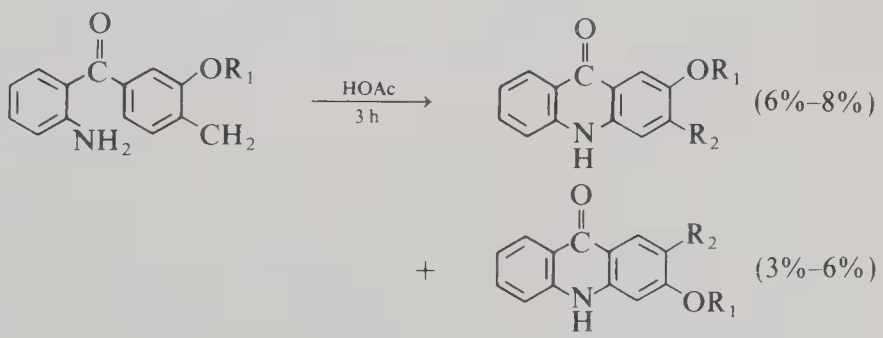
The reaction most probably involves primary formation of a dialkyl-aniline cation radical followed by loss of a proton to $\phi N(CH_3)CH_2\cdot$. This radical is subsequently oxidized to $\phi N(CH_3)CH_2OAc$, which rearranges to formaldehyde and *N*-methylacetanilide. At higher temperatures in acetic acid the main reaction product is bis-(*p*-dimethyl-aminophenyl) methane (40% yield)[99]:



This product possibly arises from an intermediate carboxy methylene adduct, loss of CO_2, and subsequent addition of the resulting radical to unconverted dimethylaniline



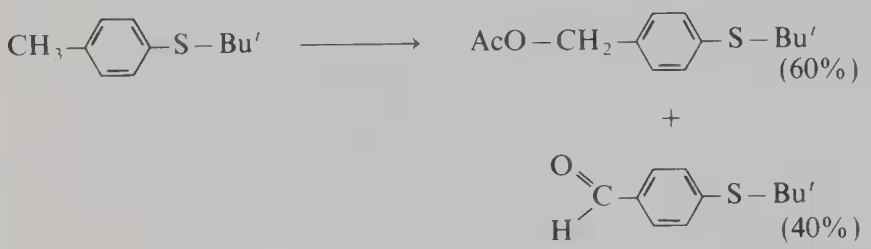
The formation of acridones from substituted 2-amino benzophenones is reported by Bowen.[101] Yields are very modest (6%–8%) although higher than with $K_2S_2O_8$ as oxidizing agent:



8.4. Thio Compounds

Thioanisole reacts with manganese (III) acetate with formation of acetoxy methylene-phenylsulfide, ϕSCH_2OAc.[98,102] Intermediate formation of a thioanisole cation radical by electron transfer, subsequent loss of a proton to $\phi SCH_2\cdot$ followed by ligand-transfer oxidation of this radical to ϕSCH_2OAc is generally accepted. In a comparative study[98] it was found that manganese (III) acetate is a much more selective oxidant to this substrate than either $Pb(OAc)_4$ or peroxides.

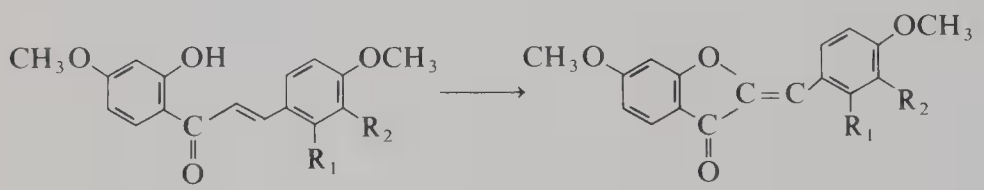
Formation of the cation radical is rate determining, and a fast nucleophilic attack occurs at a site determined by the nature of the cation radical. Normally a preference is found for nucleophilic attack at the thioalkyl group as opposed to aromatic ethers (Section 8.6). Only when this attack becomes more difficult is there nucleophilic attack at other sites, as in the formation of *t*-butyl-acetoxy methylene phenylsulfide from *t*-butyl-*p*-tolyl sulfide:



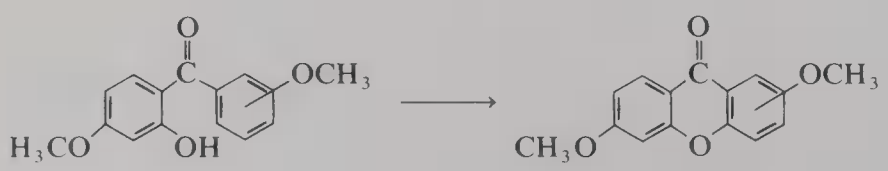
Interestingly the normal course of the reaction can be completely altered by addition of KBr,[102] the main product being in this case $Me-S-\phi CH_2OAc$ from *p*-methylthioanisole.

8.5. Phenols

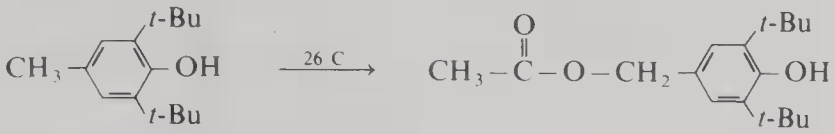
Simple phenols are oxidized to diphenoquinones[104,105] or polymerized to polyphenylene ethers, depending on reaction conditions. The primary product must be a phenoxy radical, which can undergo a variety of reactions. Thus, in some methoxy-substituted 2′-hydroxy-chalcones the phenoxy radical adds on the double bond and the resulting adduct radical is further oxidized to the *trans*-aurone[106,107] in 20%–55% yield:



Similar yields are reported with Pb(IV) acetate.[107] With Tl(III) acetate skeletal rearrangement takes place.[108] The phenoxy radical obtained from methoxy-substituted benzophenones substitutes on the neighboring phenyl ring thus providing a new synthesis for methoxy-substituted 9-xanthenones. Yields of up to 65% are reported,[109] oxidation with Mn(III) acetate being much more selective than that with Pb(IV) acetate.



With sterically hindered *p*-alkyl-substituted phenols the intermediate phenoxy radical is further oxidized to the acetoxybenzylphenol[105] in good yields:



8.6. Carboxylic Acids

Oxidation of carboxylic acids by manganese (III) acetate can follow two distinct pathways, depending on the substrate carboxylic acid. Acetic acid and other α-hydrogen containing alkyl carboxylic acids are oxidized by loss of an α-hydrogen. Thus carboxymethyl radicals are generated. This is covered more elaborately in Sections 3–7 on addition and substitution reactions.

However, many carboxylic acids with manganese (III) acetate suffer decarboxylative oxidation, the primary step being inner-sphere oxidation of the carboxylate moiety to the carboxy radical:

$$RCO_2H + Mn(III) \longrightarrow RCO_2\cdot + H^+ + Mn(II)$$

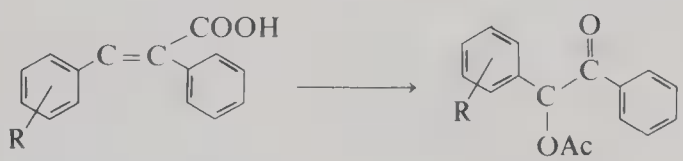
$$RCO_2\cdot \longrightarrow R\cdot + CO_2$$

Depending on the structure of R· and reaction conditions a number of common free radical reactions can occur such as dimerization, further oxidation to alkenes or esters, or formation of olefins when Cu(II) salts are present.[8] Decarboxylation with Mn(III) acetate, in contrast to Pb(IV) acetate, is typically a nonchain process. Thus, phenylacetic acid yields mainly benzylacetate[86,36] according to

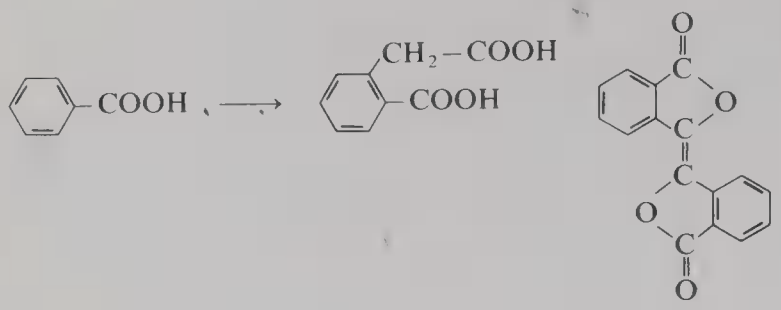
$$\phi CH_2COOH + Mn(III)\,\text{acetate} \longrightarrow \phi CH_2\cdot + CO_2 + H^+ + Mn(II)\,\text{acetate}$$

$$\phi CH_2\cdot + Mn(III)\,\text{acetate} \longrightarrow \phi CH_2OAc + Mn(II)\,\text{acetate}$$

the latter reaction probably being a ligand transfer oxidation. Similar mechanisms are proposed for oxidation of α-hydroxy acids, α-keto acids, α-amino-acids,[6] pivalic, isobutyric, and *n*-butyric acid.[8] With simple α,β unsaturated acids in aqueous acetic acid like cinnamic and crotonic acid α,β-bond breaking occurs after decarboxylation yielding benzaldehyde and formaldehyde from cinnamic acid[110] in a complex machanism. On the other hand, manganese (III) acetate in glacial acetic acid can be used in a regiospecific synthesis of 2-acetoxy-1,2-diphenylethanone (benzoin acetate)[111] in 10%–64% yields from α-phenylcinnamic acids:



Aromatic acids do not decarboxylate. Instead aromatic substitution by carboxymethyl radicals takes place when the oxidation is carried out in acetic acid. Interestingly, the *ortho*-substituted product reacts further in a sequence of reactions to biphthaloyl (I)[112]:



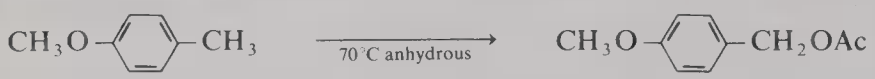
(I)

8.7. Aromatic Ethers

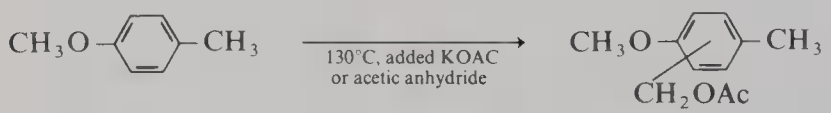
The Mn(III) acetate oxidation of aromatic ethers proceeds by two competing mechanisms[85]:

1. Aromatic ethers having ionization potentials below 8 eV are oxidized by an electron transfer mechanism. In a primary step a cation radical is formed, which loses a proton with formation of a benzyl radical. The latter is oxidized by a second Mn(III) acetate to a methoxy substituted benzyl acetate.
2. Compounds having ionization potentials beyond 8 eV are substituted by carboxymethyl radicals and products are derived from the intermediate adducts (see Section 7 on aromatic substitution).

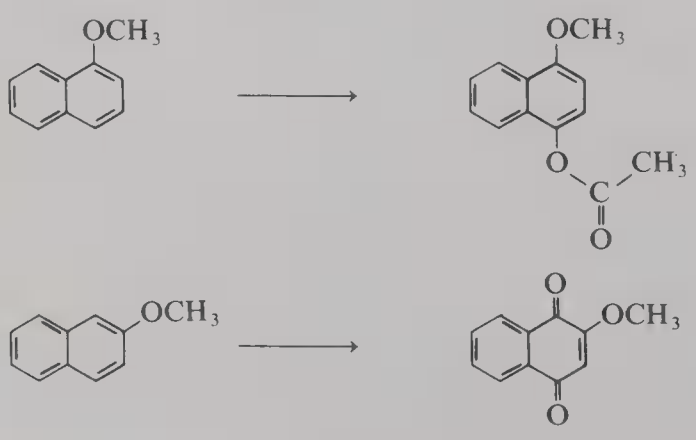
The most extensively studied example of aromatic ethers being oxidized by the first mechanism is *p*-methoxytoluene.[15,113,36,114,85,102] This compound is oxidized to *p*-methoxybenzylacetate at 70°C, a temperature where carboxymethylradical formation is negligible. Under anhydrous conditions yields of up to 90% can be obtained.[113] Traces of water lower the selectivity,[15,113] mainly in favor of *p*-methoxybenzaldehyde. The reason for this is unknown, but it could reflect the sensitivity of the *p*-methoxybenzylradical towards Mn(IV) species that are formed by water-induced disproportionation of Mn(III) acetate.



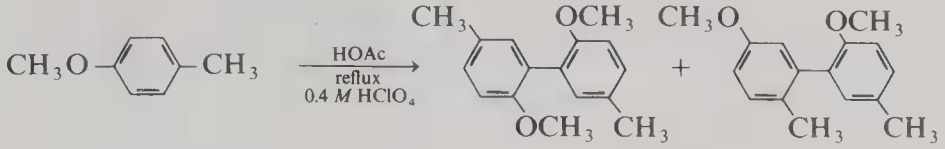
At higher temperatures, and especially in the presence of KOAc or acetic anhydride, the main reaction product from *p*-methoxytoluene is a mixture of isomeric benzylacetates, being formed via substitution by carboxymethylradicals[85]:



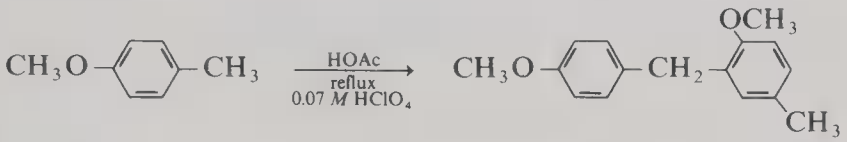
Further examples of electron transfer oxidations are found with 1- and 2-methoxy naphthalene, giving 1-methoxy-4-acetoxynaphthalene and 2-methoxy-1,4-naphtoquinone, respectively,[115,99] in good yields:



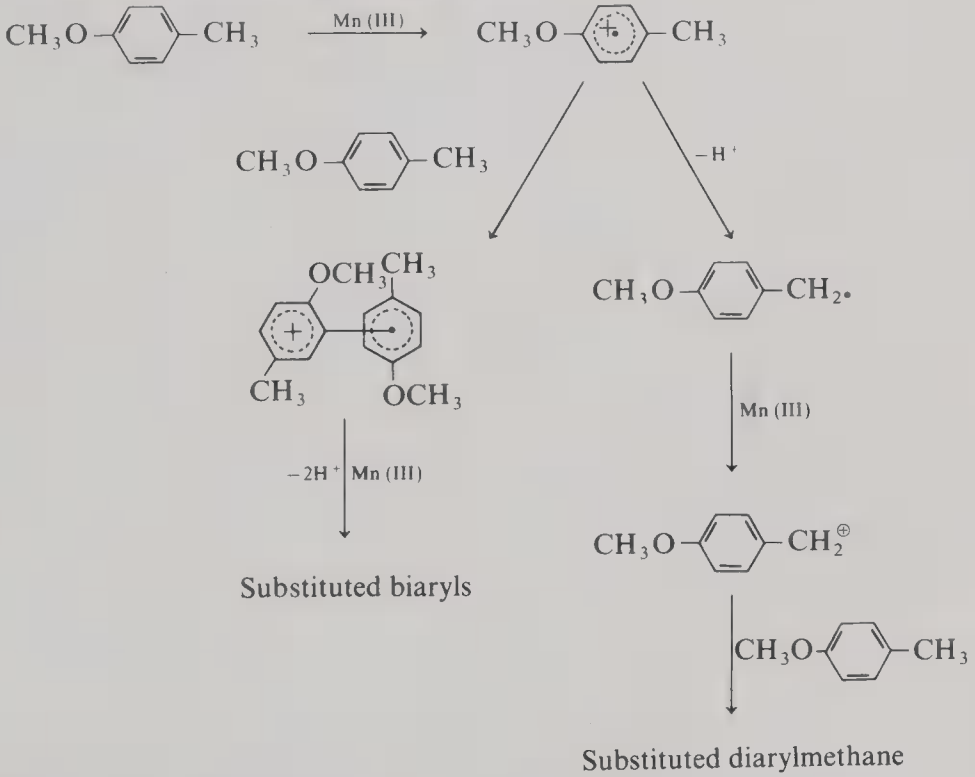
In the presence of strong acids the oxidation of *p*-methoxytoluene takes a completely different course.[116] With a strong acid like $HClO_4$ at relatively high concentrations the main products are substituted biaryls:



In the presence of a weaker acid (CF_3COOH) or at low $HClO_4$ concentrations the main product found is a substituted diarylmethane, and only minor amounts of biaryls are formed:

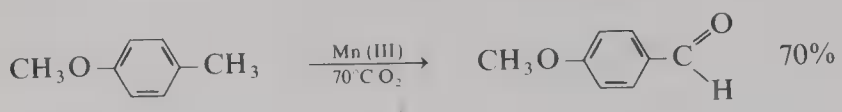


These products are only found at low conversions. At high conversions intractable tars are formed. Formation of products can be rationalized[116] in that the trinuclear oxygen-centered Mn(III) complex which constitutes Mn(III) acetate is destroyed by strong acid. The resulting Mn(III) species can oxidize *p*-methoxy toluene to its cation radical but has lost its basic sites for proton abstraction. Thus in strong acid the cation radical reacts with excess *p*-methoxy toluene with ultimate formation of biaryls.[114,*] At low $HClO_4$ concentrations, manganese (III) acetate may retain the oxygen-centered structure, allowing for proton abstraction of the primary cation radical to the benzyl radical, which is further oxidized to a benzyl carbenium ion. This may react with excess *p*-methoxy toluene with formation of the substituted diarylmethane. The latter part of this explanation does not account for the absence of *p*-methoxybenzylacetate, the main product in the absence of strong acids. Therefore it seems more reasonable that the intermediate benzylradical adds on excess *p*-methoxytoluene, the resulting radical being oxidized to the diarylmethane. This path also accounts for the direction of substitution ortho to the methoxy group.



* Similar reaction types are also described in Chapters 1 and 13.

In the presence of oxygen (45 atm) the main reaction product from *p*-methoxytoluene at 70°C is anisaldehyde (70%) together with some anisylacetate.[114]



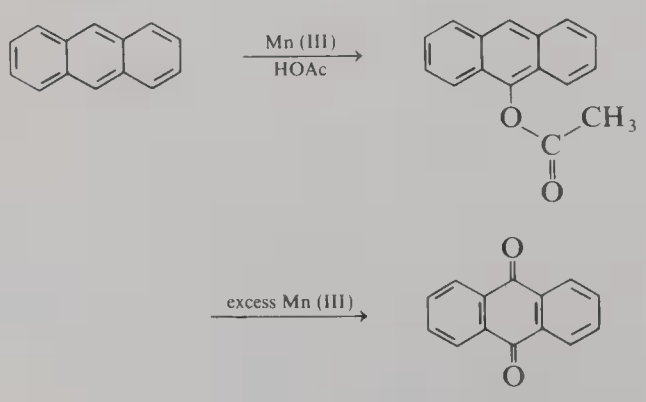
It has been argued[114] that added perchloric acid would inhibit ionization of the primary radical cation, thus accounting for biaryl formation. Certainly, any added acid will displace some if not all of the acetate ligands in manganese (III) acetate. Therefore, the oxidizing species in strong acid will always differ from that of a reaction in neat acetic acid.

8.8. Aromatic Hydrocarbons

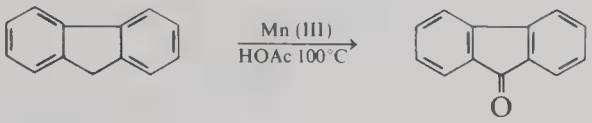
The course of oxidation of aromatic hydrocarbons by Mn(III) species is highly dependent on reaction conditions and structure of the substrate. Basically four types of reactions can be distinguished:

1. At temperatures lower than 100°C aromatic compounds with an oxidation potential lower than 8 eV prevalently undergo electron transfer to a cation radical. In acetic acid the first stable product often is a nuclear acetoxy substituted compound. With excess Mn(III) acetate these may be further oxidized to quinoid systems.
2. At temperatures higher than 100°C carboxymethylene radicals are formed from acetic acid at an appreciable rate. Mainly displacement products will be found when the substrate has an oxidation potential higher than 8 eV.
3. When bromide is added, bromine radicals are formed. At low temperature nuclear substitution can be completely suppressed and main products result from aliphatic side-chain halogenation and sequential reactions like acetoxylation.
4. In the presence of strong acids the reactivity of Mn(III) acetate is enhanced to such extent that even aromatic compounds with high oxidation potentials can be oxidized at low temperature to the cation radical. Depending on temperature, substrate, and further reaction conditions, a number of consecutive reactions will determine product composition. Thus at higher temperatures and excess substrate often substituted biaryls are formed from alkylaromatic compounds.

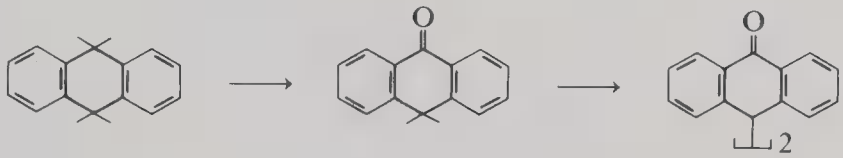
Simple polynuclear aromatics with relatively low oxidation potentials can be oxidized to acetates, quinones, or dimeric products, probably via electron transfer leading to the cation radical as a first step. Thus, with excess Mn(III) acetate anthracene is oxidized to anthraquinone[117] or 9-acetoxyanthracene when equimolar amounts are used.[117,105]



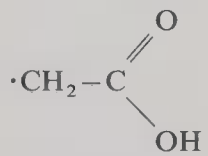
Phenanthrene yields 9-acetoxyphenanthrene[117] and 2-methylnaphthalene 1-acetoxy-2-methylnaphthalene,[85] but acenaphthene and fluorene reportedly yield acenaphthenequinone and fluorenone[117]:



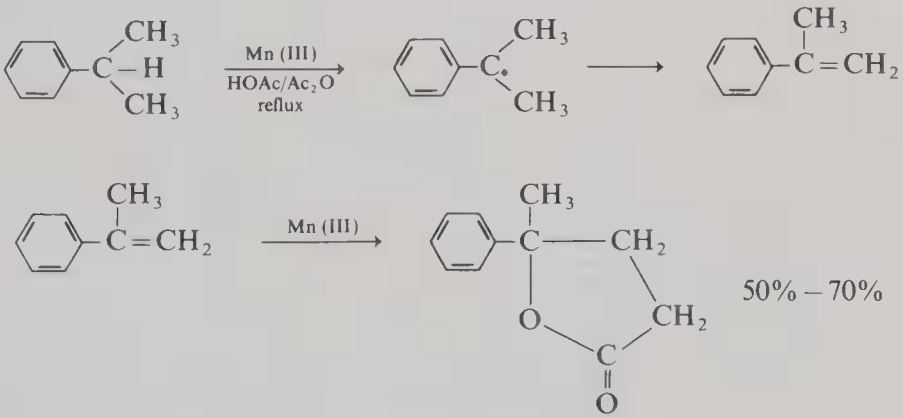
Benz[a]anthracene gives benzanthraquinone.[99] From 9,10-dihydroanthracene anthrone is obtained in a primary sequence,[6] but this compound readily dimerizes to 10,10′-dioxodianthranyl.[6,105]



At temperatures under 100°C compounds with an oxidation potential lower than 8 eV will undergo mainly electron transfer and consecutive reactions with Mn(III). At higher temperatures and higher oxidation potentials aromatic substitution by

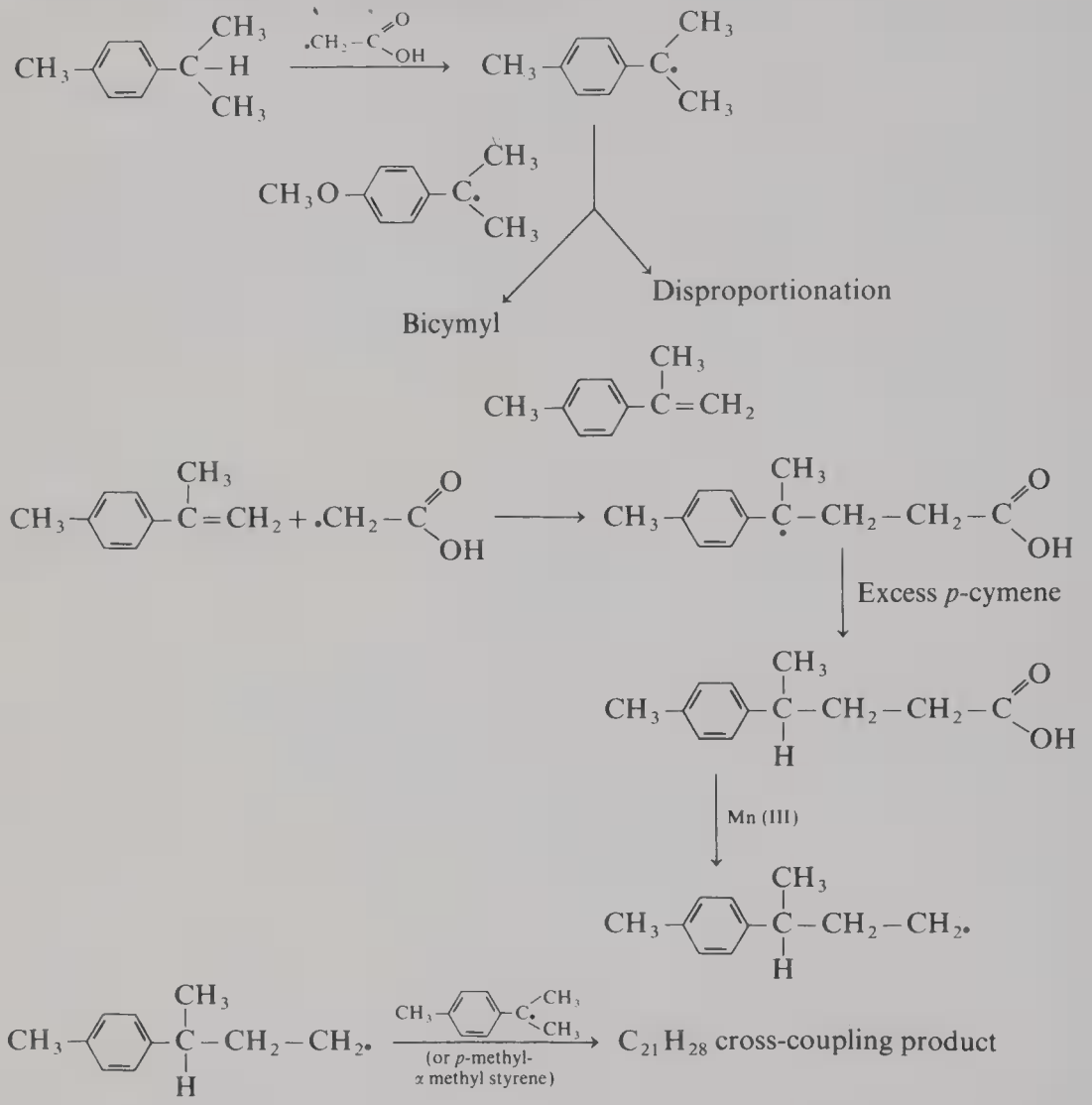


radicals and consecutive reactions become more predominant,[85] yielding more complex reaction mixtures. Thus benzene, toluene, and chlorobenzene yield mainly mixtures of substitution products.[87] Isopropyl substituted benzenes behave differently in that γ-butyrolactones are formed mainly.[118,36] This is via intermediate α-methyl-styrene formation on which carboxymethylradicals are readily added:



Some isopropylbenzylacetate is also formed. Remarkably at 95°C, at a large excess of *p*-cymene and in absence of acetic anhydride, no lactone is formed.[119] Instead an unidentified dimeric product is reported. The reaction probably does not proceed via intermediate cation

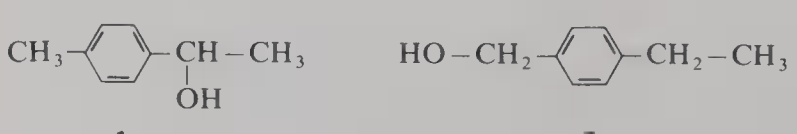
radicals as it does with Co(III). Since most of the product consists of a $C_{21}H_{28}$ dimer (the bicymyl is $C_{20}H_{26}$), a possible scheme could be



These Mn(III) oxidations can be performed at lower temperatures and made much more selective by addition of bromide or strong acids. Thus, by addition of KBr, oxidation of toluene can be performed at 40–90°C and yields predominantly benzylacetate and benzylbromide without nuclear substitution products.[6,87] The intermediate benzyl radical is probably formed directly via molecular bromine[102,120] and not via the cation radical sequence.

When strong acids like sulfuric acid or perchloric acid are added,[121–123] toluene and related alkyl substituted aromatic compounds are oxidized at low temperatures to the respective benzylacetates in high yields. The reaction proceeds exclusively through electron transfer. Product composition can be influenced by working under nitrogen or air or by addition of strong acids as exemplified in Table XVII.

In contrast with Co(III) acetate the Mn(III) acetate initiated reaction cannot be made catalytic under air.[122] By oxidation of *p*-ethyltoluene it was shown that Mn(III) acetate–H_2SO_4 is a much more selective agent than Co(III) acetate or Ce(IV) ammonium-nitrate.[123] Thus *p*-ethyltoluene gives mainly **1** and little **2**:



1 **2**

Reagent and conditions	*Products from p-ethyltoluene*	
	1	**2**
Co(III) acetate, HOAc, 60°C	47	53
Ce(IV) ammonium nitrate, HOAc, 60°C	78	22
Mn(III) acetate, 0.2 *M* H_2SO_4, HOAc, 20°C	91	9
N-Br-succinimide, AIBN, CCl_4, 80°C	94	6

In the presence of strong acid at higher temperatures the oxidation of alkylaromatics can lead to completely different products.[124,125,116] The first step under these conditions is again one-electron oxidation to the cation radical that can either add on excess aromatic compound, resulting in substituted biaryls, be oxidized further to a carbenium compound resulting in diarylmethanes, or be oxidized to the side-chain acetate, which reacts further to a diarylmethane as exemplified in Ref. 125. Some examples and products in refluxing CF_3COOH are given in Table XVIII. A comparison with Co(III), Pb(IV), Fe(III) or anodic oxidation shows that Mn(III) generally is a more selective oxidant in refluxing CF_3COOH. Further influence of strong acid or air on products is exemplified[125] in Table XIX.

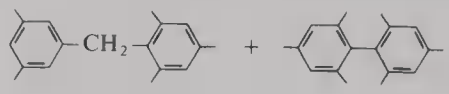
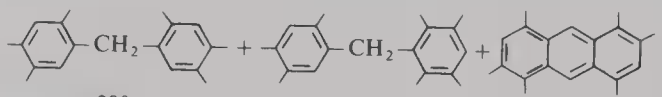
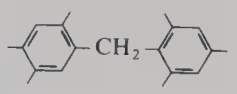
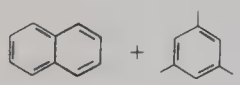
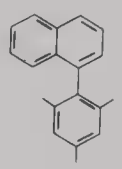
A number of other alkylbenzenes like *p*-chlorotoluene, ethylbenzene, *ortho*-, *meta*-, and *p*-xylenes, mesitylene, and durene react with manganese (III) acetate in acetic-perchloric acid under reflux predominantly to the corresponding diarylmethanes.[125] These compounds hardly give biaryls as does *p*-methoxytoluene.[116] Compared with oxidations by Fe(III), Co(III), Cu(II), Pb(IV), and Tl(III), reactions with Mn(III) are much more selective, chiefly since no polymers are formed.

TABLE XVII. Effect of Strong Acid on the Oxidation of Alkylaromatic Compounds by Mn(III) Acetate in Acetic Acid at 25°C[a]

Substrate	Acid added	Atmosphere	Product	Yield (%)
ϕCH_3	H_2SO_4	N_2	ϕCH_2OAc	74
ϕCH_3	H_2SO_4	O_2	ϕCHO	71
p-Cl-ϕCH_3	H_2SO_4	N_2	p-Cl-ϕCH_2OAc	74
ϕCH_2CH_3	H_2SO_4	N_2	$\phi-\underset{\displaystyle OAc}{\underset{\vert}{CH}}-CH_3$	93
ϕCH_2CH_3	CCl_3COOH	N_2	$\phi-\underset{\displaystyle OAc}{\underset{\vert}{CH}}-CH_3$	54
			$\phi-COOH$	46
m-C_2H_5-ϕCH_2CH_3	$HClO_4$	N_2	m-C_2H_5-$\phi-\underset{\displaystyle OAc}{\underset{\vert}{CH}}-CH_3$	95
$\phi-\overset{\displaystyle CH_3}{\overset{\vert}{\underset{\displaystyle CH_3}{\underset{\vert}{C}}}}-H$	H_2SO_4	N_2	$\phi-\overset{\displaystyle O}{\overset{\Vert}{C}}-CH_3$	75

[a] Reference 122.

TABLE XVIII. Oxidation of Alkylaromatic Compounds by Mn(III) in CF_3COOH at Reflux Temperature[a]

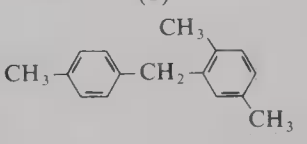
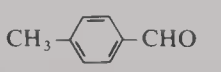
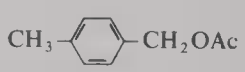
Substrate	Product
	 30%–40% 14%–20%
	 20% 25% 25%–50%
	 50%
	 40%–50%

[a] Reference 124.

8.9. Terpenes, Cycloaliphatic Compounds, and Saturated and Unsaturated Hydrocarbons

The versatility of Mn(III) acetate as an oxidizing agent is exemplified by its reaction with unsaturated hydrocarbons. In acetic acid or mixtures with anhydride the most common reaction is addition of carboxymethylene radicals and, depending on conditions, subsequent lactonization. Here some other reactions of both saturated and unsaturated hydrocarbons are given.

TABLE XIX. Oxidation of *p*-Xylene (Excess) with Mn(III) Acetate in Acetic Acid at Reflux Temperature. Yields are in Moles of Product per Mole of Mn(III) Acetate[a]

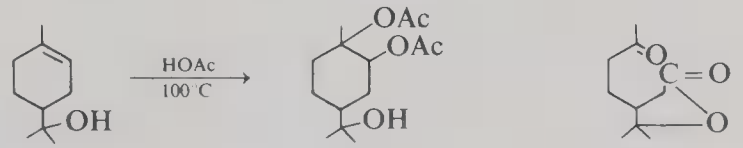
		Product		
		(1) 	(2) 	(3) 
Added acid	Atmosphere			
$HClO_4$	Air	0.83	0.2	—
$HClO_4$	O_2	0.61	0.48	—
$HClO_4$	N_2	1.05	0.06	—
CF_3COOH	N_2	0.06	0.14	0.75
CCl_3COOH	N_2	0.05	0.14	0.66

[a] Reference 125.

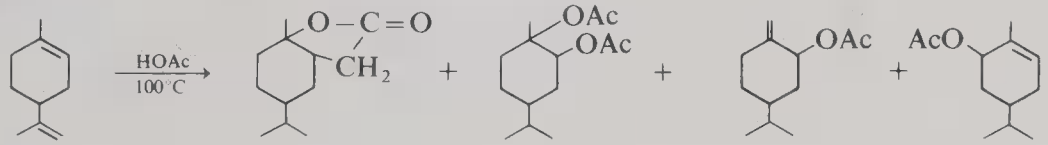
With unsaturated hydrocarbons several main types of reactions can be distinguished. Their occurence is highly dependent on substrate and reaction conditions:

1. The common addition of carboxymethylradicals generated by manganese(III) acetate and subsequent lactonization or formation of unsaturated carboxylic acids or acetoxy acids (cf. 2 below).
2. Olefins with a low oxidation potential, or when sterically hindered, are preferentially oxidized at the double bond to a cation radical at temperatures of 100°C or lower. By a sequence of further reactions the main products found are vicinal diol diacetates or unsaturated acetates.
3. In the presence of KBr bromine radicals are formed. At temperatures under 100°C main products will be allylacetates. Allylacetates are a common minor product at high temperatures and high Mn(III) concentrations.
4. In substituted cyclohexenones the double bond remains unaffected and oxidation is at the position alpha to the ketone group.

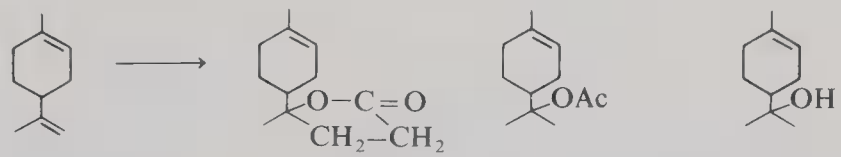
In a number of papers the oxidation of cycloaliphatic compounds and terpenes is described; reaction conditions differ considerably and interpretation of the results is therefore difficult (see Table XX). The main oxidation products from *dl*-α-terpineol in acetic acid are *d,l-p*-methane-1,2,8-triol-1,2-diacetic and homo-terpenyl-methyl-ketone[126]:



When *d*-carvomenthene is oxidized[44] the lactone is formed as the major product next to 1,2-menthyl-diacetate and a number of allyl-acetates:



From *d*-limonene the main products are γ-lactone, α-terpinyl-acetate, and α-terpineol[44,127]:



However, in the presence of KOAc and acetic anhydride the main products found from *d*-limonene and *d*-carvomenthene are unsaturated acids[128]:

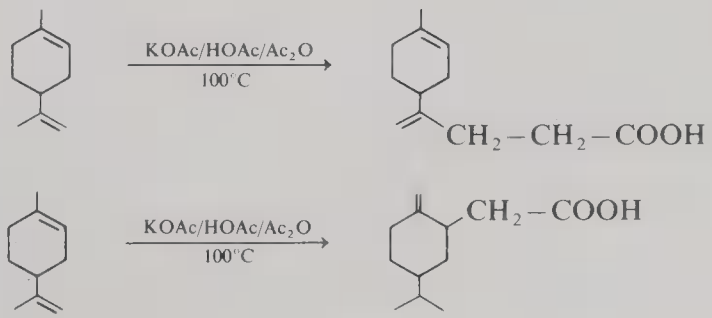
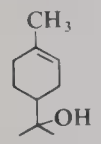
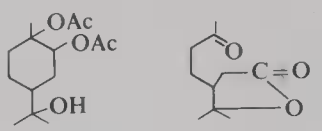
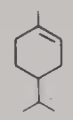
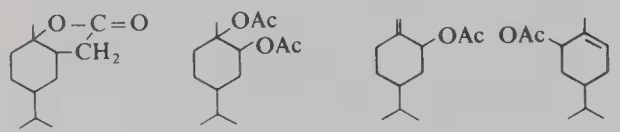
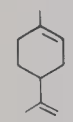
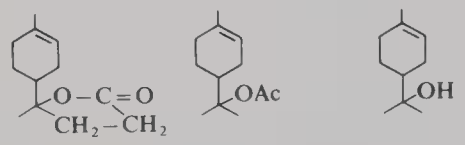
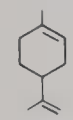
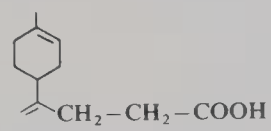
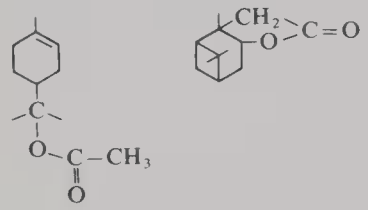
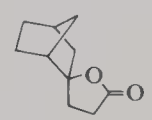
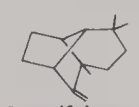
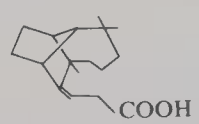
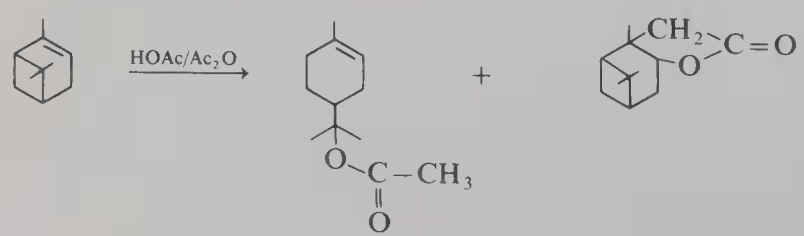


TABLE XX. Oxidation of Terpenes

Substrate	Product	Condition	Reference
 α-Terpineol		*a*	126
 *d*-Carvomenthene		*b*	44
 *d*-Limonene		?	127
 *d*-Limonene		*c*	128
 α-Pinene		*d*	48
 β-Pinene	No reaction (Wagner–Meerwein faster)	*c*	46
 Camphene		*c*	46
 Longifolene	 Unsaturated acid	*c*	46

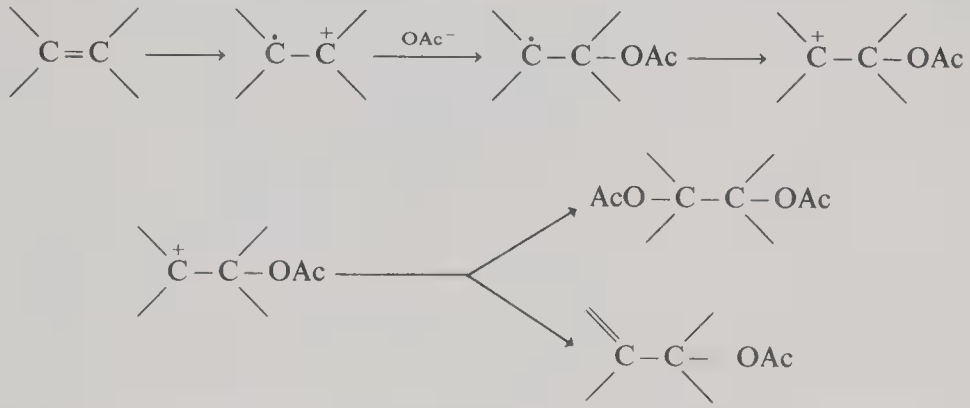
[a] Mn(III) dissolved in HOAc; add olefin in one portion; $T = 100°C$.
[b] Olefin dissolved in HOAc; add Mn(III) in small portions; $T = 100°C$.
[c] Mn(III) dissolved in KOAc/HOAc/Ac_2O; add olefin dropwise; $T = 100°C$.
[d] Olefin dissolved in HOAc/Ac_2O; add Mn(III) in small portions; $T = 110$–$130°C$.

When α-pinene is oxidized in acetic acid/anhydride the major product is α-terpineol-acetate, the lactone being formed in only minor amounts:



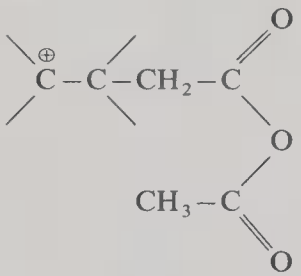
In contrast, β-pinene does not react with manganese (III) in KOAc/HOAc/Ac_2O mixtures, since at reflux it readily undergoes Wagner–Meerwein rearrangement to the saturated acetate.[46] Camphene and longifolene are readily substituted by carboxymethyl radical, leading to the lactone and unsaturated acid, respectively.

A rationale of these observations is that terpene structures that are sterically hindered to carboxymethylene radical addition and/or have relatively low oxidation potentials are preferentially oxidized at the double bond to a cation radical. This is substituted by an acetoxy ion with formation of a neutral radical which will be oxidized to a carbenium ion. This may form the diacetate, or eliminate a proton with formation of unsaturated acetates:

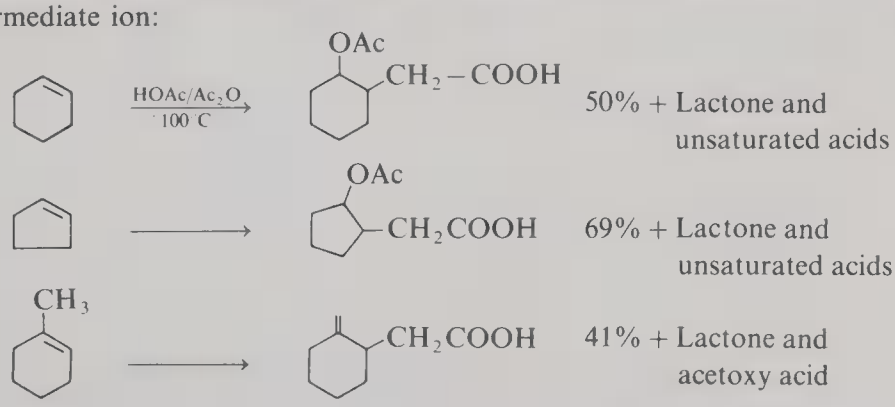


Of course some of the unsaturated acetates may also be formed from disproportionation of the intermediate acetoxy radical, or by allylic abstraction of the parent substrate.

Formation of the lactone versus the unsaturated acid will depend on the presence of acetic anhydride and steric requirements for lactonization. The adduct carboxymethylene carbenium ion is less prone to lactone cyclization than the free acid, assuming that in the presence of acetic anhydride carboxymethylene anhydride radicals are the major primary radicals formed with Mn(III) acetate.

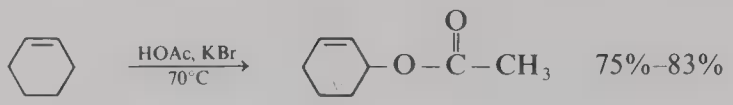


That steric and electronic factors play a part in the ease of addition of carboxymethylene radicals on cyclic olefins and subsequent reactions is demonstrated by Okano.[128,39] Thus, cyclohexene, 1-methylcyclohexene, and cyclopentene all form adducts with carboxymethyl radicals from Mn(III) acetate, although earlier work[117] indicates that cyclohexene does not react with Mn(III) acetate. The major product from each substrate depends on the stability of the intermediate ion:

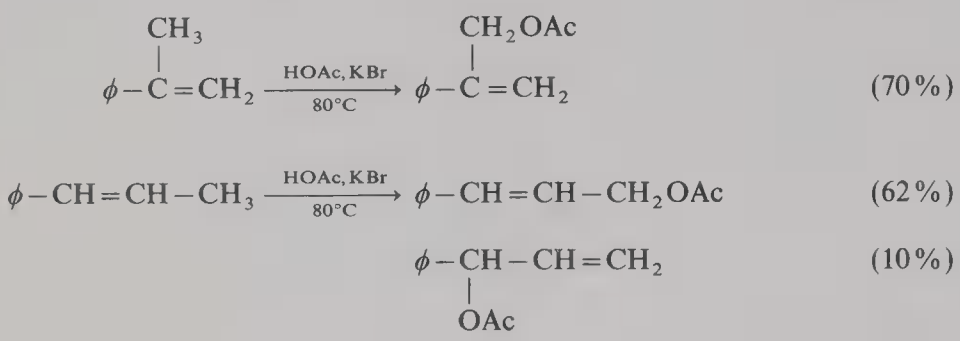


However, no diolacetates are mentioned and only small amounts of allylic acetates.

In the presence of KBr the major products from cyclohexene and cyclopentene are their respective allylacetates[129] indicating initial hydrogen atom abstraction and further oxidation of the intermediate radical:



Further examples of this reaction are given by Kasahara[130] in the allylic oxidation of α- and β-methylstyrene by Mn(III)/KBr at 80°C:

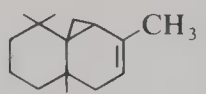


No lactones were found. Indeed, at 80°C very few carboxymethylradicals will be formed in acetic acid.

Olefins with low oxidation potentials are completly converted to the diol acetate by Mn(III) acetate in acetic acid, as exemplified by the oxidation of *cis*- or *trans*-stilbene[131,132]:

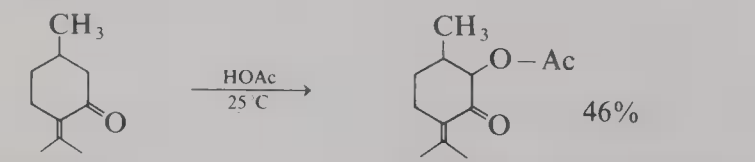
Cis or *trans* — *Meso*, *dl* mixture

Thujopsene, although readily oxidized by Pb(IV) and Tl(III) acetate does not react with Mn(III) acetate[133]:

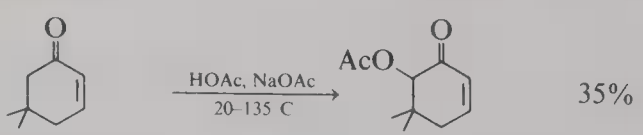


Thujopsene

Further examples of relatively unaffected double bonds are found in the oxidation of pulegone[134] and some other substituted cyclohexenones.[135] Clearly the ketone function activates these molecules, giving rise to ready oxidation to the respective α-ketone-acetates.



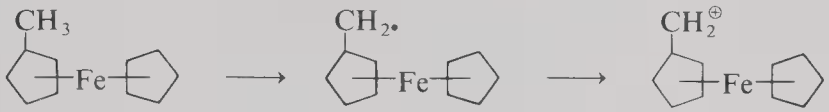
Pulegone — *Cis* + *trans* acetoxypulegone



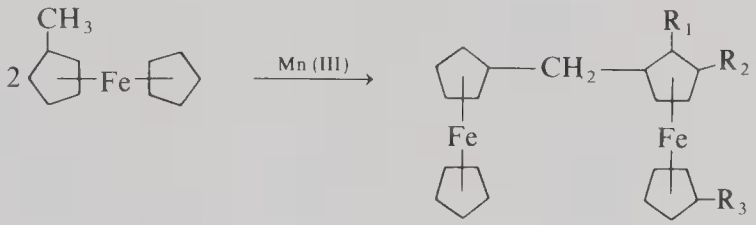
Saturated hydrocarbons can be oxidized by Mn(III) acetate to mixtures of hydrocarbon acetates or other esters, depending on the carboxylic acid used as solvent. Thus adamantane

can be oxidized to 1-adamantyl acetate in 80% yield[136,137] by refluxing in an acetic acid–acetic anhydride mixture.

In an interesting study of Onopchenko[138] and Schulz the oxidation of cyclohexane with Mn(III) and CO(III) acetate in presence or absence of nucleophiles or Cu(II) acetate is compared (Table XXI). Mn(III) is a much more selective oxidant. As a main product cyclohexylacetate is formed. When KOAc is added as a nucleophile cyclohexylmethylacetate is formed in increasing amounts at higher KOAc levels. With Cu(II) acetate and NaOAc added cyclohexenylacetate is found as a major product. There is no simple explanation how this is formed. Although aromatic in character, methylferrocene reacts with Mn(III) acetate with formation of a mixture of products arising from ferrocenylmethylation of methylferrocene.[139] In a primary step carboxymethyl radicals abstract hydrogen from the methyl group. The resulting methylene radical is rapidly oxidized by a second Mn(III) acetate to the carbenium ion, which substitutes on excess methylferrocene:



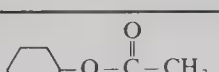
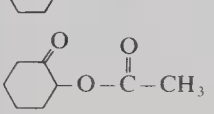
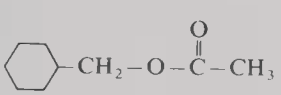
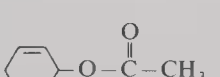
The net reaction is represented by



	R_1	R_2	R_3
I	CH_3	H	H
II	H	CH_3	H
III	H	H	CH_3

Remarkably the carbenium ion does not lead to methylferrocenyl acetate, neither is methylferrocene substituted by carboxymethylradicals.

TABLE XXI. Oxidation Products of Cyclohexane with Mn(III) Acetate in Dependence of Added Nucleophiles and Cu(II) Acetate[a] (80°C, Acetic Acid Solvent)

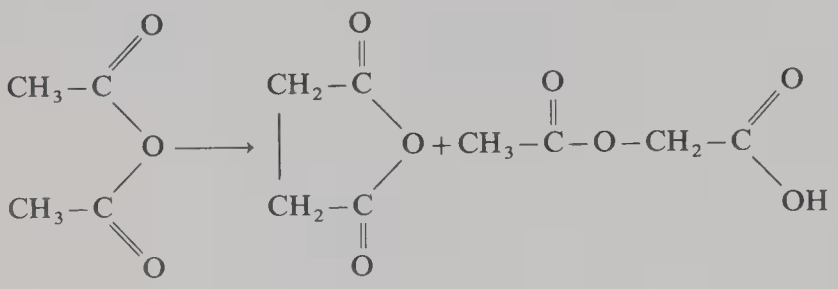
Product	Mn(III)	Mn(III)/ KOAc	Mn(III)/ Cu(II)	Mn(III)/ Cu(II)/ NaOAc	Co(III)
	86	52	63	30	32
	9	7	—	—	10
	3	41	—	3	50
	—	—	—	67	—

[a] Reference 138.

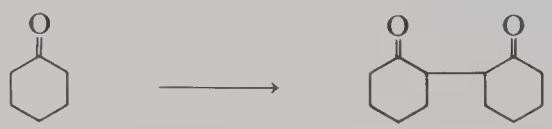
8.10. Carbonyl-Containing Compounds

Compounds that contain enolizable carbonyl groups are readily oxidized to α-keto radicals. In the absence of olefins or aromatics and depending on reaction conditions these radicals can be further oxidized or couple to dimers. Thus, at high Mn(III)/substrate ratios in the presence of acetic acid mostly acetates are formed.[76,140,24] Dimer formation is favored at low Mn(III)/substrate ratios, high temperatures, and absence of acetic acid.[140,24]

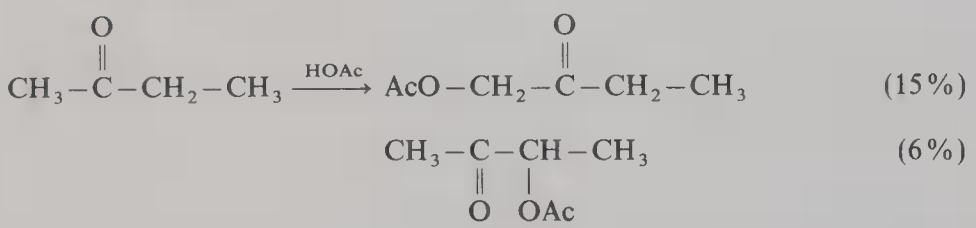
The oxidation of acetic anhydride yields succinic anhydride and acetoxyacetic acid[137,24]:



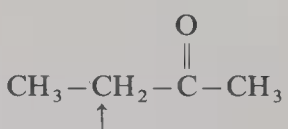
The reaction is greatly accelerated by acids and base.[24] Acetic acid favors formation of acetoxyacetic acid. Various ketones give mixtures of 1,4-diketo-derivatives and α-keto-acetates.[89,76,140,105] In the presence of acetic acid dimer formation is low. Thus, cyclohexanone yields 8% and acetone 9%–35% of its dimer.[76,140]



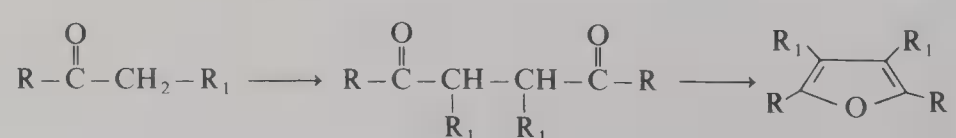
At low Mn(III)/acetone ratios, 140°C, and in the absence of acetic acid, yields of up to 80% 2,5-hexanedione can be reached from acetone.[141] In asymmetric methyl-ethylketone preferential oxidation is at the methyl group[76] (also see Section 5.1):



This does not confirm with an acid-catalyzed enolization as a primary step to oxidation where it is known that acid-catalyzed halogenations often occur at the higher substituted position in asymmetric ketones[142]:

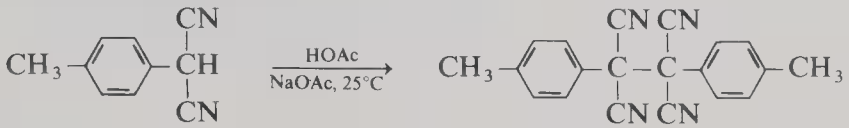


Addition of KOAc and KBr greatly enhances acetate formation. Thus acetone is oxidized to acetoxy acetone in good yields,[140,143] and no dimers are formed. α-Bromoacetone was shown to be an intermediate. With benzyl ketones the dimers formed are converted to dihydrofurans in the course of the reaction[143]:

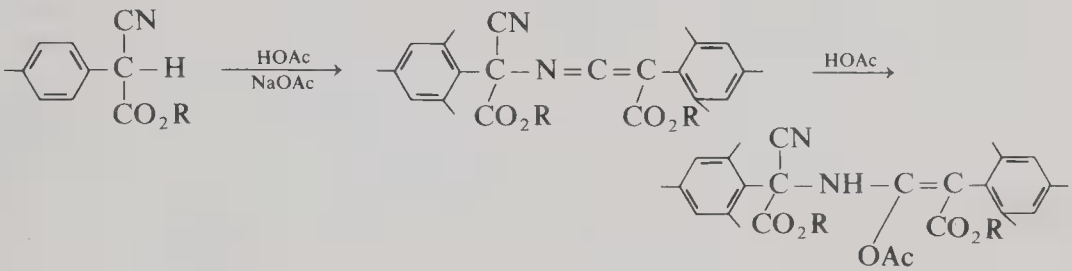


8.11. Oxidative Coupling of $-\overset{|}{\underset{|}{C}}-$ H Active Substrates

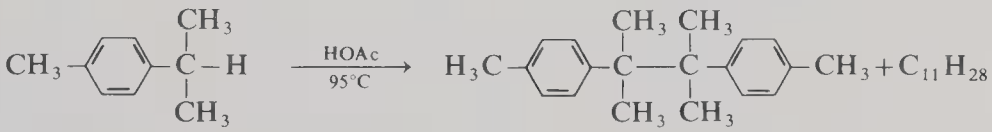
Arylmalodinitriles and arylcyanoacetic esters are readily coupled by Mn(III) acetate[144] in acetic acid in the presence of added NaOAc:



Sterically hindered arylcyanoacetic acid esters such as methylcyanoacetic ester form ketene imine instead, which is solvolyzed by acetic acid:



Onopchenko and Schultz[119] demonstrated that also less activated benzyl compounds can be oxidatively coupled; the major product from this reaction, however, is an unidentified product:



9. SYNTHETIC PROCEDURES

9.1. Synthesis of Anhydrous Manganese (III) Acetate

According to Hessel[7] a suspension of 34.6 g of powdered anhydrous $Mn(OAc)_2$ and 7.9 g of powdered $KMnO_4$ is shaken in 150 ml glacial acetic acid in a closed vessel until all solids have dissolved (30 min). The solution is filtered through a G_3 filter, 30 ml of acetic anhydride is added, and the mixture is heated to 75°C for 2 h. Then the mixture is allowed to cool to room temperature and after 24 h the dark brown crystals are collected on a glass filter. To remove potassium acetate the crystalline product is carefully washed with 100 ml warm glacial acetic acid. The product is dried for 2 h *in vacuo* at 50°C, yield 49 g (90%).

The product may be further purified as follows (e.g., for kinetic work): 40 g manganese (III) acetate is dissolved in a mixture of 150 ml HOAc and 7 ml H_2O by gentle warming. The mixture is filtered, 45 ml acetic anhydride is added, and it is warmed for 4 h at 70°C. Then the mixture is allowed to cool to room temperature, the precipitate is filtered on a glass filter, washed with 100 ml warm glacial acetic acid, and dried at 50°C *in vacuo* for 2 h, yield 32 g (80%).

Typical analysis of the crude product: 25.3% Mn, 72.0% OAc; calculated for $Mn_3(OAc)_8OH$: 25.2% Mn, 72.2% OAc.

According to de Klein[1] the following modified procedure may be used: 4.1 g powdered $KMnO_4$, 18 g powdered $Mn(OAc)_2$, 30 ml acetic anhydride, and 400 ml glacial acetic acid

are stirred in a round-bottomed flask at 50°C until all solids have completely dissolved (3 h). Half of the acetic acid is evaporated at reduced pressure (12 mm Hg) on a rotary evaporator. After 24 h the precipitated dark brown solids are collected on a glass filter, washed three times with warm (50°C) acetic acid to remove potassium acetate, and dried *in vacuo* for 2 h at 50°C.

Typical analysis of the crude product: 24.01% Mn (jodometric), 24.0% Mn (complexometric), 73.7% OAc. The material is free of manganese (II) acetate.

9.2. Synthesis of Manganese (III) Acetate Dihydrate

According to Christensen[3] and Brauer[19] 19.6 g powdered $Mn(OAc)_2 \cdot 4H_2O$ is added to 200 ml glacial acetic acid. To the well-stirred mixture 3.1 g powdered $KMnO_4$ is added in small portions.

The mixture is allowed to cool to room temperature and 3 ml of water is added. After 24 h the cinnamon brown crystalline precipitate is collected on a glass filter and washed with glacial acetic acid. 30 g of the product is dissolved in 200 ml glacial acetic acid with gentle warming and filtered. After allowing it to cool to room temperature, 3 ml of water is added. The cinnamon brown crystalline product is collected on a glass filter and dried over CaO. When the product does not crystallize, more water (1–3 ml per 200 ml solution) is added and the wall of the glass container is scratched.

9.3. Oxidation of α-Methylstyrene with Manganese (III) Acetate to γ-Methyl-γ-phenyl Butyrolactone[20]

A mixture of 360 ml of acetic acid, 180 ml of acetic anhydride, 45 g of α-methylstyrene, and 80 g of $Mn(OAc)_3 \cdot 2H_2O$ was heated to reflux until the dark brown color of manganese (III) acetate had completely disappeared (45 min). After cooling to room temperature, the manganese (II) acetate was removed by filtration and the filtrate was distilled to afford 19 g of γ-methyl-γ-phenyl butyrolactone, bp 104–106°C (0.1 mm).

9.4. Oxidation of Decene-1 with *in Situ* Prepared Manganese (III) Acetate to γ-*n*-Octylbutyrolactone[23]

For preparative purposes it is sometimes convenient to use manganese (III) acetate generated *in situ* from $KMnO_4$ and Mn(II) acetate tetrahydrate without isolating and purifying the oxidant. In a typical experiment, 212 g (0.84 mol) of manganous acetate tetrahydrate was dissolved in 1200 ml of glacial acetic acid by raising the temperature to 90°C. At this temperature, 32 g (0.2 mol) of $KMnO_4$ was added with stirring. When the exothermic reaction had subsided the temperature was allowed to drop to 90°C. Then 300 ml of acetic anhydride was added followed by 500 g of sodium acetate. Eighty-four grams (0.6 mol) of decene-1 was added, and the reaction mixture was refluxed ($\sim$130°C) until the brown color of trivalent manganese had disappeared (approximately 1 h). Extraction and distillation yielded 66.4 g of the pure lactone, γ-*n*-octylbutyro-lactone, bp 106°C (1.0 mm), which represented a 67% yield based on $KMnO_4$.

In an alternate procedure, 110 g of manganous diacetate dihydrate was dissolved in a solution containing 700 ml of glacial acetic acid, 75 g of potassium acetate, and 75 g of acetic anhydride. The mixture was heated to 95°C, at which point 19 g of $KMnO_4$ were added. The resulting manganic acetate solution was then used for the preparation of various lactones.

9.5. Oxidation of Norbornene with Manganese (III) Acetate to the Corresponding Lactone (2-Oxo-3-methylene-4,7-methanobenzofuran)[30]

The following is an example of the acetic acid–acetic anhydride–sodium acetate procedure. It is applied to effect the transformation of norbornene to its respective γ-butyrolactone. In a 1-liter round-bottom flask equipped with a condenser and covered with aluminium foil were added the following: Mn(III) $(OAc)_3 \cdot 2H_2O$ (26.8 g, 0.10 mol), NaOAc (100 g), 100% AcOH (300 ml), Ac_2O (30 ml), and norbornene (5.7 g, 61 mmol). The mixture was heated under reflux in an argon atmosphere for 1 h 30 min, after which the AcOH was removed by distillation, and the reaction mixture allowed to cool to room temperature; 500 ml of water was added and the mixture was extracted with ether (3×150 ml). The ethereal extract was washed with water (until pH 4) with a saturated sodium bicarbonate solution, and again with water and dried over $MgSO_4$. Evaporation to dryness resulted in 5.3 g of the crude extract which was chromatographed on a 250 g silicic acid column suspended in PE-E (75:25). The compounds eluted were unidentified products (0.70 g, 1.5 liter PE-E 75:25) and 3.6 g of the expected lactone [47% based on intake Mn(III) $(OAc)_3 \cdot 2H_2O$].

9.6. Synthesis of a α-Cyano-γ-butyro Lactone Derived from an Olefin and Cyanoacetic Acid[23]

The Mn(III) acetate mediated addition of cyanoacetic acid to an olefin is given in the next example. Owing to the large reactivity of cyanoacetic acid the reaction can be performed in acetic acid: 0.4 mol of cyanoacetic acid dissolved in 1 liter of acetic acid containing 10% KOAc was reacted with 0.1 mol of $Mn(OAc)_3 \cdot 2H_2O$ and 0.2 mol of olefin at 50°C. After 1 h most of the acetic acid was removed on a rotary evaporator, water was added, and the residue was extracted several times with ether. The ethereal layers were combined, washed with aqueous sodium carbonate, and dried over anhydrous magnesium sulfate. After filtration the ethereal solvent was stripped off. The yields of α-cyano γ-butyro lactones obtained were generally in the 40%–60% range based on oxidant consumed.

9.7. Oxidation of 1-Octene with Manganese (III) Acetate/Copper (II) Acetate to 4-Decenoic Acid[27]

In the presence of Cu(II) acetate 4-alkenoic acids are formed as major product with some 3-alkenoic acid as a side product. An example of a reaction procedure is given: to 300 ml of acetic anhydride, kept at 119°C, 0.2 mol of 1-octene (224 gram) and 0.005 mol of $Cu(OAc)_2 \cdot H_2O$ and water (1 gram) are added. The solution is kept under a nitrogen atmosphere and stirred well; 0.1 mol of manganese (III) acetate is slurried in 200 ml of acetic anhydride and added to the solution in small portions. After 40 min, when all manganese (III) acetate is added the reaction mixture is cooled to room temperature. The precipitated manganese (II) acetate is filtrated and the filtrate is distilled to remove acetic anhydride and unconverted 1-octene. Usually 70%–75% of *n*-octene is unconverted. To the residue are added 100 ml of acetic acid and 10 ml of water. The mixture is heated at 100°C for 1 h. Acetic acid and water are then removed by distillation and the residue is weighed and analyzed for reaction products; 4-decenoic acid (63%) 3-decenoic acid (7.9%), decanoic acid (2%), and only traces of lactone and 4-acetoxy acid are found. The residue may be further distilled to yield the unsaturated acids. These can be separated on a $AgNO_3$-impregnated silicagel column with *n*-hexane-ethylacetate (99:1 v/v) as eluent.

9.8. Conversion of 1-Octene with Manganese (III) Acetate to Decanoic Acid[22]

Under appropriate conditions Mn(III) acetate can be used as a free radical initiator to effect the addition of acid anhydrides to α-olefins in a chain reaction. This results in the synthesis of straight chain or α-branched carboxylic acids. A typical example of a reaction procedure is given: to 300 ml of acetic anhydride, kept at 122°C, a slurry of 0.025 mol of anhydrous manganese (III) acetate in 200 ml of acetic anhydride and 0.2 mol of *n*-octene are added simultaneously. The reaction mixture is kept under a nitrogen atmosphere and well stirred. The slurry is added at such a rate that the reaction mixture remains colorless. After 3 h, when all *n*-octene and manganese (III) acetate have been added, the reaction mixture is cooled to room temperature. The precipitated manganese (II) acetate is filtered and the filtrate is distilled to remove acetic anhydride and unconverted *n*-octene. To the residue are added 100 ml of acetic acid and 10 ml of water. This mixture is heated at 110°C for 1 h. Acetic acid and water are then removed by distillation and the residue is distilled further, yielding 0.1 mol of decanoic acid, i.e., 400% with respect to intake Mn(III) acetate.

9.9. Oxidative Addition of an Aldehyde to an Olefin with Mn(III) Acetate in the Presence of Cu(II) Salts. General Procedure[59] for the Preparation of Unsaturated Aldehydes

A mixture of 1 mol aldehyde, 0.2 mol olefin, 0.1 mol $Mn(OAc)_3 \cdot 2H_2O$, and 0.01 mol $Cu(OAc)_2 \cdot H_2O$ is shaken in 40 ml glacial acetic acid in a closed vessel at 55–60°C until the brown color of manganese (III) acetate has disappeared (1–2 h). The reaction product is allowed to cool to room temperature, 100 ml water is added, and the mixture is extracted with ether.

After washing the collected ethereal layers and drying over $MgSO_4$ the products are isolated by fractional distillation. Depending on olefin and aldehyde employed it may be useful to distill unconverted olefin, aldehyde, and acetic acid before extraction with ether. All operations should be carried out in a nitrogen atmosphere.

For the preparation of ketones a similar procedure is used but without acetic acid and Cu(II) acetate added. For the preparation of mixtures of saturated aldehydes and γ-acetoxy saturated aldehydes the procedure is used with added acetic acid but without Cu(II) acetate. The procedure has to be optimized for each aldehyde–olefin couple. Telomerization and oxidation of the intermediate adduct radicals can be obviated by working at low olefin and Mn(III) concentrations.

9.10. Addition of Cyclopentanone to Isobutylene with Mn(III) Acetate to 2-Isobutylcyclopentanone[72]

A mixture of 42 g of cyclopentanone, 5.6 g of isobutylene, 30 ml of heptane, and 13.4 g of Mn(III) acetate dihydrate is shaken in a sealed tube at 40°C until the dark brown color of Mn(III) acetate has disappeared (24 h). The tube is cooled and opened and allowed to come to room temperature to remove excess isobutylene. Precipitated manganese (II) acetate is filtered and the filtrate is distilled to yield 3.5 g 2-isobutylcyclopentanone bp 43°C (1 mm Hg).

9.11. Mn (III) Acetate-Initiated Addition of Acetone to 1-Hexene. Formation of Methyl-heptylketone[28]

A solution of manganese (III) acetate is prepared by adding 2.5 mmol of finely powdered potassium permanganate in small portions to 10 mmol of manganese (II) acetate

tetrahydrate in 3.3 mol of acetic acid containing 0.05 mol acetic anhydride. The mixture is well stirred at ambient temperature for 1 h. The solution is transferred to a dropping funnel and added dropwise over 5 h to a solution of hexene-1 (0.1 mol) in acetic acid (0.17 mol) and 1.4 liter of acetone heated under reflux and stirred well. The reaction mixture is allowed to cool to room temperature and precipitated manganese (II) acetate is filtered. Excess acetone is removed by distillation, water is added to the residue, and this is extracted with ether. The residue obtained by distillation of the dried, combined ether extracts is distilled and yields 41 mmol of methyl *n*-heptylketone, i.e., 330% based on intake Mn(III) acetate.

9.12. Oxidative Addition of Acetylacetone to α-Methylstyrene with Mn(III) Acetate to 2,5-Dimethyl-3-acetyl-5-phenyl-dihydrofuran[78]

0.25 mol of $Mn(OAc)_3 \cdot 2H_2O$ is dissolved in 1 liter of glacial acetic acid at 45°C in a nitrogen atmosphere. A mixture of 0.13 mol of α-methylstyrene (15.3 g) and 0.75 mol of acetylacetone (75 g) is added. After 10 min the brown color of manganese (III) acetate disappears and the reaction mixture is allowed to cool to room temperature. Precipitated manganous acetate is filtered and excess acetic acid is distilled off. Water is added and the product dihydrofuran is isolated by extraction with ether followed by distillation.

9.13. Addition of Cyclohexanone to Isopropenylacetate with Mn(III) Acetate to 2-Acetonyl-cyclohexanone[77]

0.5 mol of manganese (III) acetate dihydrate is dissolved in 500 ml of acetic acid at 70°C. To this solution 0.5 mol of cyclohexanone and 0.5 mol of isopropenylacetate are added. After 10 min the brown color of Mn(III) acetate disappears and the reaction product is allowed to cool to room temperature. Precipitated manganous acetate is filtered, excess acetic acid is distilled off, and water is added. The mixture is extracted with ether and distilled, yielding 8 g of 1,4-diketone [22% based on manganese (III) acetate].

9.14. Mn(III) Acetate-Initiated Addition of Carbontetrachloride to 1-Octene with Formation of 1,1,1-Trichloro-3-chlorononane[84] from 1-Octene, Carbontetrachloride, and $Mn(OAc)_3$

A 2-liter autoclave equipped with an efficient stirrer is charged with 100 ml of acetone, 900 ml of carbontetrachloride, 4.6 g of anhydrous manganese (III) acetate, and 22.4 g of 1-octene. The reaction mixture is heated in a nitrogen atmosphere at 120°C for 75 min. After cooling to room temperature any precipitated material is filtered off and excess carbon tetrachloride and acetone are distilled. The residue is further distilled under reduced pressure and yields 45 g of 1,1,1-trichloro-3-chloro-nonane [85% on added Mn(III) acetate].

9.15. Oxidative Addition of Acetone to Benzene with Manganese (III) Acetate to Yield Methylbenzyl Ketone[68] from Benzene, Acetone, and $Mn(OAc)_3$

116 g of acetone, 39 g of benzene, and 27 g of manganese (III) acetate dihydrate were heated in a nitrogen atmosphere in 100 ml of acetic acid at 70°C. After 4.5 h the reaction mixture was allowed to cool to room temperature and precipitated manganese (II) acetate was filtered off. Unreacted acetone, benzene, and acetic acid were distilled and to the residue water was added. The resulting mixture was extracted with ether and the collected ether fractions dried over $MgSO_4$ and distilled yielding 2.4 g of methylbenzylketone [36% on the basis of intake Mn(III) acetate] bp 50–52°C (1 mm Hg).

9.16. Oxidative Addition of Nitromethane to Benzene with Manganese (III) Acetate to Yield Phenylnitromethane[91]

Manganese (III) acetate dihydrate (0.01 mol) was dissolved in glacial acetic acid (25 ml) at 70°C. Benzene (25 ml) and nitromethane (25 ml) were added and the mixture was heated to 83°C under a nitrogen atmosphere while stirred well until the brown color of manganese (III) acetate had disappeared (2 h). The reaction mixture was allowed to cool to room temperature, precipitated manganese (II) acetate was filtered off, and the filtrate was washed with water. The organic layer was dried over anhydrous sodium sulfate and distilled yielding 78% phenyl nitromethane.

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5

Oxidations by Cobalt Compounds

Fillmore Freeman

1. INTRODUCTION

Transition metal organometallic chemistry has been one of the most active areas of chemical research for the past 25 years.[1–26] A significant part of this academic and industrial research has been concerned with the use of transition metal organometallics in organic synthesis. Although the majority of the processes utilized industrially involve catalysis by metal complexes, an increasing variety of catalytic processes are being developed for conventional laboratory syntheses. Moreover, since catalytic processes are generally more selective and do not produce large amounts of inorganic compounds which are difficult to dispose of, this discussion of cobalt oxidations will include catalytic processes and traditional stochiometric oxidation procedures.

The redox potential (E_0) for $Co(III) + e \rightarrow Co(II)$ is 1.82 V in aqueous solution. Redox potentials are influenced by the nature of the ligands and the solvent. It appears that the redox potentials for cobalt complexes in organic solvents are not yet available.

Among the cobalt compounds included in this discussion are cobaltous acetate [$Co(OAc)_2$], acetabromocobalt(II) [Co(OAc) Br], cobaltic acetate [$Co(OAc)_3$], cobaltic trifluoroacetate [$Co(O_2CCF_3)_2$], cobalt carboxylates, hydridodinitrogentris(triphenylphosphine) cobalt(I) [$CoH(N_2)[P(C_6H_5)_3]_3$, **1**], cobaltacene [$Co(\eta^5-C_5H_5)_2$, **2**], cobalticenium ion [$Co(\eta^5-C_6H_5)_2^+$, **3**], the oxygen adduct of cobaltacene (**4**), dicobaltoctacarbonyl ($Co_2(CO_2)_8$, **5**, also **6** in solution], μ-peroxo complexes (e.g., **7**, $L = NH_3$), superoxo complexes (e.g., **8**), *N*,*N*′-ethylenebis(acetylacetoniminato)cobalt(II) [Co(acacen), **9**], *N*,*N*′-ethylenebis(salicylideneiminato)cobalt(II) [(Salen) Co(II), Salcomine, **10**), and polymer supported cobalt catalysts. Owing to the extensive literature references[27–33] and vigorous experimental conditions, examples of dicobalt octacarbonyl (**5**, **6**) hydroformylation of olefins will not be discussed.

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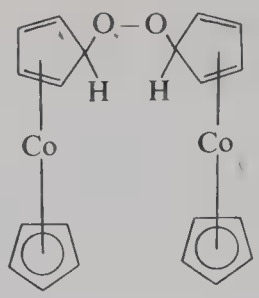

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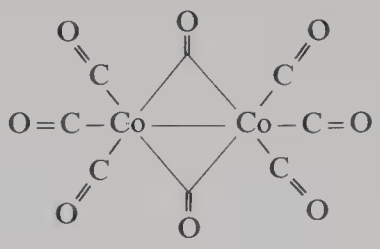

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$(OC)_4Co-Co(CO)_4$

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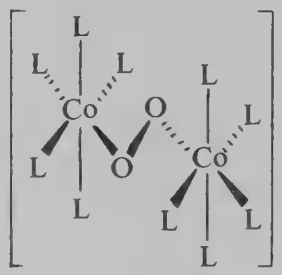

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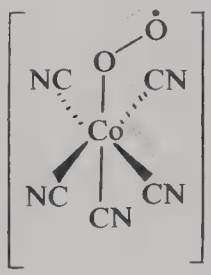

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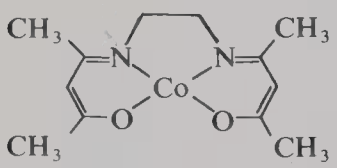

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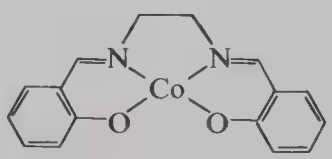

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2. MECHANISMS

2.1. Carbon–Hydrogen Bonds

2.1.1. Alkanes and Cycloalkanes

The autoxidation of alkanes and cycloalkanes, which is facilitated by the presence of cobalt compounds, involves alkyl hydroperoxides as intermediates. Autoxidation proceeds via a free radical chain mechanism. Although autoxidations may be performed without a metal catalyst, a radical initiator (ROOH, ROOR) may be added. Alkyl hydroperoxides may be oxidized [Eq. (2)] or reduced [Eq. (3)] by metal complexes. Thus, since cobalt(II) and cobalt(III) are of comparable stabilities, alkyl hydroperoxides are concurrently oxidized and reduced in the presence of cobalt [Eq. (4)]. This catalytic decomposition of alkyl hydroperoxides leads to alkoxy and alkylperoxy radicals.[31–37] The relative rates of Eqs. (2) and (3) are solvent dependent.[33,37] The cobalt catalyzed decomposition of *tert*-butyl hydroperoxide in chlorobenzene has been studied [Eq. (5)].[36]

$$\mathrm{R-\overset{|}{\underset{|}{C}}-H + O_2 \longrightarrow R-\overset{|}{\underset{|}{C}}-O-OH} \qquad (1)$$

$$\mathrm{R-O-OH + Co(III) \longrightarrow R\dot{O}_2 + Co(II) + H^+} \qquad (2)$$

$$\mathrm{R-O-OH + Co(II) \longrightarrow R\dot{O} + Co(III) + {}^-OH} \qquad (3)$$

$$2R-O-OH \xrightarrow[Co(III)]{Co(II)} R\dot{O} + R\dot{O}_2 + H_2O \tag{4}$$

$$CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-O-OH \xrightarrow{Co(II)} O_2 + CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-OH + CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-O-O-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-CH_3 \tag{5}$$

In these catalyzed autoxidations, there is competition between the cobalt ion induced and radical induced decompositions of alkyl hydroperoxides. Thus, chain initiation may occur via cobalt catalyzed decomposition of the alkyl hydroperoxide under autoxidizing conditions,[34] or via oxidation of Co(II) to Co(III).[35] The concentration of Co(III) reaches a maximum which coincides with the formation of aldehydes in the oxidation mixture. The decrease in the concentration of Co(III) after the maximum is explicable in terms of Eq. (6).[35]

$$R-\overset{\displaystyle O}{\overset{\|}{C}}-H + Co(III) \longrightarrow R-\overset{\displaystyle O}{\overset{\|}{C}}\cdot + Co(II) + H^+ \tag{6}$$

The mechanism for the cobalt oxidation of *n*-butane to acetic acid is shown in Eqs. (7)–(11),[38–48] The 2-butyl hydroperoxide that forms initially [Eqs. (8), (11)] affords the ultimate oxidation products in many different ways. Catalytic decomposition by cobalt salts gives $C_4H_9\dot{O}$ and $C_4H_9\dot{O}_2$ radicals that replace radicals lost by chain termination processes and thereby sustain the oxidation cycle. A β-cleavage of the 2-butoxy radical provides one

$$CH_3CH_2CH_2CH_3 + Co(III) \longrightarrow CH_3CH_2\dot{C}HCH_3 + Co(II) + H^+ \tag{7}$$

$$CH_3CH_2\dot{C}HCH_3 + O_2 \longrightarrow CH_3CH_2\underset{\displaystyle OO\cdot}{\overset{|}{C}}HCH_3 \tag{8}$$

$$CH_3CH_2\underset{\displaystyle OO\cdot}{\overset{|}{C}}HCH_3 + Co(II) \longrightarrow CH_3CH_2-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3 + Co(III)\,OH \tag{9}$$

$$CH_3CH_2-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3 + O_2 \longrightarrow CH_3-\underset{\displaystyle O}{\overset{\displaystyle OOH}{\underset{\|}{\overset{|}{C}}}}-CHCH_3 \tag{10}$$

$$CH_3CH_2CH_2CH_3 + O_2 \longrightarrow CH_3CH_2\underset{\displaystyle OOH}{\overset{|}{C}}HCH_3 \tag{11}$$

pathway for C–C bond fission [Eq. (12)]. The acetaldehyde intermediate is easily oxidized to acetic acid *(vide infra)*. Other reasonable C–C bond fission mechanisms are shown in Eqs. (13) and (14).[44]

$$CH_3CH_2\underset{\displaystyle OOH}{\overset{|}{C}}HCH_3 \xrightarrow{Co(II)} CH_3CH_2\underset{\displaystyle O\cdot}{\overset{|}{C}}HCH_3 \longrightarrow CH_3CHO + \dot{C}_2H_5 \tag{12}$$

$$CH_3-\overset{\overset{O}{\|}}{C}-\overset{\overset{OO\cdot}{|}}{CH}CH_3 \longrightarrow CH_3-\overset{\overset{O}{\|}}{C}\cdot + CH_3CO_2H \qquad (13)$$

$$CH_3CH_2\overset{\overset{OOH}{|}}{C}HCH_3 \xrightarrow{Co(III)} CH_3\overset{\overset{O-\!-O}{|}}{C}H_2-CHCH_3 \longrightarrow CH_3CHO + C_2H_5\dot{O} \qquad (14)$$

The beneficial effect of 2-butanone addition is due in part to its conversion to the α-hydroperoxide which can oxidize cobalt(II) to cobalt(III) [cf. Eqs. (3), (9), (10)].

In order to eliminate the induction period in the autoxidation process, ozone may be used to preoxidize part of the cobalt(II) salt to a μ_3-oxo bridged trimer $[Co_3(OAc)_6(AcOH)_3]$ which is a good initiator.[45]

The oxidizing activity of cobaltic acetate in acetic acid is enhanced by strong acids to such an extent that the *n*-alkanes can be oxidized at low temperatures.[49–52] Acetate esters or alkyl chlorides are formed under nitrogen while ketones are mainly produced if dioxygen is present [Eq. (15c)].[49] A combination of trifluoroacetic acid and carbon tetrachloride also gives the alkyl chloride. Thus, trichloroacetic acid acts not only as a strong acid, but also as a source of chlorine atoms.[49] Interestingly, tertiary carbon–hydrogen bonds are oxidized at significantly lower rates than secondary C–H bonds [Eq. (17)].[52] Unusual selectivities have also been reported for the liquid phase autoxidation of alkanes in the presence of $Co(OAc)_3$.[40,53–55]

$$n\text{-}C_7H_{16} + Co(OAc)_3 \xrightarrow[N_2]{CF_3CO_2H,AcOH} CH_3(CH_2)_4-\overset{\overset{OAc}{|}}{C}H-CH_3 \quad 81\%\text{ selectivity} \qquad (15a)$$

$$n\text{-}C_7H_{16} + Co(OAc)_3 \xrightarrow[N_2]{CCl_3CO_2H,AcOH} CH_3(CH_2)_4-\overset{\overset{Cl}{|}}{C}H-CH_3 \quad 80\%\text{ selectivity} \qquad (15b)$$

$$n\text{-}C_7H_{16} + Co(OAc)_3 \xrightarrow[O_2]{CF_3CO_2H,AcOH} CH_3(CH_2)_4-\overset{\overset{O}{\|}}{C}-CH_3 \quad 83\%\text{ selectivity} \qquad (15c)$$

$$CCl_3CO_2H + R^{\cdot} \longrightarrow R-Cl + \dot{C}Cl_2CO_2H \qquad (16)$$

$$(CH_3)_2CHCH_2CH_2CH_3 + Co(OAc)_3 \xrightarrow[AcOH,N_2]{CCl_3CO_2H} (CH_3)_2CHCH_2-\overset{\overset{Cl}{|}}{C}H-CH_3 \quad 74\%\text{ selectivity} \qquad (17)$$

2-Methylpropane is less reactive toward $Co(OAc)_3$ than *n*-butane and no kinetic isotope effect was observed with deuterated alkanes. These data are at variance with a mechanism simply involving hydrogen atom abstraction by a free radical in the rate-determining step. Moreover, the higher oxidation potential of *n*-butane versus 2-methylpropane suggests that the former should be oxidized more slowly. Thus, this argues against a mechanism involving electron transfer as the rate-determining step. Although the mechanism of the Co(III) oxidation of alkanes remains to be elucidated, these catalyzed reactions may involve reversible formation of alkyl radicals by direct reaction of the alkane with Co(III) [Eqs. (7), (18), (19)] or via electrophilic substitution at the saturated carbon center [Eq. (20)].

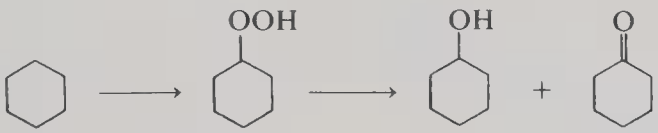
$$R-H + Co(III) \rightleftharpoons R^{\cdot} + Co(II) + H^{+} \tag{18}$$

$$R^{\cdot} + Co(III) \longrightarrow Co(II) + R^{+} \longrightarrow \text{Products} \tag{19}$$

$$R-\overset{|}{\underset{|}{C}}-H + Co(OAc)_2{}^{+} \longrightarrow \left[R-\overset{|}{\underset{|}{C}}\cdots\begin{matrix}H\\ Co(OAc)_2\end{matrix}\right]^{\ddagger} \xrightarrow{-H^{+}} R-\overset{|}{\underset{|}{C}}-Co(OAc)_2$$

$$\longrightarrow R-\overset{|}{\underset{|}{C}}{}^{\bullet} + Co(OAc)_2 \tag{20}$$

The oxidation of alkanes with metal oxidants has been compared with electrochemical oxidations.[56–58] Cyclohexane is converted to cyclohexyl hydroperoxide, which is decomposed to cyclohexanol and cyclohexanone.[59–62] The reaction is performed by reacting air with a cyclohexane solution of soluble Co(II) carboxylate such as 2-ethylhexanoate or naphthenate.[59] Other metal ions such as Mn(II) or Cr(III) are frequently used in addition to cobalt in order to control product distribution. The metal ions may not have a direct role in the formation of cyclohexyl hydroperoxide, but they have a controlling role in converting the hydroperoxide to cyclohexanol and cyclohexanone [Eqs. (2), (3), (4), (5), (12), (21)].[44] Once formed, cyclohexanol and cyclohexanone are converted to adipic acid with various catalysts.[63–69]



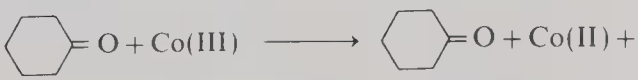
(21)

At high concentrations of $Co(OAc)_2$, cyclohexane is oxidized directly to adipic acid at 90°C in acetic acid.[54,70,71] By analogy with the oxidation of *n*-butane, the autoxidation of cyclohexane may involve Co(III) as the chain transfer agent in a direct reaction with the substrate [Eqs. (22)–(26)].[54] Depending on the experimental conditions, one can also obtain high yields of succinic and glutaric acids along with adipic acid from the cobalt catalyzed autoxidation of cyclohexane.[54,71–76]

(22)

(23)

(24)



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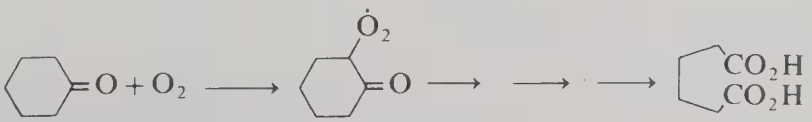
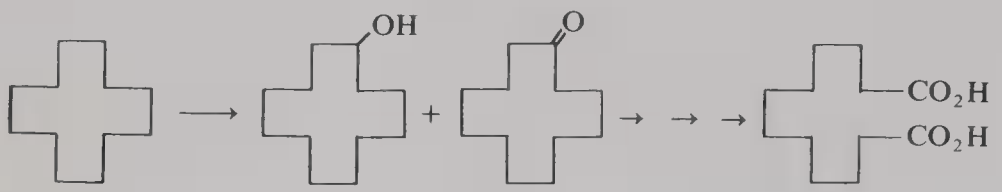


(26)

As with alkanes, unusual selectivities are observed in the cobalt(III) acetate oxidation of cyclohexane and substituted cyclohexanes. Methylcyclohexane is less reactive than cyclohexane, and cyclohexane, which has a higher oxidation potential than benzene, is oxidized significantly faster than benzene.[40,53–55,77–80]

The one-step conversion of cyclododecane to 1,12-dodecanedioic acid with $Co(OAc)_2$ in acetic acid does not proceed in good yield owing to the nonselectivity of the catalyst.[81,82]



(27)

2.1.2. Benzylic Oxidations

Autoxidation of alkylbenzenes under mild conditions generally leads to alcohols, aldehydes, and ketones.[50,83–88] The primary products are benzylic hydroperoxides, which ultimately lead to the observed products. Using a wide variety of metal catalysts, one can easily convert alkylbenzenes to the corresponding carboxylic acids.[90–139]

$$Ar-CH_2-R + O_2 \longrightarrow Ar-\underset{\displaystyle \dot{O}_2}{\underset{|}{CH}}-R \tag{28}$$

The generally accepted mechanism for the $Co(OAc)_3$ oxidation of methylbenzenes is shown in Eqs. (29)–(32).[94,103–114] Equations (33)–(36) describe the mechanism for the cobalt catalyzed autoxidation of alkylbenzenes. During the autoxidative process, the efficient trap-

$$Ar-CH_3 + Co(III) \rightleftharpoons [Ar-CH_3]^{+\cdot} + Co(II) \tag{29}$$

$$[Ar-CH_3]^{+\cdot} \longrightarrow Ar-\dot{C}H_2 + H^+ \tag{30}$$

$$Ar-\dot{C}H_2 + Co(III) \longrightarrow Ar-\overset{+}{C}H_2 + Co(II) \tag{31}$$

$$Ar-\overset{+}{C}H_2 + AcOH \longrightarrow Ar-CH_2-OAc + H^+ \tag{32}$$

ping of the benzylperoxyl radical by the high concentration of Co(II) essentially eliminates the expected reaction of alkylperoxy radicals [Eq. (37)]. Benzyl acetates [Eq. (32)] are formed in the absence of oxygen and the benzaldehydes [Eq. (35)] may be isolated in certain

$$Ar-\dot{C}H_2 + O_2 \longrightarrow Ar-CH_2-O-\dot{O} \tag{33}$$

$$Ar-CH_2-\dot{O}_2 + Co(II) \longrightarrow Ar-CH_2-O_2Co(III) \tag{34}$$

$$Ar-\underset{\displaystyle H}{\underset{|}{CH}}-O-\overset{\curvearrowright}{O}-Co(III) \longrightarrow Ar-CHO + Co(III)\,OH \tag{35}$$

$$Co(III)\,OH + AcOH \longrightarrow AcOCo(III) + H_2O \tag{36}$$

cases[118] at relatively high Co(III) concentrations and low oxygen pressure or autoxidized to the corresponding carboxylic acid.[119,120]

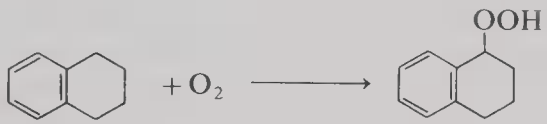
$$Ar-CH_2-\dot{O}_2 + Ar-CH_3 \longrightarrow Ar-\dot{C}H_2 + Ar-CH_2-OOH \tag{37}$$

Some of the important results, hypotheses, and concepts from the extensive studies of the cobalt oxidation of alkylbenzenes are as follows:

1. The relative rates of oxidation of alkylbenzenes by $Co(OAc)_3$ in acetic acid are opposite of that expected from a classical free radical mechanism.[106,107,108,121]
2. The ESR spectra of radical cations have been observed during the $Co(OAc)_3$ in trifluoroacetic acid oxidation of alkylbenzenes.[105,122]
3. Under nitrogen and in the absence of strong acid, the $Co(OAc)_3$ oxidation of ethylbenzene in acetic acid obeys kinetics that can be explained by assuming that cobalt atoms are associated in the dinuclear species Co(III) and Co(II)–Co(III), with only the former being the active oxidant. Similar kinetics are observed in the presence of trichloroacetic acid except that no inactivation of Co(III) by Co(II) takes place. A mechanism is proposed whereby the cobaltic species oxidizes ethylbenzene to yield reversibly a benzylic radical.[51]
4. The rates of oxidation of alkylbenzenes by Co(III) acetate are dramatically enhanced in the presence of strong acids such as sulfuric or trifluoroacetic acid.[50,51,123–125]
5. Bromide, as R-Br, HBr, NH_4Br or NaBr, has a significant synergistic effect on the cobalt catalyzed oxidation of alkylaromatics.[105,126–128] The optimum 1:1 molar ratio of $Co(OAc)_2$ to NaBr yields Co(OAc) Br.
6. The rate of $Co(OAc)_2$ catalyzed oxidation of *p*-xylene to terephthalic acid is enhanced significantly by small amounts of Zr(IV) and Hf(IV) acetates, but the relative rates of oxidation of toluenes were not affected by these additives.[95,100,129]

2.1.3. Tetralins

The discussions above for alkyl hydroperoxides are also applicable to the cobalt autoxidation of tetralin.[31,34,130]



(38)

Transition metal complexes (Co, Cu, Fe, Mn, etc.) in solvents of low polarity behave as catalysts at low concentrations or as inhibitors at high concentrations during autoxidations. If the alkyl hydroperoxide concentration is less than that of the metal, this catalyst–inhibitor conversion leads to long induction periods. In the cobalt catalyzed oxidation of tetralin, a catalyst–inhibitor conversion was observed at about 0.1 *M* $Co(OAc)_2$.[140,141] Equations (39)–(42), which include metal–hydroperoxide complexes, have been proposed to explain the catalyst–inhibitor conversion.[141]

$$RO_2H + Co(II) \rightleftharpoons [Co(II)\,RO_2H] \tag{39}$$

$$[Co(II)\,RO_2H] \longrightarrow RO^{\cdot} + Co(III)\,OH \tag{40}$$

$$RO_2H + Co(III) \rightleftharpoons [Co(III)\,RO_2H] \tag{41}$$

$$[Co(III)\,RO_2H] \longrightarrow R\dot{O}_2 + Co(II) + H^+ \tag{42}$$

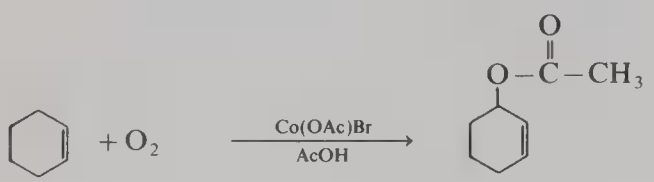
The phenomenon of the limiting rate, whereby reaction rates ultimately level off at some limiting value during metal catalyzed autoxidation, is also explicable in terms of the metal hydroperoxide concept. These concepts have been applied to the cobalt catalyzed autoxidation of tetralin in acetic acid.[141–144]

2.1.4. Allylic Oxidations

Selective allylic oxidation under autoxidation conditions has been observed in the cobaltic naphthenate catalyzed oxidation of 2-methyl-2-pentene to the α,β-unsaturated

ketone [Eq. (43)][145] and in the cobalt catalyzed autoxidation of cyclohexene and 2-phenylpropene.[55,130,146] Allylic hydroperoxides and/or allylic radicals are reaction intermediates.

$$(CH_3)_2C{=}CHCH_2CH_3 \longrightarrow (CH_3)_2C{=}CH{-}\overset{\overset{O}{\|}}{C}{-}CH_3 \tag{43}$$



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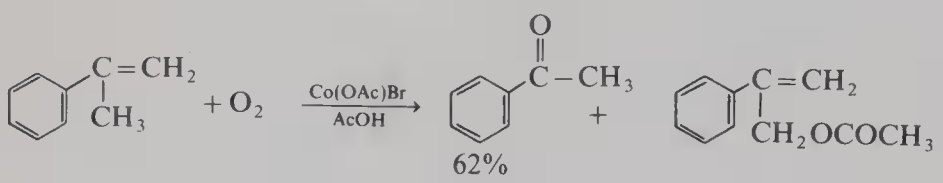
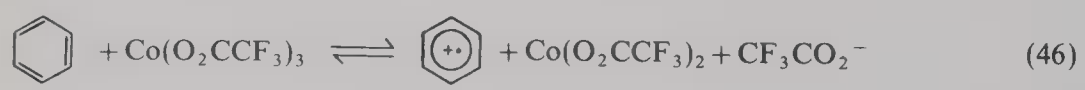


(45)

2.2. Arenes

Although arenes are inert to $Co(OAc)_3$ in acetic acid at high temperature, benzene and halobenzenes are oxidized at 23–25°C by $Co(OAc)_3$ in trifluoroacetic acid.[123] This is another example of the enhancement of the electrophilic character of cobalt in the presence of strong acids. Equations (46)–(48) describe a reasonable mechanism for the trifluoroacetoxylation of arenes by $Co(O_2CCF_3)_3$.[123,147] The reaction of Co(III) with methylbenzene affords oligomeric products resulting from the reaction of toluene with the toluene radical cation.[148]

The Co(III) oxidation of benzene in aqueous solution has been reported.[149] The ultimate products were 1,4-benzoquinone and muconic acid ($HO_2CCH{=}CHCH{=}CHCO_2H$).



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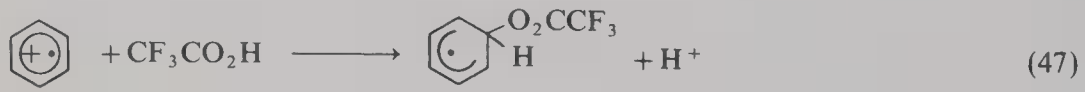

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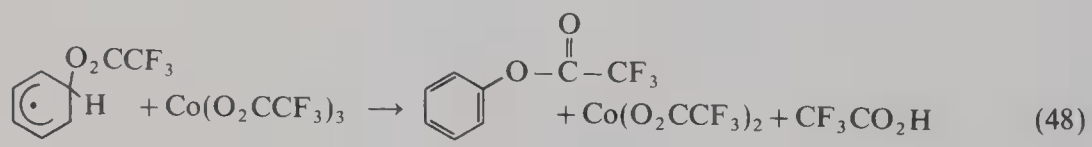


(48)

2.3. Carbon–Carbon Double Bonds

The oxidation of ethene by cobaltic trifluoroacetate in trifluoroacetic acid gives ethylene glycol di(trifluoroacetate).[124] Kinetics and ESR studies support a radical cation mechanism [Eqs. (49)–(52)].[124,150,151]

$$CH_2{=}CH_2 + Co(O_2CCF_3)_2{}^+ \longrightarrow \overset{+}{C}H_2{-}\dot{C}H_2 + Co(O_2CCF_3)_2 \tag{49}$$

$$\overset{+}{C}H_2{-}\dot{C}H_2 + CF_3CO_2H \longrightarrow CF_3CO_2CH_2{-}\dot{C}H_2 + H^+ \tag{50}$$

$$CF_3CO_2CH_2-\dot{C}H_2 + Co(O_2CCF_3)_2^+ \longrightarrow CF_3CO_2CH_2-\overset{+}{C}H_2 + Co(O_2CCF_3)_2 \quad (51)$$

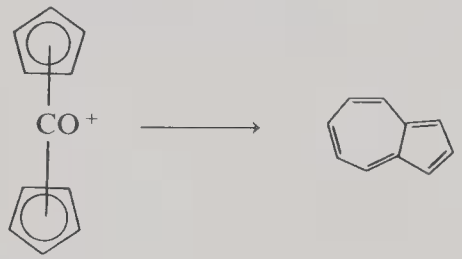
$$CF_3CO_2CH_2-\overset{+}{C}H_2 + CF_3CO_2H \longrightarrow CF_3CO_2CH_2-CH_2O_2CCF_3 + H^+ \quad (52)$$

The kinetics of the cobaltic sulfate catalyzed oxidation of eight unsaturated hydrocarbons in dilute sulfuric acid obey a second-order rate law.[152] Radical cations resulted from attack of the cobaltic ion at the double bond. In contrast, similar olefins were not oxidized by a cobaltic solution in glacial acetic acid.[152,153]

The oxidation of styrene,[154] and α- and *cis*- and *trans*-β-methylstyrene[155] with cobaltic acetate in acetic acid has been studied. The product distribution was greatly affected by the composition of the solvent. In dry acetic acid, extensive formation of radical products was observed, while in wet acetic acid the reaction led exclusively to 1,2-addition products.[154]

A mechanistic scheme has been presented for the epoxidation of nobornene, *tert*-butylethylene, and 1,1-dineopentylethylene using dioxygen in the presence of cobaltic acetylacetonate.[156]

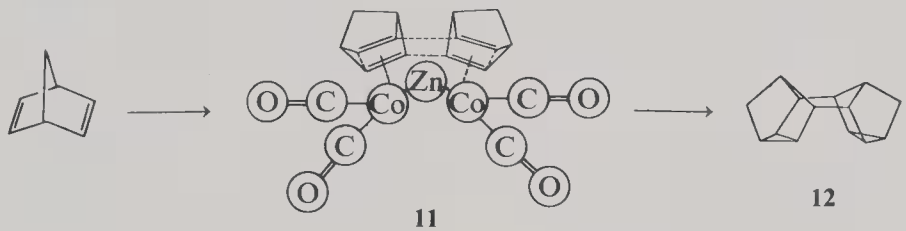
Several mechanisms have been proposed for the conversion of cobalticinium ion (**3**) into azulene.[157,158]



(53)

3

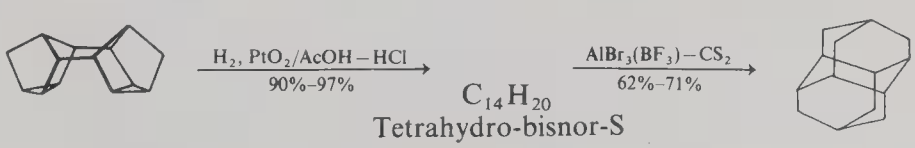
The principle of binuclear catalysis has been applied to the dimerization of bicyclo-[2.2.1] heptadiene to Bisnor-S (**12**) using $Zn[Co(CO)_4]_2$ with or without $BF_3 \cdot O(C_2H_5)_2$[159] or more accessible catalyst systems such as $CoBr_2 \cdot 2P(C_6H_5)_3 \cdot BF_3/O(C_2H_5)_2$ or $CoI_2 \cdot 2P(C_6H_5)_3 \cdot BF_3 \cdot O(C_2H_5)_2$ [Eq. (54)].[160] In this stereospecific dimerization of norbornadiene,



(54)

11 **12**

intermediate π complexes giving rise to only one activated complex are formed. Bisnor-S (**12**) is an intermediate in the formation of diamantane (**13**).[161] Cobalt carbonyl hydride $[HCo(CO)_4]$ is a strong acid and its sodium salt [sodium cobalt carbonylate, $NaCo(CO)_4$] is colorless and air sensitive.[162] The moderately nucleophilic anion $[Co(CO_4^-]$ reacts with organic halides *(vide supra)* to produce alkylcobalt tetracarbonyl complexes, which in the presence of carbon monoxide rapidly convert to the corresponding acylcobalt tetracarbonyl (**14**). These complexes (**14**) react with 1,3-dienes to form acylated η^3-allylcobalt carbonyl compounds (**15**). Treatment of **15** with base affords acyldienes.[162]

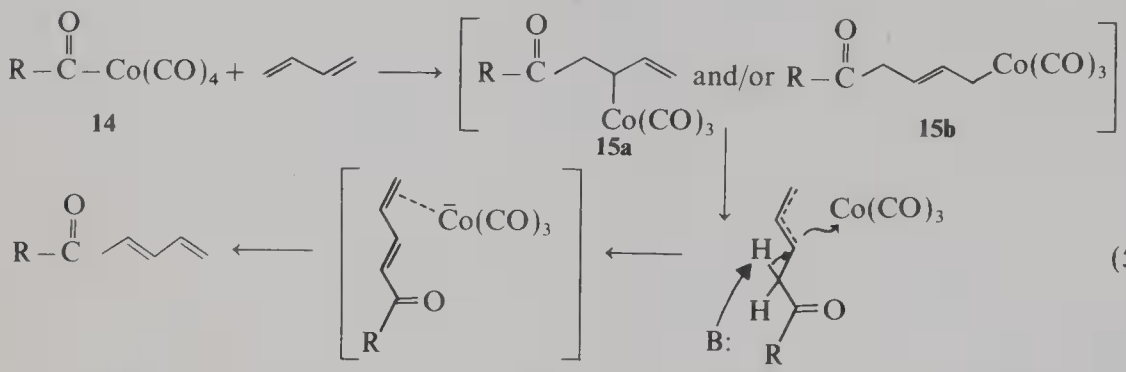


(55)

12 $C_{14}H_{20}$ Tetrahydro-bisnor-S **13**

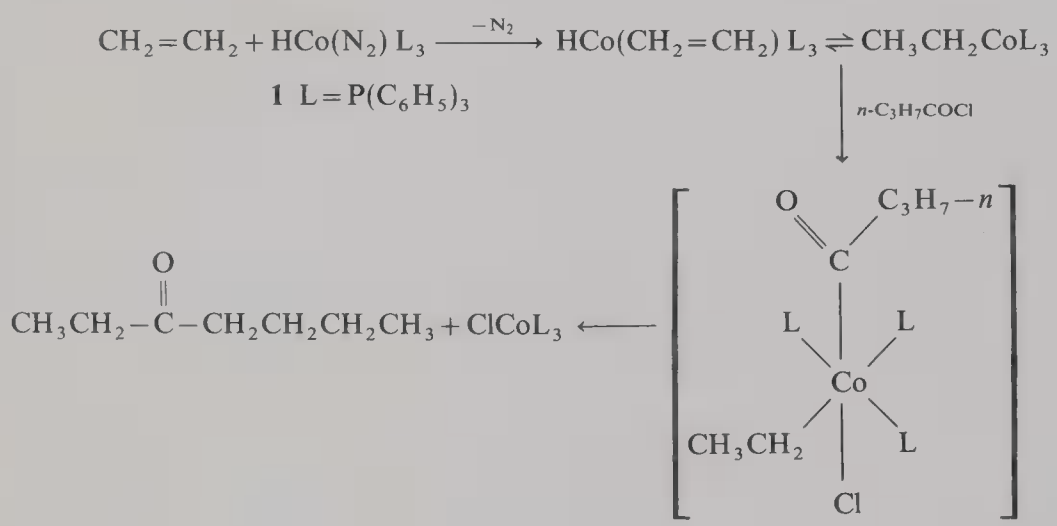
$$Co(CO_4)^- + RX \longrightarrow RCo(CO)_4 \xrightarrow{CO} R-\overset{O}{\overset{\|}{C}}-Co(CO)_4 \qquad (56)$$

14



(57)

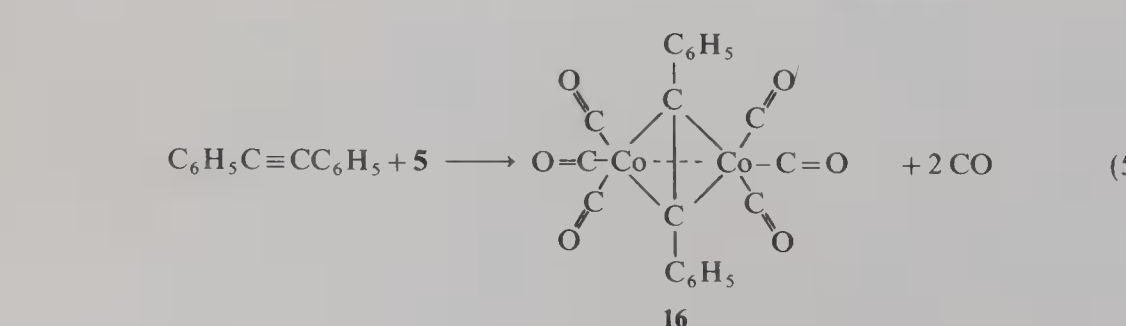
Hydroacylation [cf. Eq. (57)] provides a facile route to ketones from terminal olefins under neutral reaction conditions at 22–25°C with inexpensive reagents.[163] An example of hydroacylation, using **1**,[164] is shown in Eq. (58).



(58)

2.4. Carbon–Carbon Triple Bonds

Although Co(III) may attack ethyne,[165] there are many alkynes in which the triple bond is inert to cobalt. It has been found[166] that ethyne and substituted acetylenes readily displace the two bridge carbonyl groups in dicobalt octocarbonyl (**5**) to yield a new type of organometallic compound (acetylenic dicobalt hexacarbonyls, **16**).[167] At higher temperatures



16

(65–280°C), acetylenes are trimerized to benzene derivatives by **5** [Eq. (60)].[168] This methodology led to the first synthesis of a benzene ring having two ortho *t*-butyl groups.[169]

$$HC{\equiv}C{-}CH_2CH_2OH + \mathbf{5} \longrightarrow \text{1,2,3-tris(2-hydroxyethyl)benzene} \qquad (60)$$

$$3(CH_3)_3CC{\equiv}CH \xrightarrow[-4\,CO]{5} Co_2(CO)_4[(CH_3)_3CC_2H]_3 \xrightarrow[70\%]{Br_2} \text{1,2,3-tris(tert-butyl)benzene} \qquad (61)$$

The dicobalt octacarbonyl–alkyne complexes (e.g., **16**), which result when the alkynes bridge the two metals using their π bonding orbitals, are relatively stable and may be used as alkyne protecting groups in electrophilic addition and hydroboration reactions.[170–173]

Among the transition metals capable of cyclotrimerizing alkynes to aromatics, $CpCoL_2$ complexes are some of the most efficient.[174–196] A proposed mechanism involves coordination of two molecules of alkyne (**17**), formation of the metallacyclopentadiene [**18**, Eq. (62)],

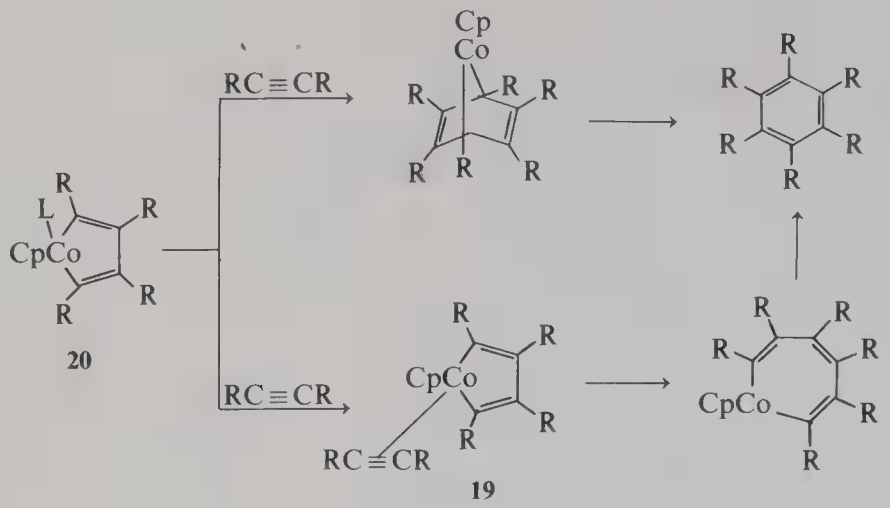
$$2\,RC{\equiv}CR + CpCoL_2 \xrightarrow{-2L} \underset{\mathbf{17}}{CpCo(RC{\equiv}CR)_2} \longrightarrow \underset{\mathbf{18}}{\text{metallacyclopentadiene}} \qquad (62)$$

coordination of another molecule of alkyne (**19**), and collapse to products with regeneration of catalyst [Eq. (63)]. The cobalt complex $CpCo[P(C_6H_5)_3]_2$ reacts with alkynes to give isolable metallacyclopentadiene complexes (**20**) which catalytically cyclotrimerize alkynes.[193]

$$\mathbf{18} + RC{\equiv}CR \longrightarrow \underset{\mathbf{19}}{\text{CpCo(metallacyclopentadiene)(RC≡CR)}} \longrightarrow \text{hexasubstituted benzene} + CpCo \xrightarrow{2L} CpCoL_2 \qquad (63)$$

Several reasonable mechanisms, including insertion to give a metallacycloheptatriene [Eq. (64)], a Diels–Alder-type cycloaddition without prior coordination of alkyne, and a Diels–Alder type cycloaddition within the coordination sphere of the metal, have been proposed for the formation of arenes from cobalt catalysts and alkynes.[194,195]

Several cobaltacyclopentadiene complexes (**20**) react with olefins (ethene, propene, phenylethene, methyl acrylate, dimethyl maleate) to give the corresponding cyclohexadiene complexes.[196] The first step of the reaction involves replacement of triphenylphosphine by olefin. These reactions may proceed via metallacyclopentadienes[196] or metallacyclopentenes,[185] depending on the relative coordinating abilities of the unsaturated species [Eq. (65)]. The complex $CpCo[P(C_6H_5)_3]_2$ reacts in a stepwise manner with two different alkynes to give mixed cobaltacyclopentadiene complexes (**21**) which react with olefins to yield cyclohexadiene complexes (**22**) or cyclohexadienes [Eqs. (66) and (67)]. Although



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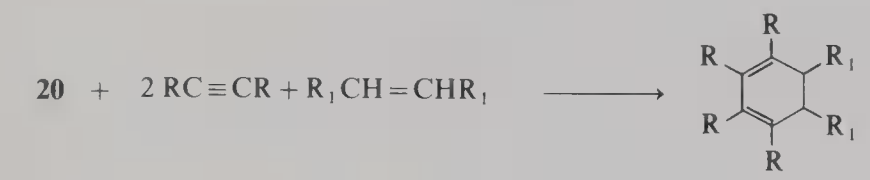

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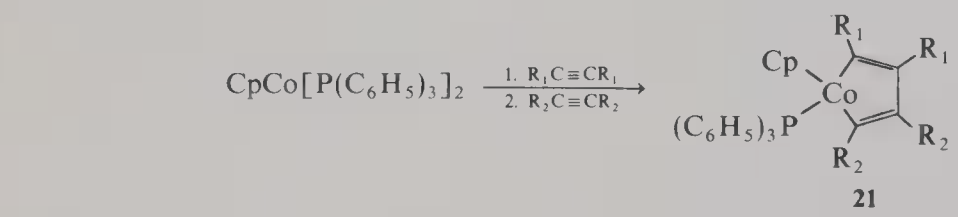

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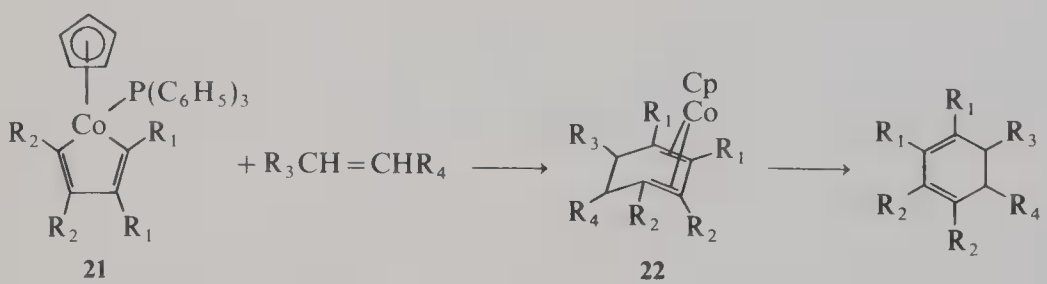

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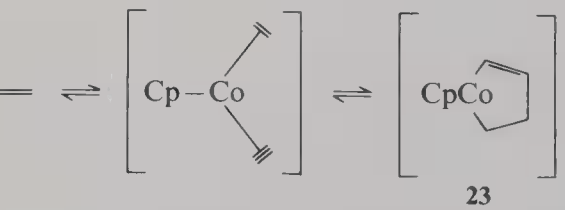

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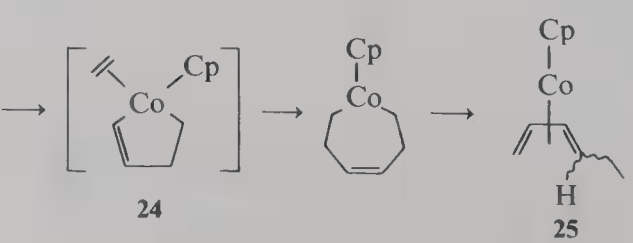
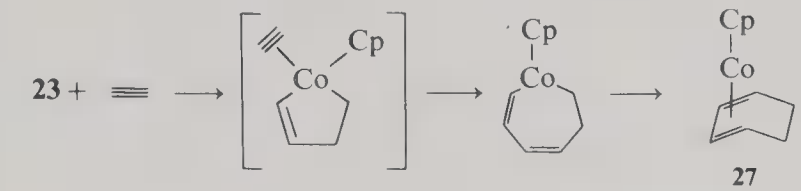


(69)

there are still unanswered questions concerning the last step, the proposed mechanism [Eqs. (66), (67)] is reasonable.

Cocyclotrimerization involving electron deficient olefins such as crotononitrile, fumaronitrile, dimethyl fumarate, and dimethyl maleate occurs with **19** to form metallacyclopentenes (**23**).[185] The metallacyclopentene **23** can react with acrylonitrile to afford open chain diene complexes [**25**, Eq. (69)], or **23** can react with diphenylethyne or methyl phenylpropiolate to produce cyclohexadienes [Eq. (70)].



27 (70)

2.5. Organic, Organomagnesium, and Organomercuric Halides

Cobaltous chloride is not a very effective catalyst in the preparation of alkylmagnesium fluorides.[197] However, a catalytic amount of $CoCl_2$ influences the course of Grignard reactions through intermediate formation of RCoCl, which promotes coupling with an organic halide.[198–203] In the presence of $CoCl_2$, alkynyl Grignard reagents also react with alk-1-enyl and alkyl halides to give vinylacetylenes and alkyl substituted acetylenes, respectively.[199]

$$C_6H_5MgBr + C_6H_5Br \xrightarrow[86\%]{CoCl_2} C_6H_5-C_6H_5 \quad (71)$$

$$C_6H_5MgBr + CH_2=CHCl \xrightarrow[50\%-75\%]{CoCl_2} C_6H_5CH=CH_2 \quad (72)$$

$$C_6H_5MgBr + C_6H_5C\equiv CBr \xrightarrow[75\%]{CoCl_2} C_6H_5C\equiv CC_6H_5 \quad (73)$$

Dicobalt octacarbonyl and some of its derivatives [$NaCo(CO)_4$, $Co_4(CO)_{12}$, $Hg[Co(CO)_4]_2$, $Co(CO)_3P(C_6H_5)_3$, $NaCo(CO)_3P(C_6H_5)_3$] react with activated *gem*-dihalides such as dichlorodiphenylmethane, 9,9-dihalofluorenes, and dimethyl dibromoalonate to give the "dimer" olefins (RRC=CRR) via a radical mechanism [cf. Eq. (56)].[162,204,205] Sodium cobalt carbonylate [$NaCo(CO)_4$][206] reacts with organic halides which are normally reactive in S_N2 processes (e.g., sulfates and sulfonates) to afford alkylcobalt–tetracarbonyl complexes that convert to the corresponding acylcobalt tetracarbonyls in the presence of carbon monoxide [Eq. (55)].[162] Carboalkoxylation of the halide occurs if the acylcobalt tetracarbonyl is treated with alcohol in the presence of a hindered amine such as dicyclohexylethylamine.[162,207–209] Less hindered (more nucleophilic) amines react with acylcobalt tetracarbonyls to produce amides.[207]

$$n\text{-}C_8H_{17}I + CO + CH_3OH + (C_6H_{11})_2NCH_2CH_3 \xrightarrow[56\%]{NaCo(CO)_4} n\text{-}C_8H_{17}CO_2CH_3 \quad (74)$$

Many organomercuric halides react with dicobalt octacarbonyl (**5**, **6**) in tetrahydrofuran solution at 22–25°C to give the ketone ($R_2C=O$) derived from R in RHgX [Eq. (75)].[210] A probable mechanism involves the following steps: solvent induced redox disproportionation

$$C_6H_5HgCl + Co_2(CO)_8 \xrightarrow[THF]{-CO} (C_6H_5)_2C=O + Hg[Co(CO)_4]_2 + CoBr_2 \quad (75)$$

5, **6** 83% 80%

of dicobalt octacarbonyl (**5**, **6**) to give $THF \cdot Co(CO)_4^+$ and $Co(CO)_4^-$; nucleophilic displacement of halide ion from mercury by $Co(CO)_4^-$; electrophilic cleavage of the C–Hg bond in $RHgCo(CO)_4$ formed (or in its disproportionation product, R_2Hg) by $THF \cdot Co(CO)_4^+$, forming $RCo(CO)_4$; organic group migration in $RCo(CO)_4$ to give $RCOCo(CO)_3$; and reaction of $RCOCo(CO)_3$ with $RCo(CO)_4$ to produce the ketone and cobalt carbonyl.[210]

Diphenylmercury also reacts with dicobalt octacarbonyl in tetrahydrofuran to give benzophenone and $Hg[Co(CO)_4]_2$.[210]

2.6. Hydroxy Compounds

2.6.1. Alcohols

Although oxochromium(VI) reagents are the oxidants of choice for converting primary and secondary alcohols to aldehydes and ketones (Chapter 2), several mechanistic studies of the cobalt oxidation of alcohols have been reported.[18,21,211–222] Isotope effects are observed and carbon–carbon bond fission occurs during the oxidation of secondary alcohols [Eqs. (76), (77)].[215,222] Several examples of the reaction of cobalt compounds with alcohols are described below.[223,224]

$$(C_2H_5)_2CDOH \longrightarrow CH_3CH_2-\overset{\overset{O}{\|}}{C}-CH_2CH_3 + CH_3CH_2CDO \tag{76}$$

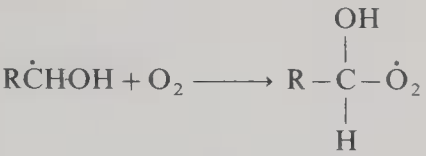
$$CH_3CH_2CH_2\underset{\underset{CH_3}{|}}{CHOH} \longrightarrow CH_3CH_2CH_2-\overset{\overset{O}{\|}}{C}-CH_3 + CH_3CHO \tag{77}$$

2.6.2. Diols

It has been found that cobalt(II) salts are catalysts for the cleavage of 1,2-diols by molecular oxygen in aprotic polar solvents.[225] The mechanism probably involves initiation by a one-electron oxidation followed by the regeneration of the Co(II) by reoxidation with the peroxy acids formed from the oxidation of the aldehydes. Cleavage of the intermediate alkoxy radicals can also lead to carboxylic acid formation [Eqs. (79)–(81)].[226,227]

$$\begin{array}{l} H \\ | \\ R-C-OH \\ | \\ R-C-OH \\ | \\ H \end{array} + Co(III) \longrightarrow \begin{array}{l} H \\ | \\ R-C-\dot{O} \\ | \\ R-C-OH \\ | \\ H \end{array} + Co(II) + H^+ \tag{78}$$

$$\begin{array}{l} H \\ | \\ R-C-\dot{O} \\ | \\ R-C-OH \\ | \\ H \end{array} \longrightarrow RCHO + R\dot{C}HOH \tag{79}$$



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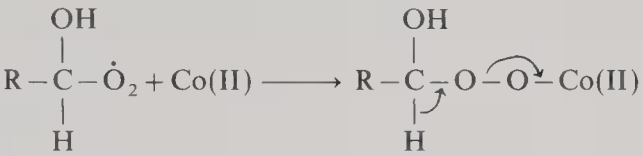


(81)

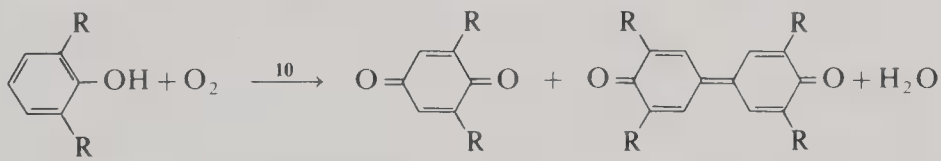
2.6.3. *Carbohydrates*

ESR spectra, obtained during the oxidation of 1,2-dihydroxyethane, xylitol, glucitol, glyceraldehyde, glucose, and methyl α-D-glucopyranoside by Co(III) in aqueous perchloric acid at 0–60°C to give carbonyl compounds, showed the presence of singlet oxygen radicals. The radical in the glucopyranoside is localized at position 1.[228] In a subsequent study,[229] the ESR spectra of free radicals formed during the Co(III) oxidation of glucitol, D-glucose, and methyl α-D-glucopyranoside confirmed that a carbon–hydrogen bond is broken in the process. Kinetic parameters confirmed the formation of an intermediate Co(III)–monosaccharide complex.

2.6.4. *Phenols and Hydroquinones*

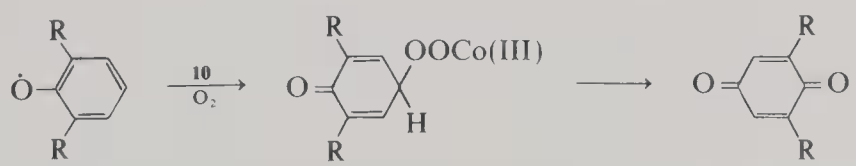
The oxidation of phenols to afford coupled products has received considerable study.[230–270] Substitution-inert oxidants such as manganese(III) and cobalt(III) acetylacetonate oxidize via outer sphere processes.[233,234] After the substitution labile Co(II) species have accumulated, the Co(III)$(acac)_3$ outer-sphere process for the oxidation of phenol is 50 times faster than the inner-sphere oxidation.[234]

(Salen)Co(II) (**10**) catalyzes the oxidation of alkyl-substituted phenols to 1,4-benzoquinones[238] or diphenoquinones,[239] depending on reaction conditions. Benzo-



(82)

quinones are favored at low temperatures and high catalyst concentrations, while diphenoquinones predominate at high temperatures and low catalyst concentrations.[239] Thus, benzoquinones are formed via the reaction of the phenoxy radicals with the cobalt catalyst. Dimerization of phenoxy radicals, followed by oxidation, yields diphenoquinones.



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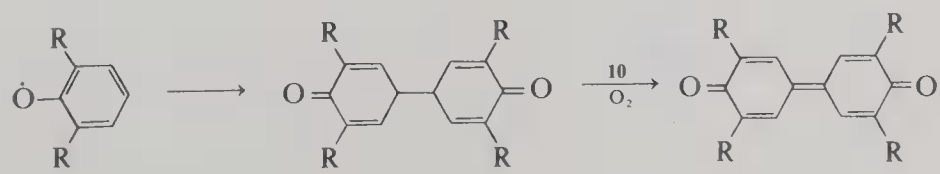
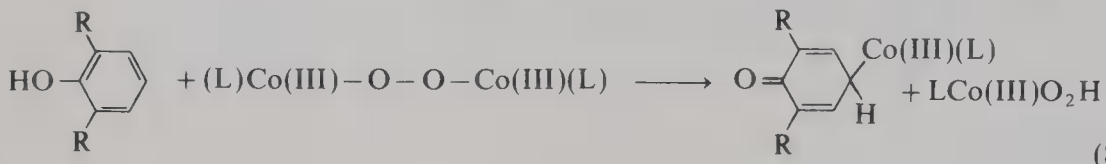


(84)

The initial step in the oxidation could involve hydrogen atom abstraction by the super oxocobalt(III) or nucleophilic displacement by the phenol on either the peroxo- or μ-peroxocobalt(III) complex.[242] Insertion of oxygen into the Co(III) complex to form the alkylperoxocobalt(III) complex is a reasonable second step [Eq. (86)]. A γ-hydrogen elimination from the alkylperoxocobalt(III) complex [Eqs. (87), (88)] or a second nucleophilic dis-



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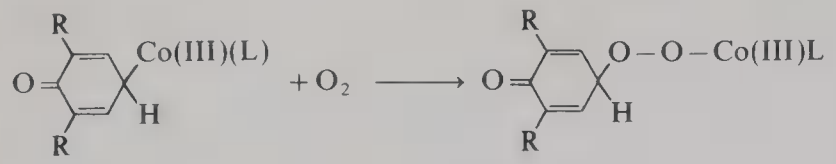

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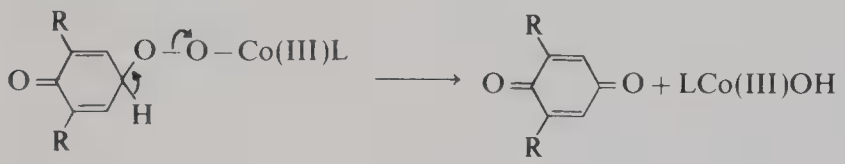

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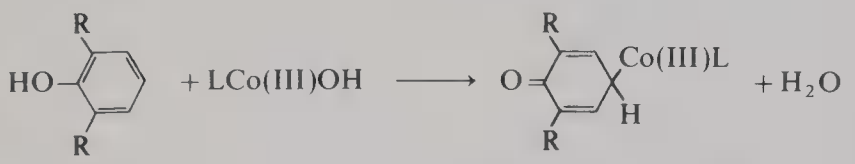
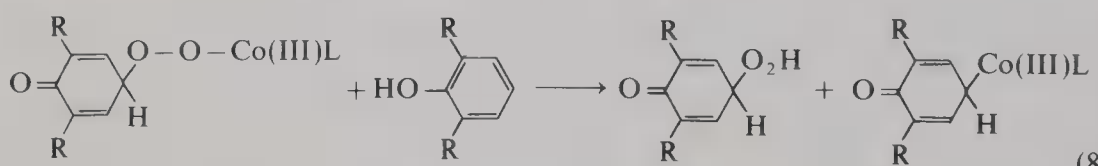


(88)

placement to regenerate the organocobalt(III) complex [Eqs. (89), (90)] is a reasonable third step in the mechanism.[242,244] Although the organocobalt(III) intermediate has not been identified in all systems, it is easily interconverted as shown in Eq. (91).[4,242,244]



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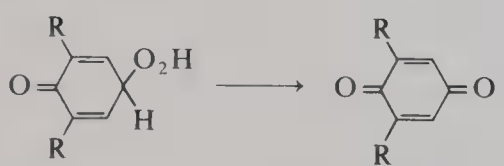

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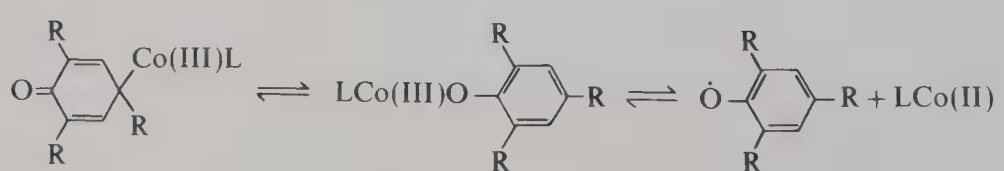
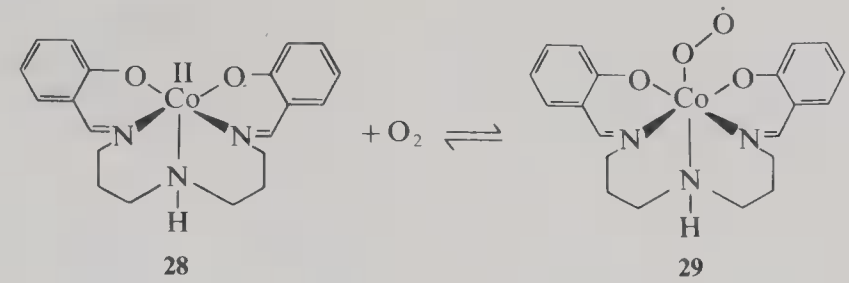


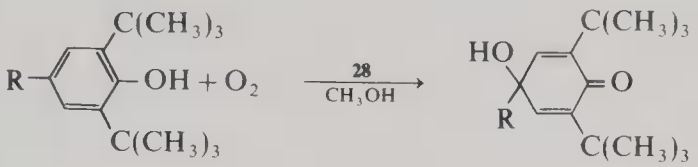
(91)

The catalytic oxidation of 4-alkyl-2,6-di-*tert*-butylphenols with (Salpr) Co [**28**, Eq. (92)] at 22–25°C gives the corresponding *p*-quinols (100%).[245–250] At 0°C in dichloromethane or methanol, the intermediate alkylperoxycobalt(III) complex is formed [Eq. (94)].

The first step in the (Salpr) Co (**28**) oxidation of phenols could involve initial removal of a proton by the superoxo complex [Eq. (95)],[4,251–255] or via an initial hydrogen atom



28 29 (92)



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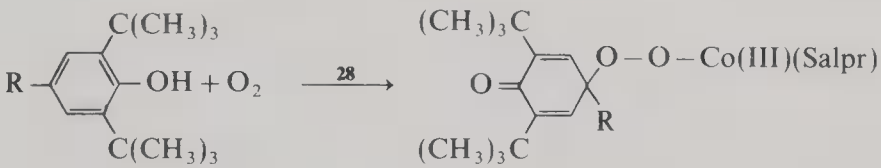

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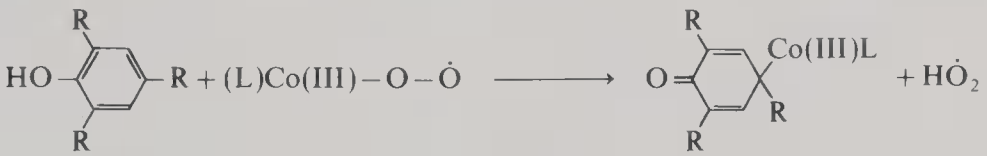
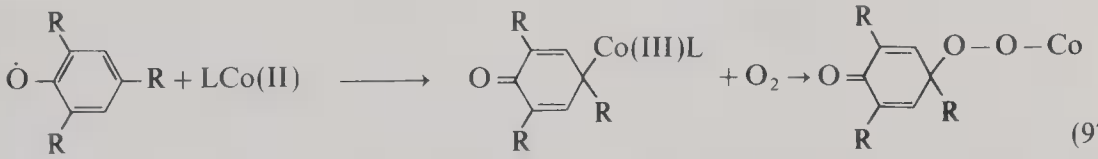


(95)

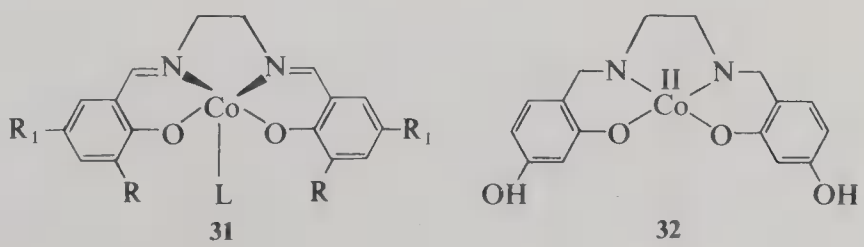
abstraction from the phenol by the superoxo complex [Eq. (96)].[245–250] The phenoxy radical generated in Eq. (96) may undergo reduction to give an organocobalt complex that inserts oxygen. Alternate mechanisms, the reaction of the alkylperoxocobalt(III) complex with the phenol, and the mechanism of cobalt catalysis have been discussed.[245–250,256] The effects of

(96)



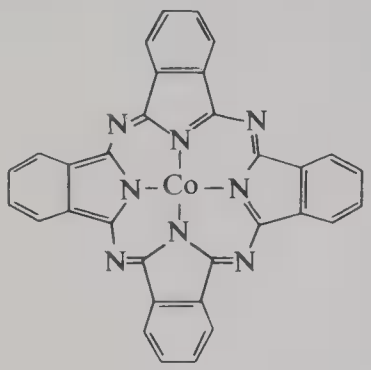
(97)

ring substituents (R and R_1) in the Salen ligand (**31**) on the rates and selectivities of these oxidations have been studied.[257] 4-Hydroxy-(salen) cobalt(II) (**32**) catalyzes the autoxidation of 2,6-di-*tert*-butylphenol to the *p*-benzoquinone in aqueous organic media under basic or



31 32

neutral conditions.[240] Phthalocyanine Co(II) (**33**) catalyzes the oxidation of phenols in dimethylformamide.[242] (Acacen) Co(II) (**9**),[235–237] which forms an oxygen complex (**34**),[258–260] catalyzes the autoxidation of phenols and hydroquinones.[235–237]



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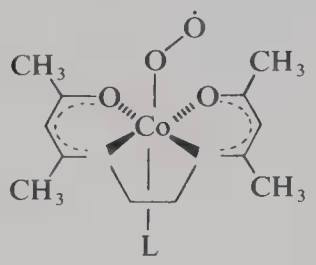
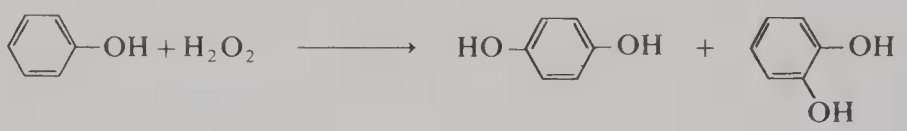


34

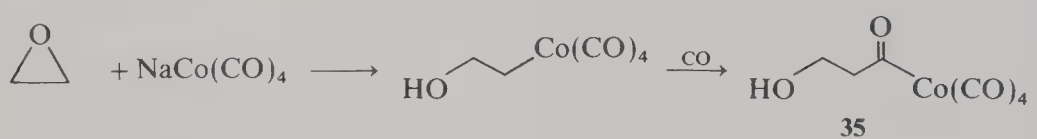
The hydroxylation of phenol with hydrogen peroxide in the presence of cobalt(II) probably involves hydroxyl radicals.[270]



(98)

2.7. Oxiranes

Oxiranes (epoxides) react with $HCo(CO)_4$ or $NaCo(CO)_4$ to give β-hydroxyalkylcobalt carbonyls which insert carbon monoxide to afford alcylcobalt complexes (**35**). These β-hydroxyacyl complexes (**35**), which are isolable, are cleaved by alcohols to yield β-hydroxyesters.[162]



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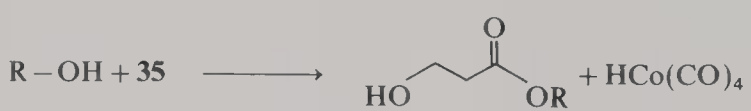


(100)

The use of $Co_2(CO)_8$, (**5**, **6**) for the stereospecific deoxygenation of oxiranes is described below.[271,272]

2.8. Carbonyl Compounds

2.8.1. Aldehydes

The mechanism for the autoxidation of aldehydes is similar to that of hydrocarbons *(vide supra)*. The principal chain carriers are acylperoxy radicals and the primary products are peroxy acids [Eqs. (101)–(103)]. Although it is known that cobalt can catalyze the decomposition of peroxy acids via redox reactions similar to those proposed for alkyl hydroperoxides, the details of the mechanism are not well understood.[35,37,273–280] The kinetics

$$RCHO + I^{\cdot} \longrightarrow R\dot{C}{=}O + IH \quad (101)$$

$$R\dot{C}O + O_2 \longrightarrow RCO_3^{\cdot} \quad (102)$$

$$RC\dot{O}_3 + RCHO \longrightarrow R\dot{C}O + RCO_3H \quad (103)$$

of the cobalt oxidation of aldehydes have been summarized,[280] and the cobalt catalyzed autoxidation of aldehydes to carboxylic acids is described in Eqs. (6) and (101)–(105).[277–280]

$$RCHO + Co(III) \longrightarrow R\dot{C}O + Co(II) + H^+ \quad (6)$$

$$RCO_3H + Co(II) \longrightarrow RCO_2Co(III) + {}^{\cdot}OH \quad (104)$$

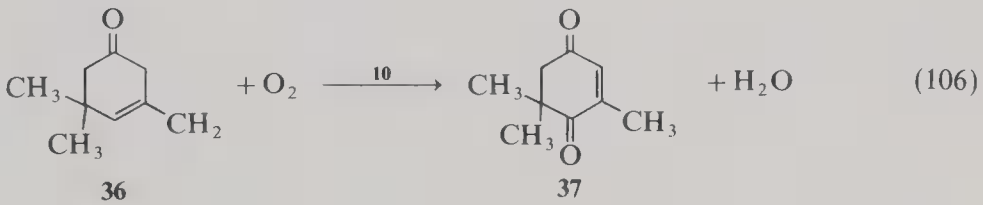
$$RCO_3H + Co(II) \longrightarrow R\dot{C}O_2 + Co(III)\,OH \quad (105)$$

2.8.2. Ketones and o-Quinones

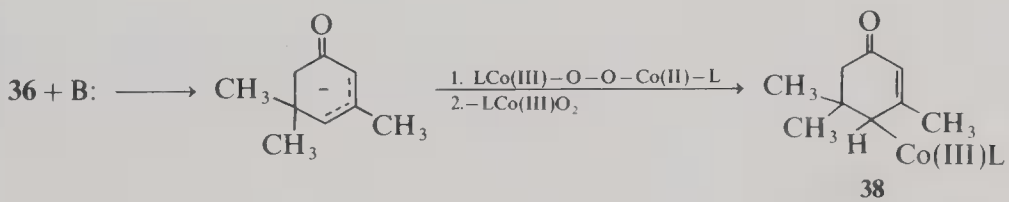
The kinetics of the cobalt oxidation of ketones have been described.[281]

Complex formation has been reported during the liquid phase cobalt catalyzed oxidation of 3,4-dihydro-1,2-naphthoquinones, α-tetralone, and *o*-toluic acid.[282] Complexing of ions with oxygen containing products explains catalyst deactivation, precipitate formation, color changes, and the direction of reaction in the liquid phase oxidation of hydrocarbons which are catalyzed by transition metals.

(Salen) Co (**10**) catalyzes the oxidation of β-isophorone (**36**) in the presence of triethylamine.[283] A mechanism similar to the ones described above for the oxidation of phenols is probably operative [Eq. (106)–(108)].[283]



36 **37** (106)



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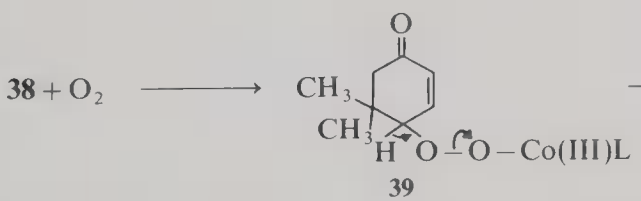


39 (108)

Treatment of cobaltacene (**2**) with oxygen in ether at low temperatures produces a novel oxygen adduct of cobaltacene with an oxygen bridge between two cyclopentadienyl groups (**4**).[284] Complex **4** is a very active reagent for the oxidative cleavage of a C–C bond in α-diketones or *o*-quinones, which affords cobalticinium carboxylates (**40**).[285] Treatment of **40** with hydrogen chloride in ether gave the carboxylic acid and cobalticinium chloride (**41**) in quantitative yields. Similar results were obtained with phenanthrene quinone and acenaphthene quinone.

Superoxo Co(III) complexes derived from (Salper) Co (**28**) and $[Co(CN)_5]^{3-}$ reacted

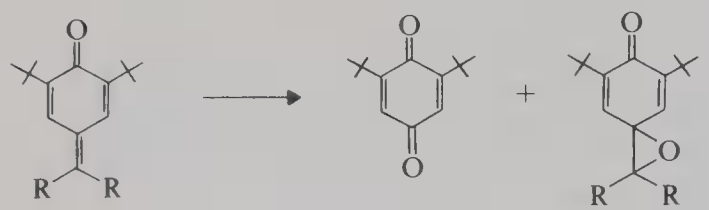
$$R-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-R + \mathbf{4} \longrightarrow 2[(\pi\text{-}C_5H_5)_2Co]^+ [RCO_2]^- \quad (109)$$

$R = CH_3$ or C_6H_5 **40**

$$\mathbf{40} + HCl \longrightarrow RCO_2H + 2[(\pi\text{-}C_5H_5)_2Co]^+ Cl^- \quad (110)$$

41

with 2,6-di-*t*-butyl-*p*-benzoquinone methides (**42**) to give 2,6-di-*t*-butyl-*p*-benzoquinone and 2,6-di-*t*-butyl-2,5-cyclohexadienonespirooxiranes as the main products.[286] The mechanism is considered to involve nucleophilic attack by the superoxo species on the exocyclic double bond of **42**. The superoxo complex $[Co(CN)_5O_2]^{3-}$ (**8**) acts as a reducing agent towards quinones.[287]



(111)

42

2.9. Carboxylic Acids

The kinetics of the cobalt oxidation of amino acids,[288,289] ascorbic acid,[290,291] dicarboxylic acids,[292] formic acid,[293] malic acid,[294] mandelic acid,[295] nitrilotriacetic acid,[296] oxalic acid,[295–297] and phenylethanoic acid[295] have been studied.

2.10. Nitrogen Compounds

The oxidation of acetamide, formamide, *N*-methylformamide, and *N*,*N*-dimethylformamide by cobalt(III) in perchloric acid at 20°C has been investigated.[298] The reaction requires nearly three moles of cobalt(III) for one mole of amide, except for acetamide, which

$$HCONH_2 \xrightarrow{Co(III)} NH_3 \quad (112)$$

$$CH_3CONH_2 \xrightarrow{Co(III)} NH_3 + CH_3CO_2H \quad (113)$$

$$HCONHCH_3 \xrightarrow{Co(III)} CH_3NH_2 \quad (114)$$

$$HCON(CH_3)_2 \xrightarrow{Co(III)} (CH_3)_2NH \quad (115)$$

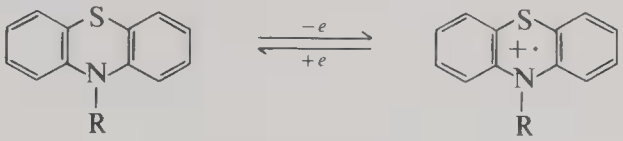
requires one mole of cobalt(III) per mole of amide. The oxidation of the amides obeys the rate law

$$-d[Co(III)]/dt = (k_1 + k_2[H^+])[amide][Co^{3+}] \quad (116)$$

A free radical mechanism was proposed and the activation parameters were calculated for each reaction.[298]

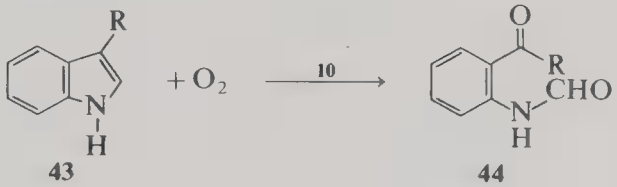
The kinetics of electron transfer between aquacobalt(II) and some *N*-alkylphenothiazines have been investigated via stopped flow techniques.[299] The reaction consists

of a one-electron transfer with formation of the corresponding cation radicals. The results are discussed in terms of the Marcus cross-reaction equation for outer-sphere electron transfer reactions.



(117)

(Salen) Co(II) (**10**) or the cobalt porphyrin complex catalyzes the oxidative cleavage of 3-substituted indoles (**43**) at 22–25°C.[330,331] A mechanism involving nucleophilic displacement and oxygen insertion is shown in Eqs. (119)–(122).[300] The conversion of **43** to **44** is a model reaction for the tryptophan 2,3-dioxygenase conversion of tryptophan (**48**) to formylkynurenin (**49**).



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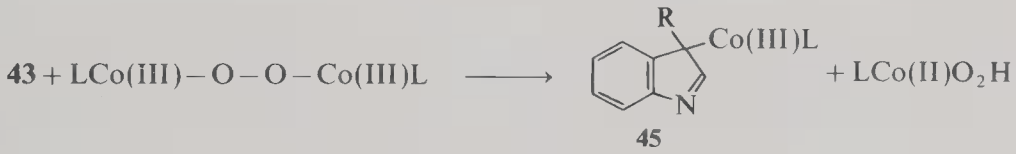

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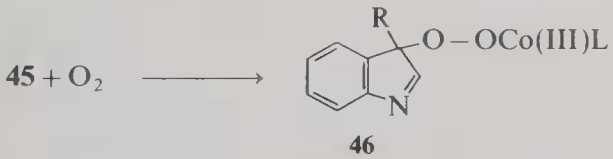

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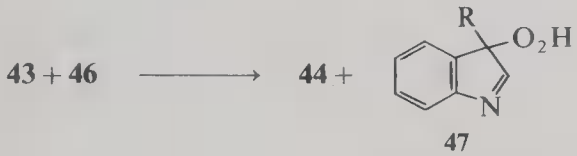

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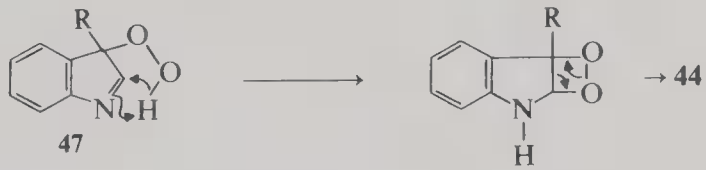

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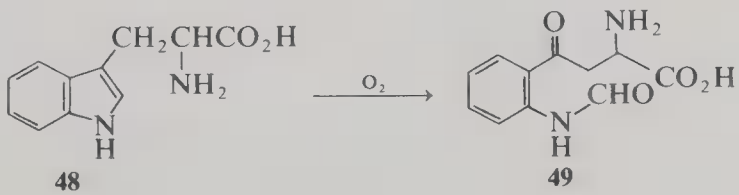


(123)

The treatment of azirines with dicobalt octacarbonyl (**5**, **6**) to give 2-styrylindoles[302] and the interaction of cobalt compounds with other nitrogen containing substrates are described below.[303,304]

2.11. Phosphorus Compounds

$Co(Saloph) \cdot py \cdot NO_2$ (Saloph = *N.N'*-bisalicyclidene-*o*-phenylenediamino) can be used in the stoichiometric and catalytic oxidation of triphenylphosphine to triphenylphosphine oxide.[305–307]

2.12. Sulfur Compounds

Although the use of cobalt complexes with organosulfur compounds remains to be explored,[308–313] transient intermediates have been observed in the Co(III) oxidation of α-mercaptans.[308] The kinetics of the Co(III) oxidation of thiomalic acid have been studied,[309] the kinetics and mechanism of the conversion of a coordinated thiol to a coordinated disulfide by Co(IV) in aqueous perchloric acid have been investigated,[310] and the cobalt (III) oxidations of thiourea and its *N*-substituted derivatives have been evaluated.[311]

3. SCOPE AND LIMITATIONS

3.1. Oxidation of Alkanes and Cycloalkanes

Acetic acid is a major intermediate in the organic chemical industry.[38,39] Although further plants for manufacture of acetic acid may be superceded by the rhodium catalyzed carbonylation of methanol, most synthetic acetic acid is now made by the autoxidative process. The liquid phase autoxidation of *n*-butane and other alkanes is the largest-scale process. The best yield of acetic acid is obtained using ca. 0.2 *M* $Co(OAc)_2$ catalyst with 2-butanone (from *n*-butane) as a promoter [Eqs. (7)–(13)].[40] The major byproducts are 2-butanone, propanoic acid, and 1-butanoic acid.

Alkanes are readily oxidized by cobaltic acetate in acetic acid with strong acid promoters (H_2SO_4, $HClO_4$, CCl_3CO_2H).[49] Acetate esters and alkyl chlorides are formed under nitrogen [Eqs. (15), (124)] while ketones are formed in high yield in the presence of dioxygen (Table I).

$$n\text{-}C_7H_{16} + O_2 \xrightarrow[N_2]{Co(III)} \underset{70\%}{CH_3(CH_2)_4-\underset{\displaystyle OAc}{\underset{|}{CH}}-CH_3} + \underset{24\%}{CH_3(CH_2)_3-\underset{\displaystyle OAc}{\underset{|}{CH}}-CH_2CH_3} + \underset{6\%}{(CH_3CH_2CH_2)_2CH-OAc} \qquad (124)$$

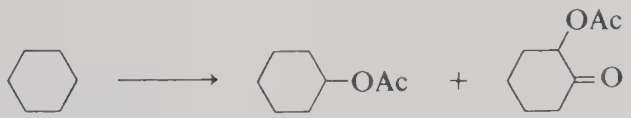
$$n\text{-}C_7H_{16} + O_2 \xrightarrow[O_2]{Co(III)} \underset{78\%}{CH_3(CH_2)_4-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3} + \underset{15\%}{CH_3(CH_2)_3-\overset{\displaystyle O}{\overset{\|}{C}}-CH_2CH_3} + \underset{7\%}{(CH_3CH_2CH_2)_2C=O} \qquad (125)$$

TABLE I. Isomer Distribution in the Products from the Oxidation of *n*-Alkanes by $Co(OAc)_3$ in Acetic Acid in the Presence of Strong Acids[a]

n-Alkane	Atmosphere	Added acid	Principal products	Yield (%)	Isomer distribution (%)					
					1	2	3	4	5	6
C_7H_{16}	N_2	H_2SO_4	Acetates	69	0	64	27	9		
C_7H_{16}	N_2	$HClO_4$	Acetates	88	0	70	24	6		
C_7H_{16}	N_2	CF_3CO_2H	Acetates	85	0	81	16	3		
C_7H_{16}	N_2	CCl_3CO_2H	Chlorides	76	6	80	9	5		
C_7H_{16}	O_2	H_2SO_4	Ketones	69	0	60	27	13		
C_7H_{16}	O_2[b]	CCl_3CO_2H	Ketones	96	0	66	23	11		
$C_{10}H_{22}$	O_2	CCl_3CO_2H	Ketones	81	0	67	13		20	
$C_{12}H_{24}$	O_2	CCl_3CO_2H	Ketones	78	0	65	13		22	6

[a] Reference 49.
[b] Pressure: 10 kg cm^{-2}; experiment performed in a 316 stainless steel autoclave.

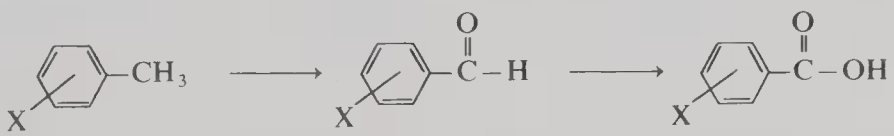
Cyclohexane may be autoxidized in the presence of cobalt catalyst to succinic, glutaric, and adipic acids in good to excellent yields,[54,70–76] or to cycloheyl acetate and 2-acetoxycyclohexanone.[54]



(126)

3.2. Oxidation of Alkylbenzenes

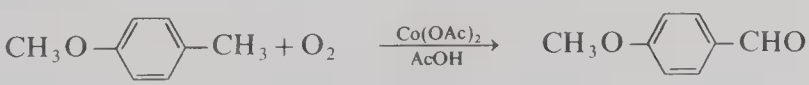
During the autoxidation of methylbenzenes, the initially formed benzaldehydes, which are more reactive than the methylbenzenes, undergo rapid oxidation to the corresponding carboxylic acids. However, in the presence of high concentrations of cobalt catalysts, the rate determining step is oxidation of the substrate by Co(III) via electron transfer. In this system, since the electron withdrawing effect of the carbonyl group increases the ionization potentials



(127)

of the benzaldehyde, it is now oxidized at a slower rate than the corresponding methylbenzene. Thus, perhaps with the exception of the $Co(OAc)_2$/NaBr catalyst system, it is possible to oxidize methylbenzenes to benzaldehydes under mild conditions in the presence of high concentrations of cobalt catalysts [Eqs. (128), (129)].[83–85]

In the presence of strong acids, $Co(OAc)_3$ oxidizes alkylbenzenes at 23–25°C in acetic



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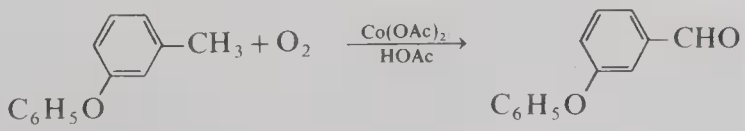
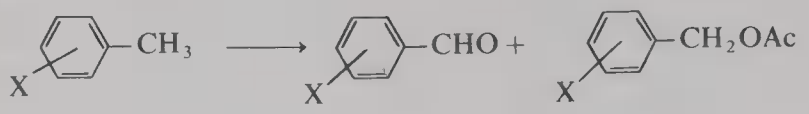
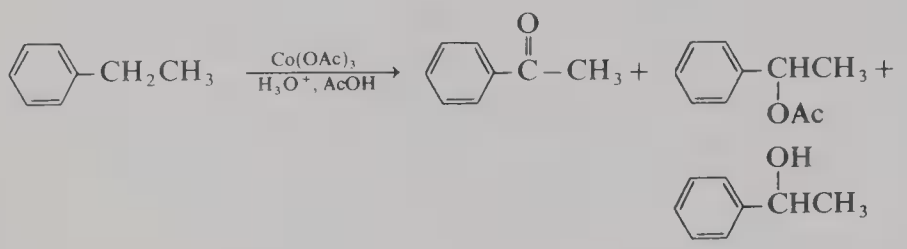


(129)

acid to the corresponding benzaldehydes and benzyl acetates.[50,86] Under similar experimental conditions, ethylbenzene is oxidized primarily to methyl phenyl ketone.[87]



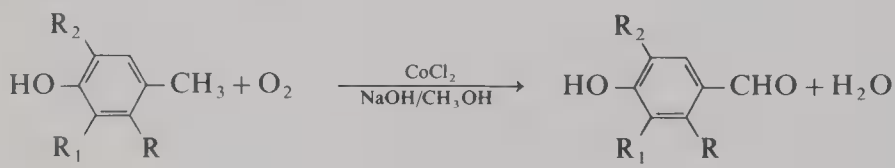
(130)



(131)

The cobaltic acetate oxidation 1-ethyl-4-methyl-, 1,2,3-trimethyl-, 1,2,3,5-tetramethyl-, 5-*tert*-butyl-1,2,3-trimethyl-, and 5-*tert*-butyl-1,3-dimethyl-2-(trideuteriomethyl)benzene was studied under nitrogen in ethanoic acid at 60°C.[11a,11b] The products are mainly benzylic acetates accompanied by small amounts of carbonyl compounds (1%–5%).

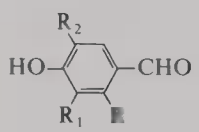
The mild and selective properties of cobalt catalysts are shown in the autoxidation of 4-hydroxymethylbenzenes to the corresponding 4-hydroxybenzaldehydes in the presence of catalytic amounts of $CoCl_2$ (Table II).[88]



(132)

The industrial oxidation of methylbenzene to benzoic acid (80%) is easily accomplished with air in the presence of cobalt(II) 2-ethylhexanoate.[90] The Co(OAc)Br and

TABLE II. $CoCl_2$-Catalyzed Autoxidation of 4-Hydroxymethylbenzenes to 4-Hydrobenzaldehydes[a]

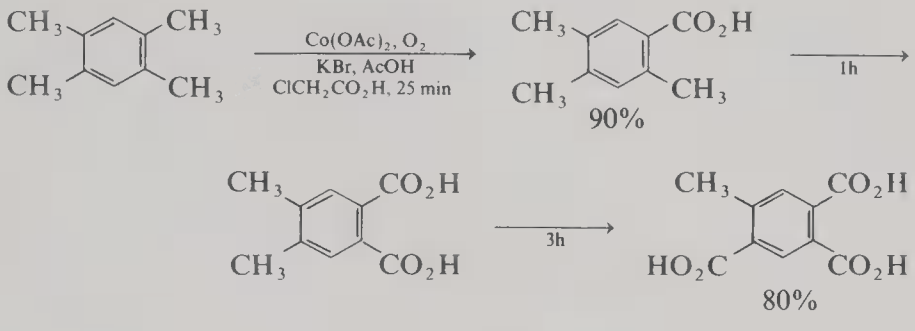


R	R_1	R_2	Conversion (%)	Selectivity (%)
H	H	H	92	78
H	H	CH_3	100	66
H	CH_3	CH_3	100	59
CH_3	H	H	100	62
H	H	*t*-C_4H_9	100	58
H	*t*-C_4H_9	*t*-C_4H_9	100	52
H	OCH_3	OCH_3	100	55
H	H	OC_2H_5	100	61
H	H	Cl	70	63
H	Cl	Cl	60	70
H	H	Br	65	66
H	Br	Br	58	68

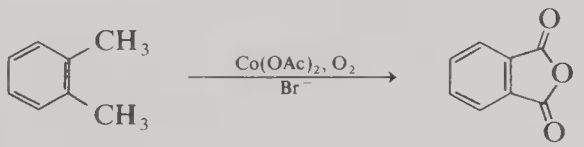
[a] Reference 88.

$Co(OAc)_2$/2-butanone catalysts have been used for laboratory and industrial scale oxidation of methylbenzenes to the corresponding carboxylic acids (Table III).[100,130]

In the presence of bromide ion, $Co(OAc)_2$ oxidizes mono-, di-, and trimethylbenzenes to the corresponding mono-, di-, and tricarboxylic acids in good yields.[99] Alternatively, one can perform the stepwise oxidation of 1,2,4,5-tetramethylbenzene in excellent yields [Eq. (133)].[24] 1,2-Dimethylbenzene is oxidized to phthalic anhydride with Co(OAc) Br [Eq. (134)].[24]



(133)



(134)

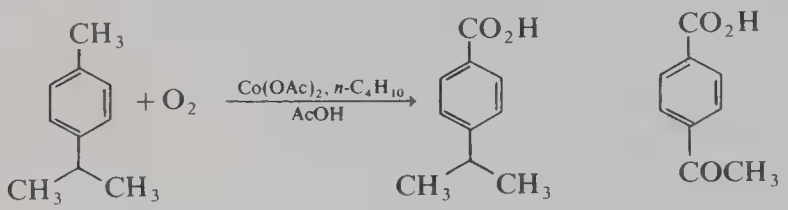
p-Xylene is oxidized to terephthalic acid in acetic acid when high concentrations of $Co(OAc)_2$ are used in combination with promoters such as 2-butanone,[100,131] ozone,[45,101,102] or bromide ion.[130] A promoter is not necessary for the oxidation of *p*-xylene if $Co(OAc)_2$ is at sufficiently high concentrations (e.g., 0.4–0.5 mole of catalyst/mole of substrate).[95] Synergistic effects have also been observed with added zirconyl acetate [$ZrO(OAc)_2$],[129] amines (e.g., triethanolamine, *N*,*N*-diethylaniline),[134,135] and mixed metal catalysts [e.g., 80% $Co(OAc)_2$ and 20% $Mn(OAc)_2$].[126,133]

TABLE III. Oxidation of Methylbenzenes to the Corresponding Carboxylic Acids with Cobalt Catalysts

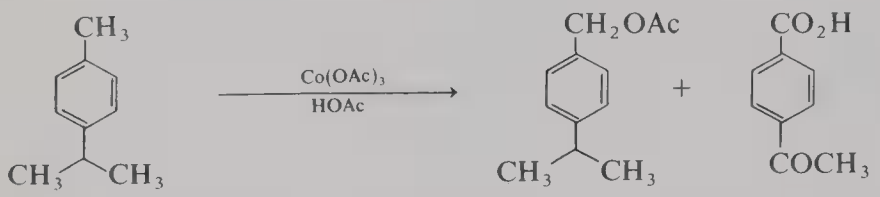
Substrate	Catalyst	Carboxylic acid	Yield (%)
Methylbenzene	A[a]	Benzoic	89
	B[b]	Benzoic	86
2-Chlorotoluene	B	2-Chlorobenzoic	86
2-Bromotoluene	B	2-Bromobenzoic	91
4-Chlorotoluene	B	4-Chlorobenzoic	88
p-Toluic acid	A	Terephthalic	92
o-Xylene	A	*o*-Toluic	76
m-Xylene	A	Isophthalic	90
	B	Isophthalic	67
p-Xylene	A	Terephthalic	95
	B	Terephthalic	72
Chloro-*p*-xylene	A	Chloroterephthalic	75
p-Ethyltoluene	B	4-Acetylbenzoic	78
$4\text{-}CH_3C_6H_4\text{-}\overset{\overset{O}{\|}}{C}\text{-}C_6H_4CH_3\text{-}4$	B	$4\text{-}HO_2CC_6H_4\text{-}\overset{\overset{O}{\|}}{C}\text{-}C_6H_4CO_2H\text{-}4$	76
$4\text{-}CH_3C_6H_4\text{-O-}C_6H_4CH_3\text{-}4$	B	$4\text{-}HO_2C\text{-}C_6H_4\text{-O-}C_6H_4CO_2H\text{-}4$	87

[a] $Co(OAc)_2$/2-butanone catalyst (Ref. 100).
[b] $Co(OAc)_2/NaBr \equiv Co(OAc)$ Br catalyst (Ref. 130).

p-Cymene is selectively oxidized to *p*-isopropylbenzoic acid in the presence of $Co(OAc)_2$/2-butanone catalyst.[107,121] If the oxidation of *p*-cymene is carried out with stoichiometric amounts of $Co(OAc)_3$, the products are the acetate (81%) and 4-acetylbenzoic acid (15%).[106–108,121]

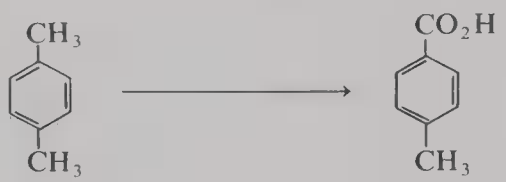


90% (135)

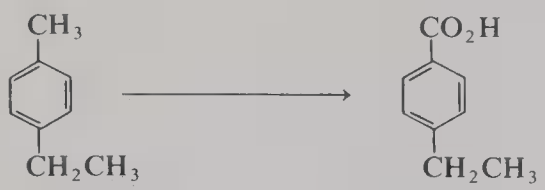


(136)

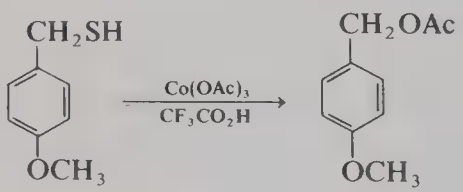
Other examples of the versatile selectivity available with various cobalt catalyst systems are shown in Eqs. (137),[100,130] (138),[106] (139),[105] (140),[24] and (141).[106]



(137)



(138)



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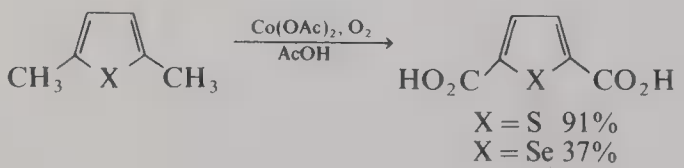
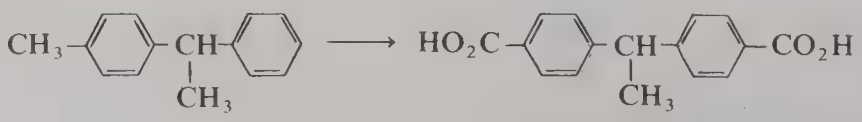
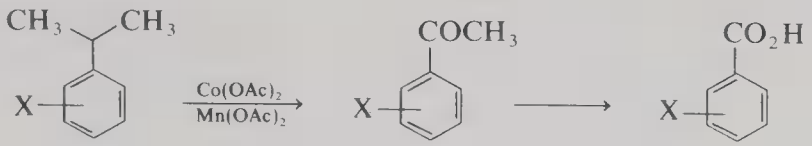


X = S 91%
X = Se 37% (140)



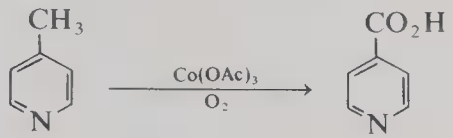
70% (141)

A combination of $Co(OAc)_2$ and $Mn(OAc)_2$ is an excellent catalyst system for converting isopropylbenzenes to the corresponding carboxylic acids.[136,137] Methyl phenyl ketone is probably an intermediate.



(142)

Alkylpyridines are oxidized selectively to the corresponding carboxylic acids in acetic acid at 60°C in the presence of dioxygen and $Co(OAc)_3$.[138]



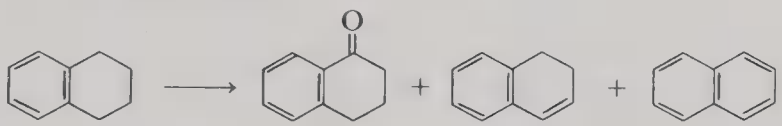
(143)

Neat ethylbenzene was oxidized with dioxygen at 70–135°C with a recyclable catalyst consisting of Co(II) attached to a copolymer of acrylic acid and diethylvinyl phosphonate.[139] No induction period was observed.

Activation of molecular oxygen has often been proposed to explain the catalytic effect of certain transition metal compounds on the oxidation of organic substrates. However, it has been shown that the catalytic effect is due to a catalyzed homolysis of adventitious hydroperoxides. A detailed kinetic investigation of the metal (Co, Cu, Mg, Ni, V, Zn) phthalocyanine autoxidation demonstrated that initiation arose via a catalyzed homolytic cleavage of hydroperoxides.[314]

3.3. Oxidation of Tetralins

The Co(OAc) Br catalyzed autoxidation of tetralin gave α-tetralone, 1,2-dihydronaphthalene (10%–15%), and naphthalene (0.5%–3%).[130] In a limited supply of oxygen, the major product was 1,2-dihydronaphthalene (62%).



(144)

Several cobalt complexes on silica gel catalyzed the oxidation of tetralin to alcohol, hydroperoxide, and ketone.[11c] The highest conversion was with the 2,2′-bipyridine complex.

3.4. Allylic Oxidations

Examples of cobalt catalyzed allylic oxidations are shown in Eqs. (43)–(45). Oxidation of cyclohexene in chloroform solution by dioxygen in the presence of cobalt naphthenate gave a mixture of cyclohex-2-enol (40%) and cyclohex-2-enone (60%). This mixture was oxidized by dichromate to give 2-cyclohexen-1-one in an overall yield of >80%.[146b]

3.5. Oxidation of Arenes

Benzene and other electron-poor aromatic compounds are oxidized by cobaltic trifluoroacetate to ring substituted aryl esters in solutions of trifluoroacetic acid.[123]

3.6. Oxidation of Carbon–Carbon Double Bonds

1,2-Dibromoethane was proposed as an intermediate during the autoxidation of ethene in the presence of cobaltous acetate–sodium bromide catalyst.[323]

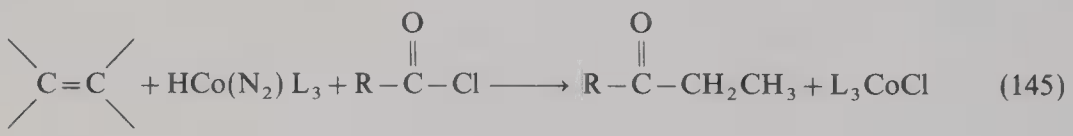
Cobalt nitro complexes such as py · Co(saloph) · NO_2 (saloph = *N*,*N*′-bis(alicyclidene-*o*-phenylene) diamino) and py · Co(TPP) · NO_2 (TPP = tetraphenylporphyrin) have been used as oxygen transfer agents to alkenes.[324,325] The nitro ligand may be regarded as a monoanionic oxygen-centered nucleophile. This activation of olefins toward nucleophilic attack by π coordination to palladium (II) or thallium (III) leads to carbonyl compounds[324] or oxiranes,[325] respectively. Some of the alkenes studied were ethene, propene, and 1-octene.

The selective oxidation of terminal olefins (1-hexene, 3-methyl-1-hexene, phenylethene, and 3-buten-1-ol) by molecular oxygen to the corresponding 2-ketone and 2-alcohol by using CoSalMDPT (CoSalMDPT = cobalt (II) bis(salicylidene-γ-imino propyl) methylamine) has been studied.[326] The oxidations, which were conducted in Parr pressure bottles, are remarkably solvent dependent and do not proceed by an autoxidation mechanism.

Cobalt and molybdenum are effective catalysts for the oxidation of 2-phenylpropene.[327] Aryl substituted olefins were converted to benzyl alcohols regioselectively by the use of oxygen and tetrahydroborate in the presence of a catalytic amount of bis(dimethylglyoximato)chloro(pyridine)cobalt(III) ($Co(DH)_2$ ClPy).[328] Addition of hydroxyl group occurred exclusively at the phenyl substituted olefinic carbon atom.

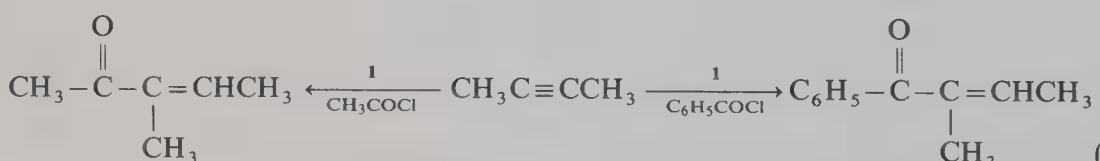
The conversion of norbornadiene to Bisnor-S (**12**) is shown in Eq. (54)[159,160] and the transformation of **12** to diamantane (**13**) is shown in Eq. (55).[161] The reaction of acyl cobalt carbonyl complexes (**14**) with 1,3-dienes to give acyldienes [Eq. (57)] is described above. This reaction can be made catalytic by preparing the acylcobalt carbonyl complexes (**14**) from $Co(CO_4)^-$ and alkyl or acyl halides in the presence of the diene, base, and carbon monoxide.[162] The usefulness of this system remains to be evaluated.

Hydroacylation of alkenes with acid chlorides in the presence of **1** is described in Eqs. (56)–(59).[163] Ethyl ketones are formed in good to excellent yields [Eq. (145)]. The yields are



(145)

considerably lower when 1-pentene is used in place of ethene. 2-Butyne reacts with acetyl chloride and benzoyl chloride to give 3-methyl-3-penten-2-one (12%) and caprophenone (11%), respectively [Eq. (146)].



(146)

3.7. Oxidation of Carbon–Carbon Triple Bonds

Table IV shows some of the aromatic compounds obtained from the reaction of dicobalt octacarbonyl (**5**) and mono- and disubstituted acetylenes.[168,193]

It is generally very difficult to selectively induce double bonds to undergo addition reactions in the presence of triple bonds. However, the reaction of an enyne with dicobalt octacarbonyl (**5**) leads to the formation of the corresponding dicobalt octacarbonylalkyne complex [Eqs. (60), (147)] in which the coordinated triple bond is now inert. Selective trans-

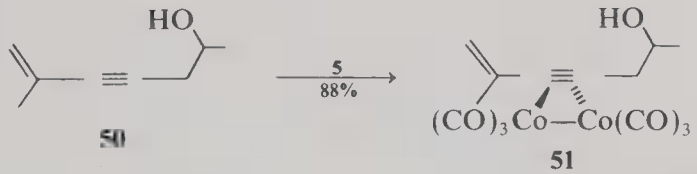
TABLE IV. Substituted Benzenes from the Cobalt Carbonyl Trimerization of Alkynes[a]

Alkyne	Catalyst[b]	Product (-benzene)	Yield (%)
$C_6H_5C{\equiv}CH$	A	1,2,4-Triphenyl-	70
$4\text{-}BrC_6H_4C{\equiv}CH$	A	1,2,4-Tris(4-bromophenyl)-	65
$C_6H_5C{\equiv}CCl$	A	1,2,4-Triphenyl-3,5,6-trichloro-	14
$C_6H_5C{\equiv}CCO_2CH_3$	A	1,2,4-Triphenyl-3,5,6-tricabomethoxy-	55
$C_6H_5C{\equiv}CCO_2H$	B	1,2,4-Triphenyl-3,5,6-tricarboxy-	11
$C_6H_5C{\equiv}CC_6H_5$	A	Hexaphenyl-	90
$4\text{-}ClC_6H_4C{\equiv}CC_6H_4Cl\text{-}4$	A	Hexakis-(4-chlorophenyl)-	95
$C_3H_7C{\equiv}CH$	A	1,2,4-Tri-*n*-propyl-	11
$C_2H_5C{\equiv}CC_2H_5$	A	Hexaethyl-	75
$C_6H_5C{\equiv}CCH_3$	A	1,2,4-Trimethyl-3,5,6-triphenyl-	90
$(CH_3)_3SiC{\equiv}CH$	C	1,2,4-Tris-trimethylsilyl-	55
$CH{\equiv}CCH_2CH_2OH$	D	1,2,4-Trisethanol-	14
$CH{\equiv}CCH_2OCH_3$	E	1,2,4-Tris-methoxymethyl-	17
$CH_3O_2CC{\equiv}CCO_2CH_3$	A	Hexacarbomethoxy-	80

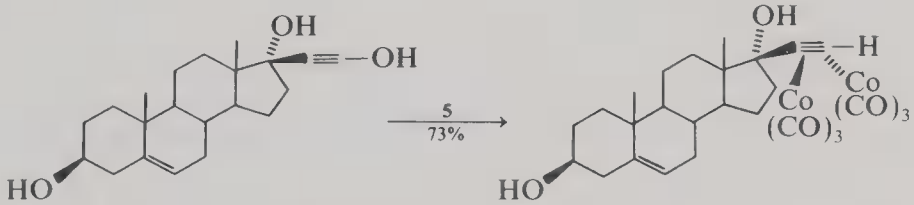
[a] Reference 168.
[b] A = $[Co(CO)_4]_2Hg$; B = $Co_2(CO)_6C_6H_5C_2CO_2H$; C = $Co_2(CO)_6(CH_3)_3SiC_2H$; D = $Co_2(CO)_6HOC_2H_4C_2H$; E = $Co_2(CO)_6CH_3OCH_2C_2H$.

formation of the double bond is now possible and the metal moiety is then easily removed in high yield.[170]

The complexes, which are prepared by stirring **5** and the alkyne overnight at 23–25°C in a hydrocarbon solvent,[168] are isolated in 70%–90% yield [Eqs. (60), (147), (148)].[170,193] The respective double bonds in **51** and **52** were selectively hydrated and reduced. The alkyne product may be recovered by oxidative degradation of the complex with $Fe(NO_3)_3 \cdot 9H_2O$ in 95% ethanol. Dilution with water and extraction with ether gives the product in excellent yield.

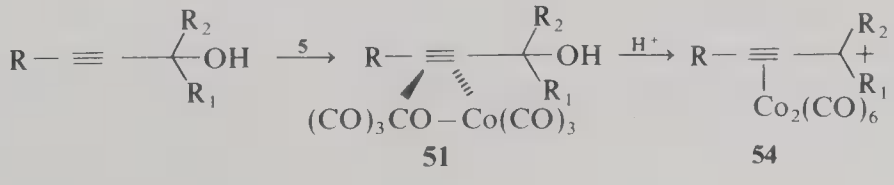


50 **51** (147)

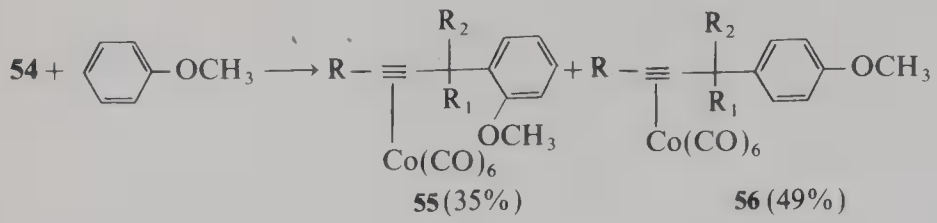


52 **53** (148)

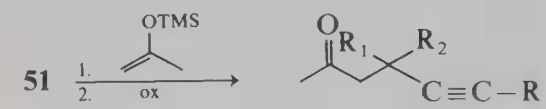
The dicobalt octacarbonyl–alkyne complex may be used to stabilize and protect propargyl carbocations.[171] These species (α-[(alkynl)dicobalt hexacarbonyl], **51**) may be used as electrophilic propargyl synthons, in organic synthesis [Eqs. (150),[171] (151),[172] and (152)[173]]. It is possible to carry out the three-step complexation–alkylation–decomplexation sequence in Eqs. (149) and (150) without purification of intermediates.[171]



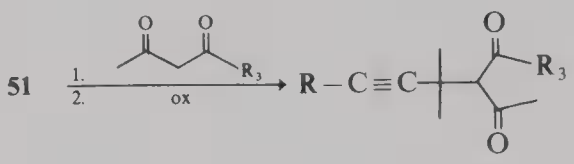
51 **54** (149)



(150)



(151)



(152)

Table V shows the products and yields from the (propargyl)dicobalt cation alkylation of β-dicarbonyl compounds. Except for the product from 2,4-pentanedione and the unsubstituted propargyl complex, all the alkylated derivatives exist entirely as the dicarbonyl tautomer in carbon sulfide solution (^{1}H NMR assay). No dialkylation was observed. Significant stereoselectivity was observed in experiments 5 and 6 (Table V). Although no products were obtained from 1,3-cyclohexanedione and indanedione, 2-acetylcyclohexanone and ethyl acetoacetate were alkylated in moderate but unoptimized yields.

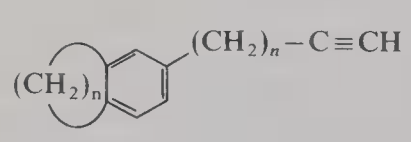
Table VI shows that (propargyl)dicobalt hexacarbonyl cations alkylate ketones regiospecifically as well as trimethylsilyl enol ethers and enol acetates.[173]

Cobaltacyclopentadiene complexes, which are useful starting materials in the synthesis of substituted benzenes, cyclohexadienes, thiophenes, selenophenes, and pyrroles, are prepared by the reaction of two molecules of an alkyne with π-cyclopentadienylbis(triphenylphosphine)cobalt ($CpCo[P(C_6H_5)_3]_2$).[174,193] Table VII summarizes the cobaltacyclopentadiene complexes obtained via this procedure.

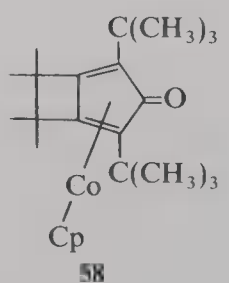
Table VIII shows the yields of cyclohexadienes from the reaction of olefins with cobaltacyclopentadiene complexes.

The complexes (**20**) react with sulfur, selenium, or nitrosobenzenes in benzene solution at 70–110°C to give substituted thiophenes, selenophenes, or pyrroles, respectively, (Table IX).

α,ω-Dialkynes ($HC\equiv C-(CH_2)_n-C\equiv CH$) give compounds of structure **57** with bis(tetracarbonylcobalt)mercury ($[Co(CO)_4]_2Hg$).[176] 1,6-Di-*tert*-butyl-3,3,4,4-tetramethyl-1,5-hexadienes react with η^5-cyclopentadienylcobalt dicarbonyl to give **58** (70%).[177]



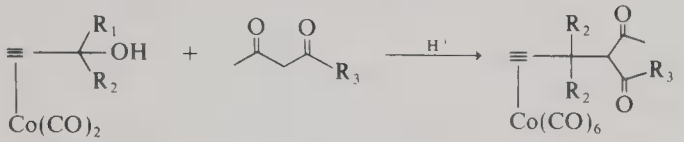
57



58

Macrocyclic alkadiynes react with commercially available $CpCo(CO)_2$ to give complex mixtures of products, depending on reaction condition.[178] Simpler ethyne complexes were formed with $Co_2(CO)_8$ (**5**, **6**).[179]

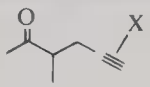
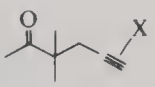
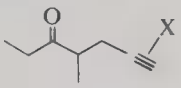
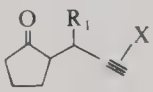
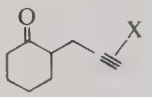
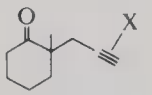
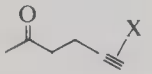
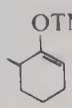
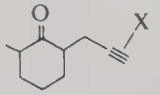
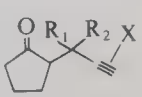
TABLE V. Alkylations of $CH_3(C(O)CH_2C(O)R_3$ with $[HC\equiv C(OH)R_1R_2]Co_2(CO)_6$[a]



R_1	R_2	R_3	Yield (%)
H	H	CH_3	95
H	CH_3	CH_3	65
H	C_6H_5	CH_3	91
H	H	C_6H_5	90
H	CH_3	C_6H_5	65
H	C_6H_5	C_6H_5	95

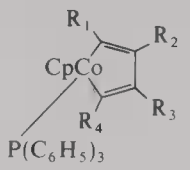
[a] Reference 172.

TABLE VI. Alkylation of Ketones[a] and Enol Derivatives[a] with $[(HC\equiv C(R_1R_2)Co_2(CO)_6]^+ BF_4^-$[b]

Substrate	Product		Yield (%)
2-Butanone			77
3-Methyl-2-butanone			70
3-Pentanone			84
Cyclopentanone		$R_1 = R_2 = H$ $R_1 = H$, $R_2 = C_6H_5$	83 62
Cyclohexanone			81
2-Methylcyclohexanone			80
			96
			51
		$R_1 = R_2 = H$ $R_1 = H_1$, $R_2 = C_6H_5$ $R_1 = R_2 = CH_3$	76 100 60

[a] $X = Co_2(CO)_6$.
[b] Reference 173.

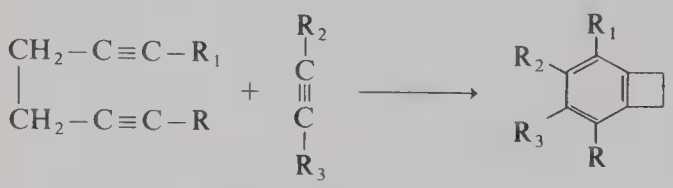
TABLE VII. Cobaltacyclopentadiene Complexes from the Reaction of Alkynes and $CpCo[P(C_6H_5)_3]_2$[a]



R_1	R_2	R_3	R_4	mp (°C)	Yield (%)
C_6H_5	C_6H_5	C_6H_5	C_6H_5	193–194	88
CO_2CH_3	CO_2CH_3	CO_2CH_3	CO_2CH_3	216–217	10
C_6H_5	CO_2CH_3	C_6H_5	CO_2CH_3	215–217	20
C_6H_5	CO_2CH_3	CO_2CH_3	C_6H_5	218–219	13
CO_2CH_3	CH_3	CH_3	CO_2CH_3	192–194	9
CO_2CH_3	CH_3	CO_2CH_3	CH_3	158–160	50
C_6H_5	CH_3	CH_3	C_6H_5	174–176	54
C_6H_5	C_6H_5	CH_2OCH_3	CH_2OCH_3	174–176	40
C_6H_5	C_6H_5	CO_2CH_3	C_6H_5	210	43
C_6H_5	C_6H_5	CH_3	CO_2CH_3	180–182	68
C_6H_5	C_6H_5	H	CO_2CH_3	149–151	48
C_6H_5	C_6H_5	CH_3	C_6H_5	169–171	67
C_6H_5	CO_2CH_3	CH_3	CO_2CH_3	179–182	39

[a] References 174, 193.

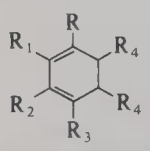
1,5-Hexadiynes react with alkynes in the presence of $CpCo(CO)_2$ to form benzocyclobutenes (Table X),[180] which are valuable precursors to theoretically interesting molecules and to the synthesis of natural products.



(153)

Cooligomerization of 1,6-heptadiyne and 1,7-octadiyne with substituted monoacetylenes, catalyzed by $CpCo(CO)_2$, provides a general synthetic entry into indans and tetralins (Table XI).

TABLE VIII. Substituted Cyclohexadienes from Cobaltacyclopentadiene Complexes[a]

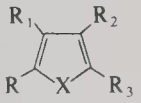


R	R_1	R_2	R_3	R_4	Method[b]	mp (°C)	Yield (%)
C_6H_5	C_6H_5	H	4-$CH_3C_6H_4$	H	A	138.5–140	93
C_6H_5	C_6H_5	H	CO_2CH_3	CO_2CH_3	B	117–119	36
C_6H_5	C_6H_5	CO_2CH_3	C_6H_5	H	A	151–154	33
C_6H_5	CO_2CH_3	CO_2CH_3	C_6H_5	H	B	179–180	33

[a] Reference 193.

[b] A: Obtained directly by the reaction of the cobaltacyclopentadiene with olefins; B: obtained by the decomposition of the cyclohexadiene complex with Ce(IV).

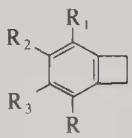
TABLE IX. Heterocycles from Cobaltacyclopentadiene Complexes[a]



X	R	R_1	R_2	R_3	mp (°C)	Yield (%)
$N-C_6H_5$	C_6H_5	CH_3	CH_3	C_6H_5	171.5–172.5	35
$N-C_6H_5$	C_6H_5	C_6H_5	C_6H_5	C_6H_5	287–288	34
S	C_6H_5	C_6H_5	C_6H_5	C_6H_5	181	75
S	C_6H_5	CH_3	CH_3	C_6H_5	159	70
S	C_6H_5	C_6H_5	H	C_6H_5	139–140	24
S	C_6H_5	C_6H_5	CO_2CH_3	C_6H_5	138–139	76
S	CO_2CH_3	CH_3	CH_3	CO_2CH_3	168–169	31
S	C_6H_5	CO_2CH_3	CH_3	CO_2CH_3	97–98	41
S	C_6H_5	CO_2CH_3	CO_2CH_3	C_6H_5	166–167	58
S	CO_2CH_3	C_6H_5	CH_3	CO_2CH_3	129–131	31
Se	C_6H_5	C_6H_5	C_6H_5	C_6H_5	180–181	77
Se	C_6H_5	CH_3	CH_3	C_6H_5	156	65
Se	C_6H_5	CO_2CH_3	CO_2CH_3	C_6H_5	174	68

[a] References 174, 193.

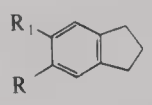
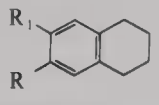
TABLE X. Benzocyclobutenes from the $CpCo(CO)_2$-Catalyzed Cyclization of 1,5-Hexadiynes and Acetylenes[a]



R	R_1	R_2	R_3	Yield (%)
H	H	CO_2CH_3	CO_2CH_3	14
H	H	C_6H_5	H	17
H	H	C_6H_5	C_6H_5	48
H	H	n-C_6H_{13}	H	13
H	H	$(CH_3)_3Si$	$(CH_3)_3Si$	65
H	H	CH_2OCH_3	CH_2OCH_3	33
H	H	CH_2OCH_3	$(CH_3)_3Si$	55
H	H	CH_2OH	H	14
CH_3	CH_3	C_6H_5	C_6H_5	20
CH_3	CH_3	CO_2CH_3	CO_2CH_3	28
CH_2OCH_3	CH_2OCH_3	$(CH_3)_3Si$	H	25
H	$(CH_3)_3Si$	$(CH_3)_3Si$	H	13
$(CH_3)_3Si$	$(CH_3)_3Si$	$(CH_3)_3Si$	H	2
H	$(CH_3)_3Si$	$(CH_3)_3Si$	CH_2OCH_3	16

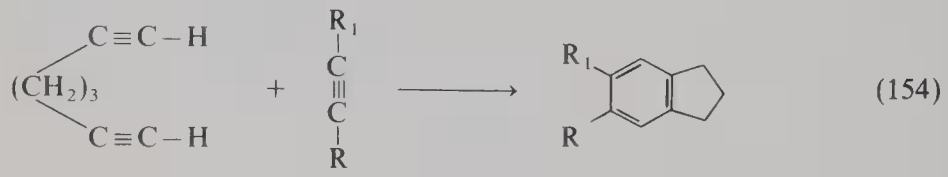
[a] References 175, 180, 182.

TABLE XI. Indans and Tetralins from the $CpCo(CO)_2$-Catalyzed Cooligomerization of Alkynes[a]

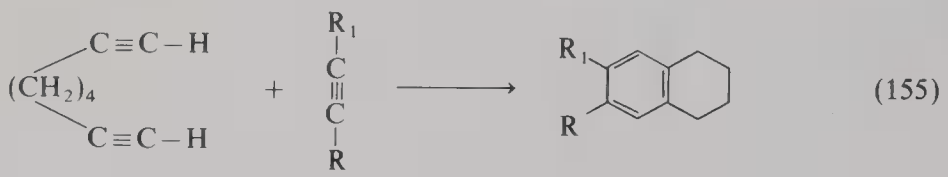



R	R_1	Yield (%)	R	R_1	Yield (%)
CO_2CH_3	CO_2CH_3	20	CO_2CH_3	CO_2CH_3	26
H	C_6H_5	26	H	C_6H_5	18
C_6H_5	C_6H_5	24	C_6H_5	C_6H_5	21
H	*n*-C_6H_{13}	14	H	*n*-C_6H_{13}	14
$(CH_3)_3Si$	$(CH_3)_3Si$	82	$(CH_3)_3Si$	$(CH_3)_3Si$	85
			CH_3	$(CH_3)_3Si$	34

[a] References 175, 181, 182.

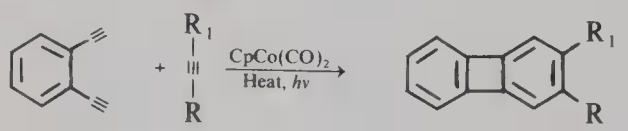


(154)



(155)

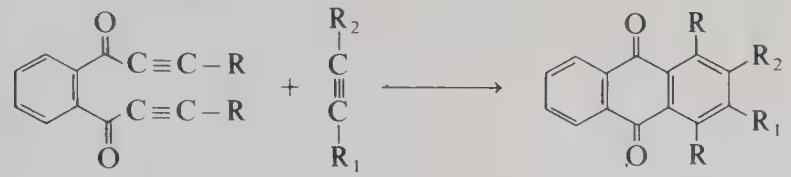
1,2-Diethynylbenzene is catalytically cocyclized with alkynes in the presence of dicarbonyl(cyclopentadienyl)cobalt to provide a versatile synthesis of the biphenylene nucleus [Eq. (156)].[330] The success of this transformation is remarkable considering the thermal instability of the product, the observation that η^4-1,2-diethynylcyclobutadienyl (η^5-cyclopentadienyl)cobalt does not lead to analogous products,[331] and the electronic destabilization of the biphenylene nucleus.



(156)

R	R_1	Yield (%)
$SiMe_3$	$SiMe_3$	96
C_5H_{11}	$SiMe_3$	58
C_5H_{11}	H	41
Bu	Bu	44
Ph	H	25
Ph	Ph	35
CO_2Me	CO_2Me	30

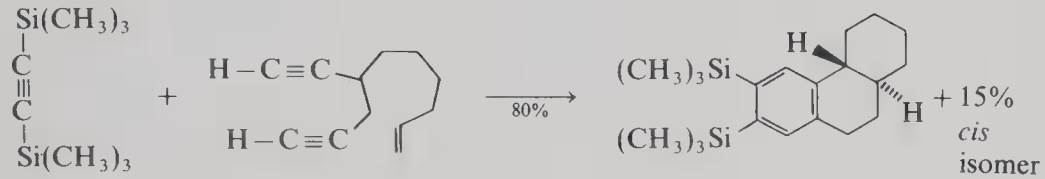
Two examples of the potential of a catalytic anthraquinone synthesis were tested in the preparation of **61** and **64**.[182]



(157)

59 R = H **60** $R_1 = R_2 = (CH_3)_3Si$ **61** R = H, $R_1 = R_2 = (CH_3)_3Si$
62 $R = (CH_3)_3Si$ **63** $R_1 = H$; $R_2 = n\text{-}C_6H_{13}$ **64** $R = (CH_3)_3Si$; $R_1 = H$; $R_2 = n\text{-}C_6H_{13}$

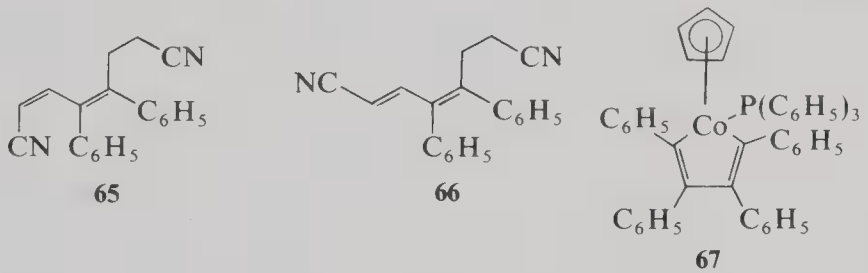
Unsymmetrical cotrimerization can be favored by using an acetylene with two bulky substituents as one reactant. An elegant application of this method, which involves several C–C bond-making and bond-breaking steps, is found in the synthesis of polycyclic compounds [Eq. (158)].[175,183,184] The versatility of this reaction is shown in Table XII.[175] Moreover, this methodology is applicable to the synthesis of steroids.[183,184]



(158)

(BTMSA)

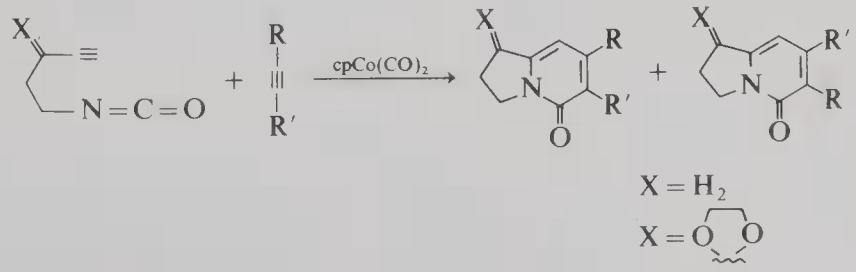
When the reaction of diphenylacetylene and acrylonitrile is carried out with π-$C_5H_5Co[(C_6H_5)_3P](C_6H_5C{\equiv}CC_6H_5)$, the linear cooligomerization products **65** and **66** are produced.[185] Two molecules of acetylene and one molecule of a nitrile cocyclotrimerize to give pyridine in the presence of a catalytic amount of cyclopentadienyltriphenylphosphinecobaltatetraphenylcyclopentadiene (**67**) or cyclopentadienyl(diphenylacetylene)triphenylphosphinecobalt.[186] A similar reaction has been performed using a Co(I) catalyst which is



65 **66** **67**

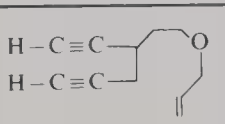
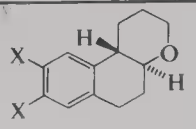
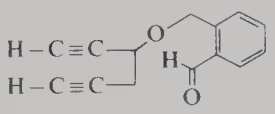
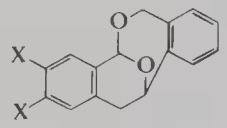
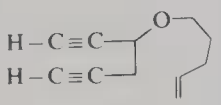
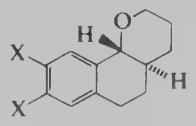
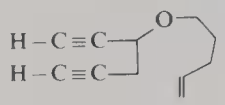
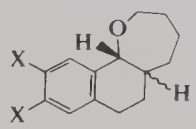
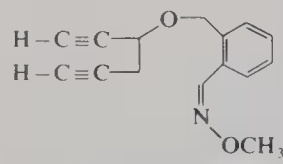
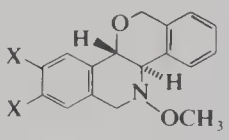
prepared *in situ* from cobalt salts and reductants.[187,188] Other cobalt systems have also been used to produce pyridines.[189] An improved method for the synthesis of pyridines from acetylenes and nitriles uses cobaltocene (di-π-cyclopentadienylcobalt) as the catalyst (Table XIII).[190,191]

Cocylization of 5-isocyanatoalkynes with a variety of alkynes in presence of catalytic η^5-$C_5H_5CO(CO)_2$ provides a chemo- and regioselective entry in the class of functionalized 2,3-dihydro-5(1H)-indolizinones [Eq. (159), Table XIV].[332] This method provides a versatile way to assemble annulated pyridones with extensive control of their substitution pattern.



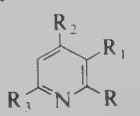
(159)

TABLE XII. Synthesis of Polycycles[a] from the $CpCo(CO)_2$ Cyclization of Alkynes with $(CH_3)_3Si-C\equiv C-Si(CH_3)_3$ (BTMSA)[b]

Reactant	Product	Yield (%)
		90
		50
		60
		65
		45

[a] X = $(CH_3)_3Si$.
[b] Reference 175.

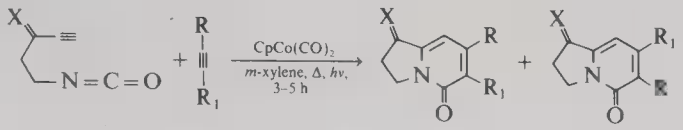
TABLE XIII. Pyridines from the Cobaltacene Catalyzed Cotrimerization of Alkynes and Nitriles



R	R_1	R_2	R_3	Yield (%)
CH_3	H	H	H	60
C_2H_5	H	H	H	62
n-C_3H_7	H	H	H	60
i-C_3H_7	H	H	H	43
$CH_2=CH$	H	H	H	31
C_6H_5	H	H	H	73
$C_6H_5CH_2$	H	H	H	19
CH_3	CH_3	H	CH_3	45
CH_3	C_2H_5	H	C_2H_5	30
CH_3	*n*-C_3H_7	H	*n*-C_3H_7	42
CH_3	*n*-C_4H_9	H	*n*-C_4H_9	40
n-C_3H_7	C_2H_5	H	C_2H_5	28
CH_3	H	CH_3	CH_3	48
CH_3	H	C_2H_5	C_2H_5	57
CH_3	H	*n*-C_3H_7	*n*-C_3H_7	47
CH_3	H	*n*-C_4H_9	*n*-C_4H_9	48
n-C_3H_7	H	C_2H_5	C_2H_5	46

[a] Reference 190.

TABLE XIV. Cocylization Products 5-Isocyanatcalkynes and Alkynes[a]



R	R_1	% yield (mp, °C)	% yield (mp, °C)
$(CH_3)_3Si$	$(CH_3)_3Si$	72 (117–119)	
n-Pr	$(CH_3)_3Si$	68 (64–66)	5 (115–120)
	$(CH_3)_3Si$	76 (150–152)	
t-Bu	$(CH_3)_3Si$	17 (79–81)	<1
	Et	41 (oil)	31 (oil)
$(CH_3)_3Si$	$(CH_3)_3Si$	68 (134–135)	
n-Pr	$(CH_3)_3Si$	60 (87–89)	3 (oil)
n-Pr	$CH_2OSi(t\text{-Bu})(C_6H_5)_2$	20 (165–167)	18 (oil)
CH_3	CO_2Et	14 (108–110)	17 (96–97)

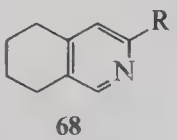
[a] Reference 332.

The chelating agent, 2,2′-bipyridine, can be prepared in 95% yield by the reaction of ethyne with 2-cyanopyridine in the presence of the 1,5-cyclooctadiene complex $Co(C_5H_5)$-(CoD).[189] α,ω-Dinitriles give similarly high yields of alkylene-bridged bipyridines. 1,2-Dithiopyrones, *N*-methyl-2-thiopyridones, thiophenes, selenophenes, and pyrroles can be prepared from the cobaltacyclopentadiene and suitable unsaturated molecules containing a heteroatom or group (Table IX).[192–194]

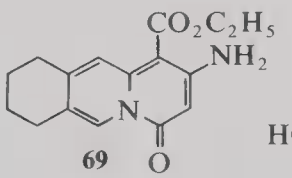
Cooligomerization of α,ω-diynes with nitriles effects direct synthesis of substituted 5,6,7,8-tetrahydroisoquinolines (**68**, 70%–80%).[175]

1,7-Octadiyne reacts with ethyl cyanoacetate in the presence of $CpCo(CO)_2$ to give quinolizine **69** in one step.[175]

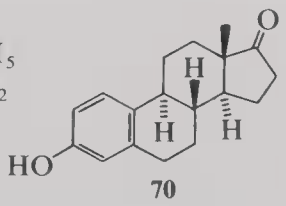
Racemic estrone (**70**)[183,184] and other natural products can be made via cobalt catalyzed cyclotrimerizations.



68



69



70

3.8. Oxidation of Organic, Organomagnesium, and Organomercuric Halides

The influence of $CoCl_2$ on the Grignard reaction in order to produce coupling of organic halides is described above [Eqs. (71)–(73)].[198–203]

The carboalkoxylation of organic halides with sodium cobalt carbonylate [$NaCo(CO)_4$] or the formation of amides from organic halides and unhindered amines is described above [Eq. (74)].[162,204–209] The reaction of $NaCo(CO)_4$ with organic halides in the presence of carbon monoxide and 1,3-dienes to give acyldienes is shown in Eqs. (56) and (57).[162]

Simple *para*-substituted arylmercuric chlorides or bromides react with dicobalt octacar-

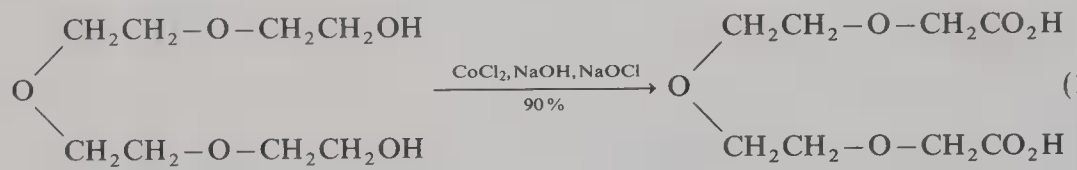
bonyl (**5**, **6**) in THF at 22–25°C to give the corresponding diaryl ketones in excellent yields [4,4′-dimethyl- (86%), 4,4′-dimethoxy- (84%), 4,4′-dichloro- (89%), and 4,4′-difluorobenzophenone (93%)].[210] No ketones were obtained from C_6F_5HgBr or C_6Cl_5HgCl. Moderate yields of dialkyl ketones were obtained from alkylmercuric halides. When two different organomercuric halides were allowed to react with dicobaltoctacarbonyl (**5**, **6**), symmetrical and unsymmetrical ketones were formed.

3.9. Oxidation of Hydroxy Compounds

3.9.1. Alcohols

Cobalt compounds may be used to oxidize alcohols to carboxylic acids [Eqs. (160) and (161)].[223]

$$CH_3CH_2CH_2CH_2OH \xrightarrow[80\%]{CoCl_2, NaOH, NaOCl} CH_3CH_2CH_2CO_2H \qquad (160)$$



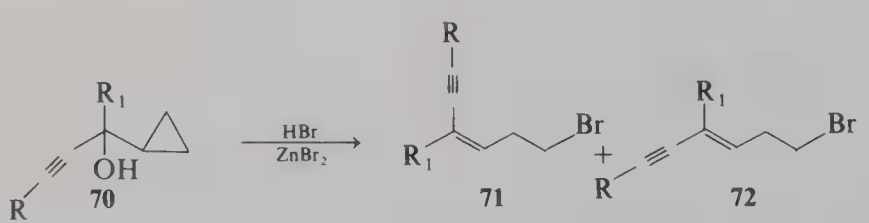
(161)

Lewis acids dramatically enhance the oxidation power of cobalt-nitro complexes. Thus, in the presence of $BF_3 \cdot Et_2O$ or $LiPF_6$, cobalt-nitro complexes such as PyCo(Saloph) NO_2 or py(TPP) NO_2 oxidize primary alcohols to aldehydes and secondary alcohols to ketones.[324b] No reaction is observed in the absence of Lewis acids.

Benzyl alcohols were converted into the corresponding one carbon-homologated amides or esters in one pot by cobalt carbonyl catalyzed carbonylation in the presence of ethyl polyphosphate (PPE) and sodium iodide.[333] Arylacetic esters were prepared in one pot (35%–77%) according to Eq. (162).[333]

$$ArCH_2-OH + CO + ROH \xrightarrow[CO_2(CO)_8, N(C_4H_9)_3]{PPE, NaI} ArCH_2-\overset{\overset{O}{\|}}{C}-OR \qquad (162)$$

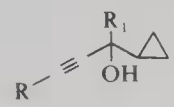
Conversion of the tertiary alcohols (**70**) to E and Z enynes (**71** and **72**) may be performed via Eq. (163) without the dicobalt octacarbonyl complex or with the complex via Eq. (164) [cf. Eq. (149)].[224] Table XV shows that the E isomer is favored when the dicobalt octacarbonyl complex is used.

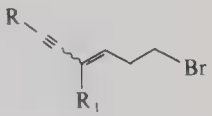


(163)

$$\mathbf{70} \xrightarrow[3.\ Fe^{3+}]{1.\ Co_2(CO)_8 \quad 2.\ HBr, ZnBr_2} \mathbf{71} + \mathbf{72} \qquad (164)$$

TABLE XV. Stereoisomers from the Dicobalt Octacarbonyl Complexes of Acetylenic Alcohols[a]



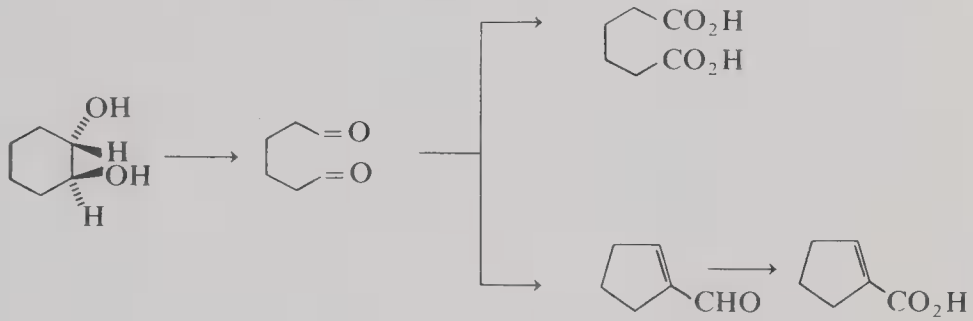


R	R_1	Reaction conditions[b]	Isomer (%) E	Isomer (%) Z	Overall yield (%)
CH_3	H	A	97	3	63
		B	48	52	80
CH_3CH_2	H	A	99	1	65
		B	33	67	80
CH_3	CH_3	A	91	9	53
		B	3	97	80
CH_3CH_2	CH_3	A	98	2	60
		B	2	98	80

[a] Reference 224.
[b] Experimental conditions: A with dicobalt octacarbonyl complex [Eq. (161)]; B without dicobalt octacarbonyl complex [Eq. (160)].

3.9.2. *Oxidation of Diols*

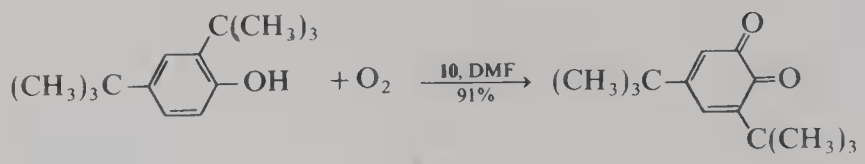
Cobalt(II) salts are effective catalysts for the autoxidation of glycols in aprotic polar solvents such as pyridine, 4-cyanopyridine, benzonitrile, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide, anisole, chlorobenzene, and thiocyclopentane-1,1-dioxide (sulfolane).[225] The reaction conditions may be adjusted to give aldehydes or carboxylic acids as the major products. The yields of aldehydes range from 60% to 80%. The cleavage of (E)-1,2-dihydroxycyclohexane is an example of this autoxidation procedure.[225]



(165)

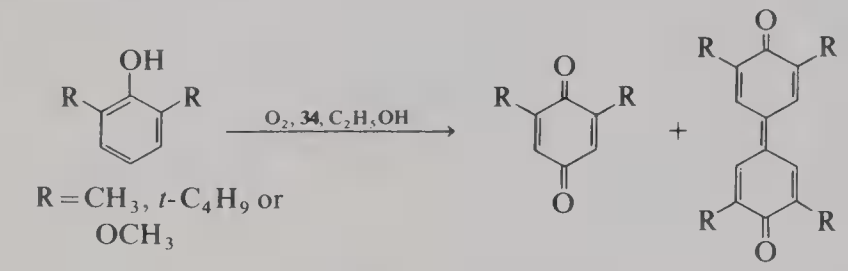
3.9.3. *Oxidation of Phenols and Hydroquinones*

Table XVI summarizes some of the 1,4-benzoquinones from the cobalt catalyzed autoxidation of phenols. Electron releasing groups in **31** enhanced the formation of 1,4-benzoquinones. Although **9** (**34**) and **10** do not catalyze the oxidation of 2,6-dichlorophenol, aquo-3-fluoro(Salen)cobalt(II) [R=H, R_1=F, L=H_2O in **31**] is effective. Increasing the number of alkyl or electron releasing groups on the phenols also facilitated oxidation. Higher rates and selectivities are obtained in DMF solvent.[241,242,261,264] Although alkyl substituted phenols are preferentially oxidized to 1,4-benzoquinones instead of 1,2-benzoquinones, a phenol with a blocked para position is oxidized to the corresponding 1,2-benzoquinone.[235,265] When the phenol is blocked at the ortho and para positions the *p*-quinol is formed [Eq. (90)].[245–250]



(166)

The (Acacen) Co(II) [**9**, **34**] complex converts hydroquinones to 1,4-benzoquinones in good to excellent yields (Table XVI).[235] Substituent groups on the aromatic ring can exert a marked influence on the rate of oxidation via electronic and/or steric effects *(vide supra)*. For example, 3,5-di-*t*-butylcatechol was oxidized to 3,5-di-*t*-butyl-1,2-benzoquinone (86%) while 2,5-di-*t*-butyl- and 2-methoxycarbonylhydroquinone were recovered unchanged. 2,6-Disubstituted phenols gave mixtures of products, including 1,4-benzoquinones and diphenoquinones [Eq. (164)].[235] 4-Methyl-, 2,6-diisopropyl-, and 2,4,6-tri-*t*-butylphenol gave mixtures of products which contained 1,4-benzoquinones, diphenoquinones, and other unidentified products.[235]

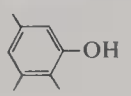
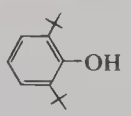
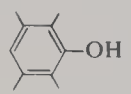
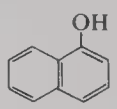
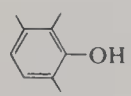
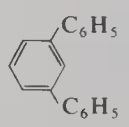
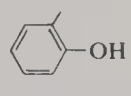
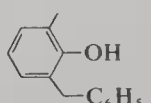
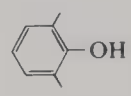
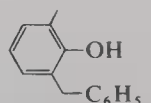
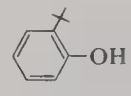


(167)

A polymer supported cobalt dioxygen catalyst, which oxidizes 2,6-dimethylphenol to the corresponding 1,4-benzoquinone, has been reported.[266] This system could become synthetically useful if the soluble cobalt complex does not require recycling.

Cobalt catalysts have been used to oxidize dihydroxynaphthalenes[268] and α-tocopherol.[269]

TABLE XVI. 1,4-Benzoquinones from the Cobalt Catalyzed Autoxidation of Phenols

Phenol	Catalyst[a]	Yield (%)	Reference	Phenol	Catalyst	Yield (%)	Reference
	A	93	235		A	*b*	235
	B	94	261		B	99	242
					D	73	242
	A	96	235		I	90	261
	B	92	241		B	91	264
	A	80	235				
	C	92	242				
					C	77	239, 257
	D	100	242				
					E	94	257
	A	79	235				
	C	96	242				

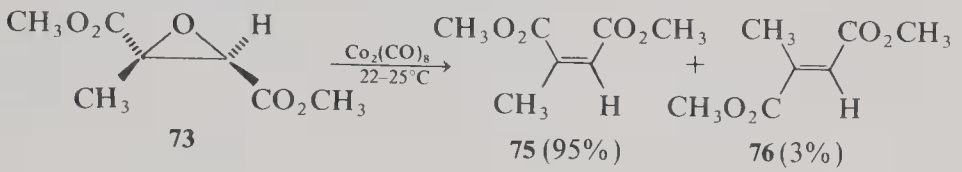
[a] A, (Acacen) Co(II) [**9**, **34**]; B, (Salen) Co(II); C, (Salen)(py) Co(II); D, phthalocyanine Co(II) [**33**]; E, 3-methoxy-(Salen)(py) Co(II).

[b] No reaction.

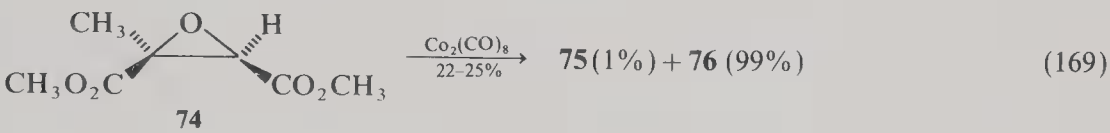
3.10. Oxidation of Oxiranes

The conversion of oxiranes to β-hydroxesters is described in Eqs. (99) and (100).[162]

A mild, high yield, and in certain instances, highly stereospecific method for the deoxygenation, with inversion, of epoxy esters using dicobalt octacarbonyl (**5**, **6**) has been reported [Eqs. (168), (169)].[271] This procedure is preferable to the lithium diphenylphosphide method which is not satisfactory for eoxy esters.[272]



73 **75** (95%) **76** (3%) (168)



74 (169)

3.11. Oxidation of Carbonyl Compounds

3.11.1. Aldehydes

The cobalt catalyzed autoxidation of ethanol is used for the manufacture of acetic acid,[277] acetic anhydride,[278] and peroxyacetic acid.[279] Better yields are obtained with linear aldehydes than with branched chain aldehydes, which are susceptible to metal catalyzed decarbonylation via the acyl radical. The use of oxochromium (VI) oxidants or permanganate ion is the preferred laboratory method for converting aldehydes to carboxylic acids.

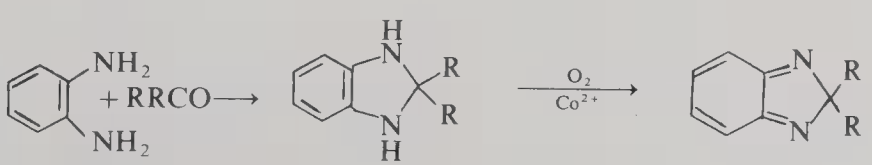
3.11.2. Oxidation of Ketones and o-Quinones

The oxidation of ketones and *o*-quinones is described in Eqs. (106)–(111).[281–287]

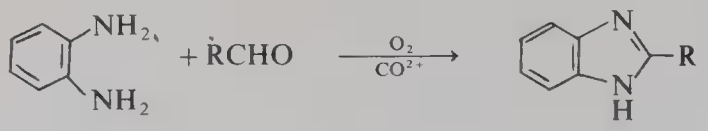
3.12. Oxidation of Nitrogen Compounds

3.12.1. Amines

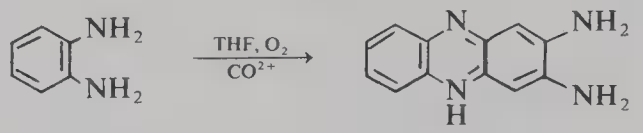
The cobaloxime (II) derivatives $Co(Hdmg)_2(PPh_3)_2$ and $[Co(Hdmg)_2Py]_2$ catalyze the oxidation (atmospheric oxygen at 22–24°C) of *o*-phenylenediamine and ketones or esters (as solvents) to substituted 2H-benzimidazoles [Eq. (170)].[334] Aldehydes react similarly [Eq. (171)]. The oxidation products are formed via catalytic dehydrogenation of intermediate substituted dehydrobenzimidazoles, which are cyclization products of *o*-phenylenediaine with the solvent. In propanone solvent with cobalt(II) as catalyst, the exclusive product is 2,2-dimethyldihydrobenzimidazole [Eq. (170)].[335] In methanol and tetrahydrofuran, *o*-phenylenediamine is converted to 2,3-diaminophenazine with 100% selectivity [Eq. (172)].



(170)

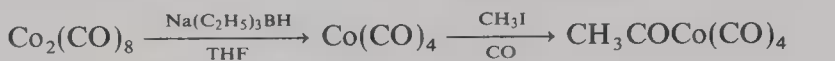


(171)

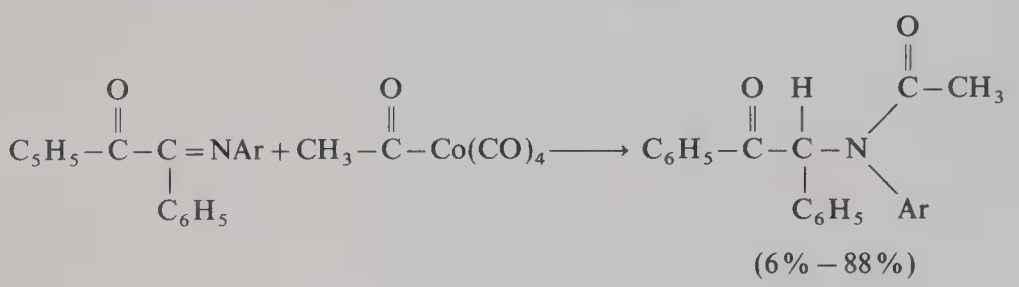


(172)

Reaction of α-keto imines with the *in situ* generated acetylcobalt tetracarbonyl occurs only at the carbon–nitrogen double bond to give β-keto amides [Eqs. (173), (174)].[336]



(173)

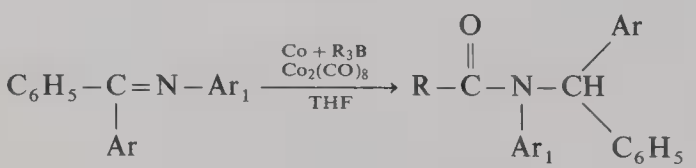


(174)

(6% – 88%)

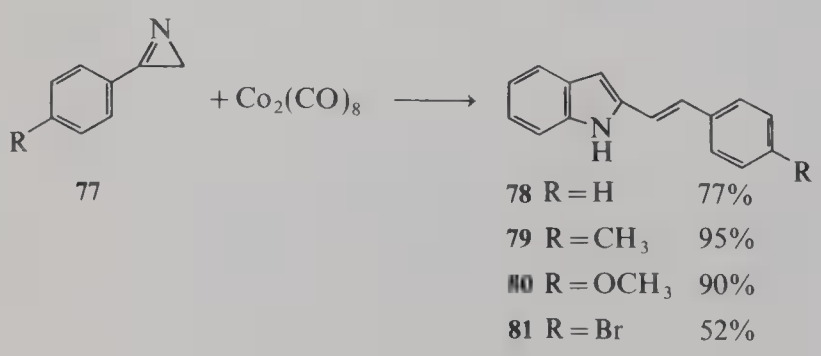
Ar = C_6H_5, 4-$CH_3C_6H_4$,
4-$CH_3OC_6H_4$, 2,4-$(CH_3)_2C_6H_3$
2,6-$(CH_3)_2C_6H_3$

The yields in Eq. (174) were improved, i.e., 60%–61%, by carbonylation of the Schiff base with an equimolar amount of an organoborane and a catalytic quantity of dicobalt octacarbonyl [Eq. (175)].[337]



(175)

Treatment of azirines (**77**) with dicobalt octacarbonyl (**5**, **6**) in benzene at 22–25°C for 24 h affords 2-styrylindoles (**78–81**) in good to excellent yields.[302]



(176)

77

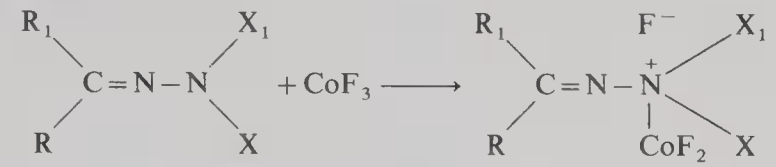
78 R = H 77%
79 R = CH_3 95%
80 R = OCH_3 90%
81 R = Br 52%

3.12.2. Amides

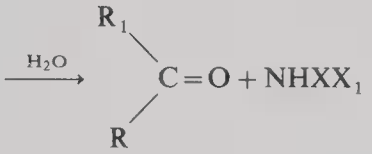
The Co(III) oxidation of amides is described in Eqs. (112)–(115).[298]

3.12.3. *Hydrazones and Oximes*

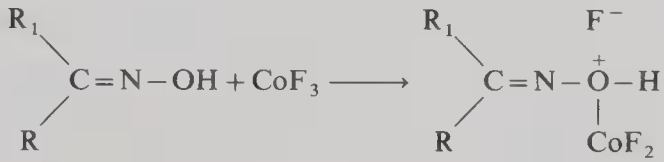
Cobalt trifluoride regenerates carbonyl compounds from hydrazones and oximes via oxidative cleavage.[303] Cobalt trifluoride is easy to handle and show significant selectivity, giving generally the highest yields with *N,N*-dimethylhydrazones.

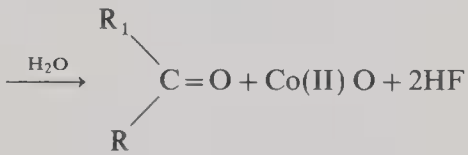


$X = Tos, X_1 = H$
$X = X_1 = CH_3$



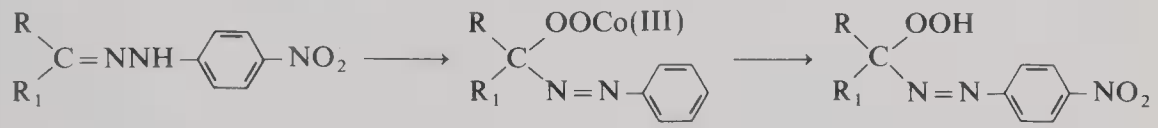
(177)





(178)

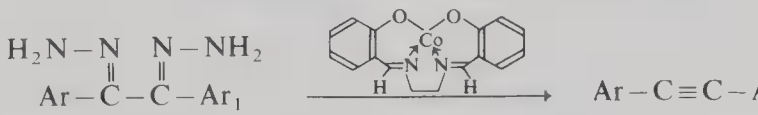
4-Nitrophenylhydrazones, unsusceptible to autoxidation, are readily oxygenated in the presence of a five-coordinate cobalt(II)–Schiff base complex, Co(II)(MeOSalen)(Py), leading to quantitative formation of novel 1-(4-nitrophenylazo)-1-peroxy Co(III) complexes which are converted to (4-nitrophenylazo)-1-hydroperoxyalkanes [Eq. (179)].[337]



R or R_1 = aryl and/or alkyl

(179)

Bis(salicylidene)ethylenediaminatocobalt(II) complexes catalyze the oxidation of dihydrazones to alkynes in excellent yields under mild conditions [Eq. (180)].[338]



Ar, Ar_1 = C_6H_5, *p*-tolyl, *p*-anisyl, 4-$Me_2NC_6H_4$, *4*-ClC_6H_4

(180)

3.12.4. *Nitrosobenzenes*

Catalytic action by the dipivaloylmethane chelate of Co(II) [$Co(dpm)_2$], which is rapidly converted to a mixture of Co(II) and Co(III) under the reaction conditions, catalyzes

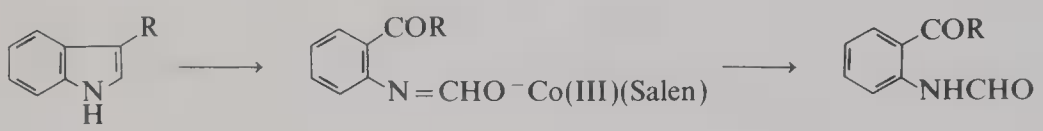
the *tert*-butyl hydroperoxide oxidation of nitrosobenzene to nitrobenzene via a straightforward two-step initiation sequence.[304]

3.12.5. Isocyanides

Cobaloxime(II) complexes, which catalyze the selective oxidation of organic substrates such as hydroquinone, hydrazobenzene, and triphenylphosphine with dioxygen under mild conditions,[339] catalytically oxidize butyl and octyl isocyanide to the corresponding isocyanates [42%–46%, Eq. (181)].[340] Similarly, nitrosobenzene is oxidized to nitrobenzene (22%–28%).

$$R-N=C \xrightarrow{O_2,Co^{2+}} R-N=C=O \tag{181}$$

The oxygenolysis of the heterocyclic ring of 3-substituted indoles related to tryptophan is catalyzed by transition metal complexes such as Co(Salen),[341,342] and Co(Tpp).[343] It has been found[341] that the Co(Salen)-catalyzed oxygenolysis of 3-methylindole in dichloromethane involves the cobalt(III) (Salen) complex of an anion of the product, *o*-formylaminoacetophenone, as the active catalyst [Eq. (182)].



(182)

R = Me, Et,
i, Pr, *t*-Bu

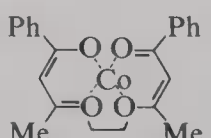
3.13. Oxidation of Sulfur Compounds

Cobalt(III) oxide oxidizes mercaptans to disulfides in low to good yields.[312]

$$2R-SH \longrightarrow R-S-S-R \tag{183}$$

The cobaltous chelate of 4,4′,4″,4‴-tetrasulfophthalocyanine adsorbed by Sephadex DEAE anion exchange resin is reduced by thiols to the cobalt(I) form and can be regenerated by air. This cobaltous-anion exchange resin system is an efficacious catalyst for the autoxidation of thiols.[344]

In the oxygenation reaction of alkyl sulfides with Co(II)(bzacen)–O_2 system, oxidative carbon–sulfur bond cleavage (S-dealkylation) was found to take place exclusively. The reactivity of S-dealkylation reaction was dependent on both acidity of the α-methylene group and steric hindrance of alkyl sulfide (Table XVII). The peroxo-Co(III) species is presumed to be the intermediate in this S-dealkylation reaction.[345]



Co(II)(bzacen)

$$C_6H_5SCH_2COC_6H_5 \xrightarrow[CH_3OH]{Co^{2+},O_2} C_6H_5SSC_6H_5 + C_6H_5COCHO + C_6H_5CO_2H \tag{184}$$

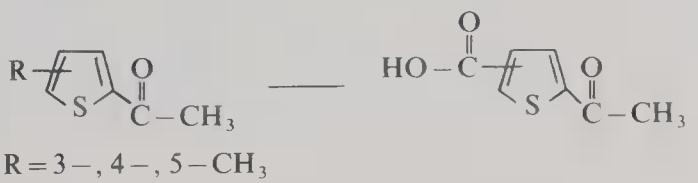
Oxidation of acetylmethylthiophenes by oxygen with cobaltous acetate–sodium bromide catalyst gave the corresponding acetylthiophenecarboxylic acids via the aldehydes [Eq.

TABLE XVII. The Oxygenation of Sulfides, Sulfoxide, and Ether Having α-Active Methylenes Catalyzed by Co(II) (bzacen)[a]

$$Ph-S-CH_2R + CO(II)\,(bzacen) \xrightarrow{O_2} PhSSPh + RCHO + RCO_2H$$

R	Time (h)	Solvent	Yield (%)		
$-COPh$	0.5	MeOH	Quant	81	13
$-CN$	15	MeOH	Quant	—	
$-CO_2Et$	15	MeOH	52	—	
$-C_6H_4NO_2$-4	72	MeOH	No reaction		
	48	MeOH-Py (1:1)	Quant	50	Trace
$-CH_2CN$	120	MeOH (or MeOH-Py)	No reaction		
$-Ph$	120	MeOH	No reaction		
$-H$	120	MeOH	No reaction		
$PhS(O)CH_2CN$	120	MeOH	No reaction		
$PhOCH_2COPh$	16	MeOH	50	(PhOH) 93	

(185)].[346] The oxidation of 2-(acetoxymethyl)thiophene with a cobaltous acetate–sodium bromide catalyst in ethanoic acid gave 2-thiophenecarboxylic acid (≥90%).[347] 2-Ethyl-3-methylthiophene yields mainly 3-methyl-2-acetylthiophene and 1-(3-methyl-2-thienyl)-ethyl acetate.



$R = 3-, 4-, 5-CH_3$ (185)

Cobalt(III) sulfate in acid solution converts alkane- and arenesulfinic acids to α-disulfones via an intramolecular dimerization dehydration process [Eq. (186)].[313] The mechanism of this interesting reaction, which provides α-disulfones in yields of 35%–56%, is not known.[313] The major byproduct is the sulfonic acid.

$$2R-SO_2H + 2Co^{3+} \longrightarrow R-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-R + 2Co^{2+} + 2H^+ \qquad (186)$$

A possible mechanism for α-disulfone formation is a one-electron abstraction to give the sulfinyl radical ($R\dot{S}O_2$), which subsequently dimerizes. An alternate mechanism, involving preliminary coordination of two molecules of sulfinate ion (RSO_2^-) with one cotaltic ion, is also reasonable [Eq. (187)]. Reduction to Co(I) followed by rapid oxidation to CO(II) has some parallel to chromium and permanganate ion oxidations.[313]

$$2RSO_2^- + Co^{3+} \longrightarrow (RSO_2)\,Co^+ \qquad (187)$$

$$(RSO_2)_2\,Co^+ \longrightarrow RSO_2SO_2R + Co^+ \qquad (188)$$

$$Co^+ + Co^{3+} \longrightarrow 2Co^{2+} \qquad (189)$$

4. EXPERIMENTAL CONSIDERATIONS AND PROCEDURES

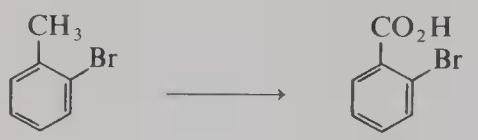
4.1. General Considerations

Procedures for the preparation of the cobalt compounds are given in the references in the text.

Simple analytical methods are available for following the reactions of cobalt.[315–322]

4.2. General Procedures and Typical Detailed Procedures

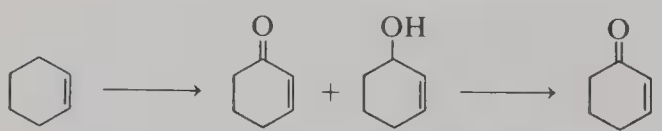
4.2.1. Alkylbenzenes



82 **83** (190)

Oxidation of o-Bromotoluene (**82**) *to o-Bromobenzoic Acid* (**83**) *by Co(OAc) Br.*[130] To the reaction flask was added 25 g (0.1 mol) of $Co(OAc)_2$. 27 g (0.1 mol) of 30% hydrogen bromide in AcOH, 500 ml of AcOH, and 86.5 g (0.5 mol) of *o*-bromotoluene (**82**). Oxygen was bubbled (600 ml/min) through the vigorously stirred reaction mixture, which was initially heated to 90°C, at which point the reaction became exothermic and kept the reaction mixture at the temperature of reflux. After 2 h, the temperature rose to a maximum of 112°C and oxygen was no longer being absorbed. The reaction mixture was cooled, ice water added to increase volume to 1 liter, and filtered. The product, *o*-bromobenzoic acid (**83**, 90.5 g, 91%) melted at 146.5–148°C.

4.2.2. Allylic Oxidation



84 **84** (191)

Oxidation of Cyclohexene to 2-Cyclohexen-1-one (**84**) *and 2-Cyclohexen-1-ol by Cobalt Naphthenate, Followed by Oxidation with Sodium Dichromate.*[146b] An apparatus, similar to a standard hydrogenation setup, was conveniently employed.

A mixture of cyclohexene (41 g, 0.5 mol), $CHCl_3$ (24 ml), and cobalt naphthenate (1.0 g, 8.78% in Co(II)) was stirred at ~50°C at atmospheric pressure in an atmosphere of oxygen until no further absorption occurred (11,300 ml, 30 h). The reaction was dried (Na_2SO_4) and freed of solvent and any unchanged cyclohexene to give a dark brown liquid (44 g).

An aliquot of the above material on usual estimation showed a peroxide content of 15%–18%. Another sample (6.05 g) was taken up in chloroform (35 ml) and stirred at 22–25°C for 1 h with saturated aqueous KI (3 ml) containing AcOH (2.0 ml). The organic layer was separated and the aqueous part saturated with NaCl and extracted with ether (3 × 20 ml). The combined organic layers were washed with $Na_2S_2O_3$ solution (10%, 3 × 20 ml), sodium hydrogen carbonate solution, and brine, and dried (Na_2SO_4). Solvent was flashed off and the residue distilled; yield: 5.56 g bp 80–85°C/40 Torr. GLC (column:

200 × 0.6 cm, stainless steel; phase: 20% diethylene glycol polysuccinate on Celite; temperature 135°C; gas: 70 ml H_2/min) showed this product to consist of cyclohexenol (RRT = 1; 40%) and 2-cyclohexene-1-one (RRT = 1.27; 60%).

To obtain 2-cyclohexen-1-one, a portion (22 g) of the original oxidized product (without KI treatment) was taken up in benzene (50 ml). To this a solution of sodium dichromate dihydrate (22 g) in glacial acetic acid (100 ml) was added and the reaction mixture stirred at 22–25°C for 6 h. After this, ethanol (10 ml) was added to destroy the excess of oxidant, and after stirring for another 15 min water (100 ml) was added and the organic layer separated. The aqueous phase was saturated with NaCl and extracted with ether-benzene (1:1; 4 × 50 ml). The combined organic phases were washed with $NaHCO_3$ solution (10%, 3 × 50 ml), then with NaCl (3 × 50 ml), and dried (Na_2SO_4). Solvent was fractionated off and the residue distilled; yield: 19.5 g: bp 80–83°C/4 Torr: GLC analysis showed that the product was ~98% pure 2-cyclohexen-1-one (**84**).

4.2.3. Alkenes

$$CoH(N_2)[P(C_6H_5)_3]_3$$

1

Preparation of Hydridonitrogentris(triphenylphosphine)cobalt(I) (**1**).[164] In a typical experiment, 26.5 g (205 mmol) of triphenylphosphine and 10.0 g (30 mmol) of cobalt(III) tris(acetylacetonate) were suspended in 300 ml of diethyl ether. To the suspension were added 30 ml (120 mmol) of triisobutylaluminium, and the mixture was cooled to −50°C under a nitrogen atmosphere. With nitrogen passing through the reaction mixture, the temperature was raised to 22–25°C with stirring. After 3 h at 22–25°C, orange crystals deposited from the dark red solution. The crystals were filtered, washed several times with ether or hexane, and dried *in vacuo*. Recrystallization from toluene gave 16.9 g (69%) of **1**.

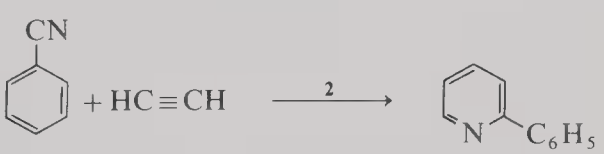
Hydroacylation. The Synthesis of Ketones from Olefins Using Metal Hydrides (**1**).[163]

$$CH_2{=}CH_2 + \mathbf{1} \longrightarrow [\ \ ] \xrightarrow{R-C(O)Cl} R-\overset{\overset{O}{\|}}{C}-CH_2CH_3 \qquad (192)$$

85

Addition of olefin to a red benzene solution of 200 mg of **1** (0.232 mmol) resulted in an immediate color change to red-brown. Addition of RC(O) Cl to this red-brown solution produced a rapid (< 10 min) color change to emerald green. Evaporative distillation of volatiles gave the ketone.

4.2.4. Alkynes

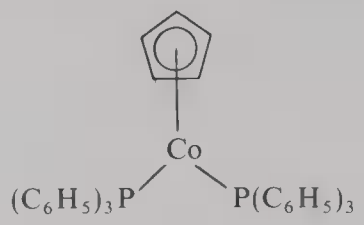


(193)

86

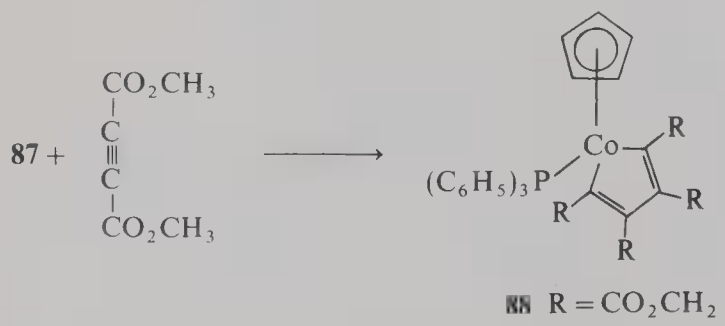
Cotrimerization of Benzonitrile and Ethyne to 2-Phenylpyridine (**86**) *Catalyzed by Cobaltacene.*[176] Cobaltacene (**2**, 378 mg, 2 mmol) was placed in an autoclave (volume 200 ml) and the vessel was filled with nitrogen. Methylbenzene (20 ml) and benzonitrile (14.5 ml, ~140 mmol) were introduced via syringes through a hole at the head of the autoclave. After the vessel was flushed with ethyne 5 times, the ethyne to be reacted was introduced up to a pressure of 9 atm while the autoclave was mechanically shaken at 23–25°C. The autoclave was heated to 150°C. Within 2 h, the pressure dropped to 3 atm and

more ethyne was added (13 atm at 150°C). After 7 h, the reaction mixture was fractionally distilled to give 2-phenylpyridine, bp 90°C at 1.5 Torr; 15.8 g (73%).



87

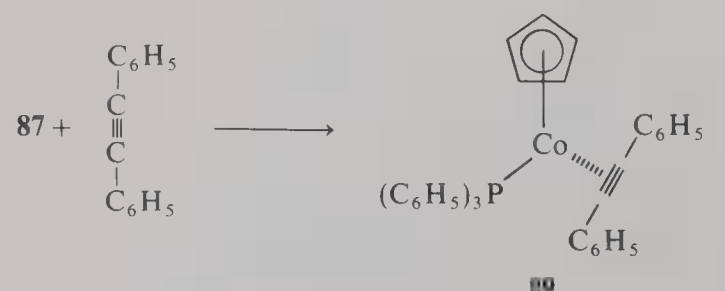
Preparation of (π-Cyclopentadienyl)bis(triphenylphosphine)cobalt(I) (**87**).[174] To freshly prepared chlorotris(triphenylphosphine)cobalt (12 g, 13.6 mmol) suspended in benzene (160 ml) was added a THF solution of sodium cyclopentadienide (1 mmol solution, 20 ml) at 23–25°C, and the resulting dark red solution was stirred for 30 min. Water (10 ml) was added at 0°C in order to hydrolyze excess sodium cyclopentadienide. The organic layer was separated, dried (Na_2SO_4), volume reduce to ca. 30 ml, and 30 ml of hexane was added. After filtering and drying, there was obtained 6.9 g (70%) of the desired complex (**87**).



(194)

88 R = CO_2CH_2

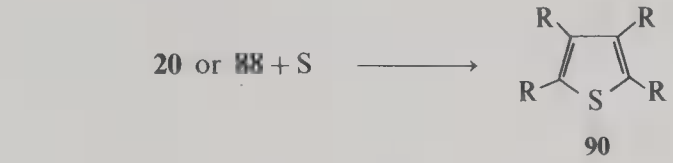
Preparation of (π-Cyclopentadienyl)(triphenylphosphine)-2,3,4,5-tetramethoxycarbonylcobaltacyclopentadiene (**88**).[174] To a solution of **87** (1.5 g, 2.1 mmol) in benzene (20 ml) was added dimethyl acetylenedicarboxylate (1.1 g, 8 mmol in 10 ml of benzene) dropwise under ice-cooling. The reaction mixture was allowed to stand overnight at 22–25°C and then was chromatographed on Al_2O_3. The orange red band was eluted with 1:1 benzene/ethyl acetate. The solvent was removed *in vacuo* and the residue was treated with benzene/hexane. The solvated benzene was removed by heating the crystals *in vacuo* at 170°C for 30 min. A 14% yield of **88** was obtained.



(195)

89

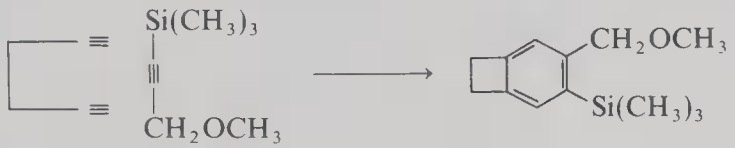
Preparation of (π-Cyclopentadienyl)(π-diphenylacetylene)triphenylphosphine)cobalt (**89**).[174] Diphenylethyne (0.9 g, 5 mmol) was added to a solution of **87** (3.6 g, 5 mmol) in C_6H_6 (25 ml) and the reaction mixture was allowed to stand at 22–25°C. After 1 h, 50 ml of hexane was added in order to precipitate shiny black crystals of **89**, which were separated by decantation and washed with hexane to give 2.4 g (85%). The crystals should be stored in a refrigerator.



(196)

90

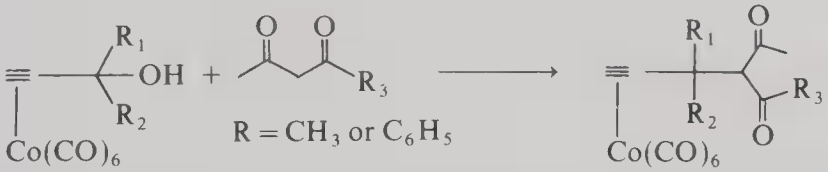
Preparation of Thiophenes from the Reaction of Cobaltacyclopentadiene Complexes with Sulfur. A General Procedure.[174] A mixture of **20**, or **88**, or other complex (0.365 mmol) and elemental sulfur (80 mg) in benzene (30 ml) was heated at 150°C for 6 h in a sealed tube. After concentration, the reaction mixture was chromatographed on Al_2O_3 (2 × 15 cm). The column was eluted with benzene (200 ml) and then with 1:1 benzene/dichloromethane (100 ml). The eluate with CH_2Cl_2 was collected and concentrated and the residue recrystallized from hexane to give crystals of **90** (Table IX).



(197)

91 **92** **93**

Preparation of 4-Trimethylsilyl-5-methoxymethylbenzocyclobutene (**93**).[182] 1,5-Hexadiyne (**91**, 780 mg, 10 mmol) and trimethylsilylpropargyl methyl ether (**92**, 1.42 g, 10 mmol) in *n*-octane (12 ml) containing $CpCo(CO)_2$ (30 ml) were added slowly with a syringe pump to refluxing *n*-octane (60 ml) containing $CpCo(CO)_2$ (20 ml) over a period of 48 h. All volatiles were vacuum transferred off to leave a brown oil, which was chromatographed on silica (150 g). Elution with pentane-ether (92:8; 200 ml fractions) and removal of solvents gave a yellow oil which was microdistilled at 60°C (oil bath, 0.01 Torr) to give 1.20 g (55%) of **93** (Table X).



(198)

Alkylation of 2,4-Pentanedione or Benzoylacetone with (Propargyl)dicobalt Hexacarbonyl Cations [HC≡C(OH) R_1R_2] $Co_2(CO)_6$. General Procedure.[172] A dichloromethane solution of the dicarbonyl compound was added dropwise to a cooled (−78°C) dichloromethane solution of the complexed alcohol and 0.5–1.5 equiv of $HBF_4O(CH_3)_2$ under nitrogen. Brief warming to 0°C (<60 min), neutralization with solid $NaHCO_3$, and chromatography over silica afforded the product complexes as dark red oils or crystalline solids (Table V).

4.2.5. Organic Halides

(199)

5, 6

Conversion of Dichlorophenylmethane to Tetraphenylethene with Dicobalt Octacarbonyl.[180] To 4.7 g (13.7 mmol) of dicobalt octacarbonyl in 60 ml of THF was added a solution of 6.5 g (27.4 mmol) of dichlorophenylmethane in 40 ml of THF. The reaction mixture was stirred and heated at 50°C for 3 h. During this time gas was evolved and the red-brown reaction mixture became green in color. The reaction mixture was treated with 300 ml of water and extracted (3 × 200 ml) with CCl_4. The combined organic layers were

dried ($MgSO_4$), filtered, and the filtrate evaporated at reduced pressure. The residual solid was recrystallized from C_2H_5OH/CH_2Cl_2 to give 4.5 g (98%) of tetraphenylethene, mp 223–224°C.

4.2.6. Phenols and Hydroquinones

General Procedure for the Autoxidation of Phenols to Benzoquinones and Diphenoquinones by the Cobalt–Dioxygen Complex of **9** [**34**, cf. Eq. (82)].[235] A mixture of the phenol (0.01 mol) and **34** (0.001 mol)[236] in 40 ml of absolute ethanol was stirred at 20–24°C for 20 h. After removal of the solvent by distillation under reduced pressure, the residue was dissolved in dichloromethane and chromatographed on silica gel. The 1,4-benzoquinones were readily separated from the diphenoquinones, and chromatographically pure products were obtained by evaporation of the appropriate eluate fractions.

General Procedure for the Autoxidation of Hydroquinones to 1,4-Benzoquinones by the Cobalt–Dioxygen Complex of **9** (**34**).[235,236] The complex **34** (0.3 g, 1 mmol)[236] was added to

(200)

solution of the hydroquinone (10 mmol) in absolute ethanol (40 ml). The resulting mixture was stirred for 16–24 h at 20–24°C while being exposed to the atmosphere. The orange mixture rapidly darkened to a dark brown color, which persisted throughout the reaction. The crude reaction mixture was concentrated under reduced pressure, filtered, and the filtrate chromatographed on silica gel using dichloromethane as eluant. Evaporation of the eluate under reduced pressure gave chromatographically pure 1,4-benzoquinone.

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6

Oxidation of Organic Compounds with Nickel Peroxide

M. V. George

1. INTRODUCTION

Although it has been known for a long time that nickel peroxide could be used for oxidizing organic compounds, only in the last few decades or so has this reagent found extensive application in synthetic organic chemistry. Weijlard[1] reported that diacetone-2-keto-*levo*-gulonic acid, an intermediate in the synthesis of vitamin C, was obtained from diacetone-*levo*-sorbose in good yields by the addition of nickel salts in a solution of sodium hypochlorite. It was suggested that the black oxide of nickel formed by the treatment of sodium hypochlorite with nickel sulfate was responsible for this type of oxidation. In recent years nickel peroxide has been used more frequently for bringing about the oxidations of several types of organic compounds.[2,3]

A literature search for examples of oxidation by nickel peroxide tends to be somewhat difficult, since the term "nickel peroxide" as such is rarely indexed in abstracts, unless indicated as the title of a publication. A number of the references cited herein therefore have been obtained from other reviews.[2,4,5] It is likely that some references might have been left out, inadvertently; however, the examples that we have included in this chapter would form a reasonable coverage of the major types of reactions which are brought about by nickel peroxide, highlighting thereby its use as a versatile reagent.

It has been difficult to decide at times whether nickel peroxide or nickel oxide peroxide has been the actual species employed for oxidation, in view of its nonstoichiometric nature. Wherever possible, the amount of available oxygen in terms of milligram per gram of nickel peroxide has been given. Reactions brought about by other oxidizing agents in combination with catalytic amounts of nickel peroxide have not been included here. However, the contrasts and similarities between nickel peroxide and manganese dioxide oxidations have been briefly indicated, wherever found necessary.

M. V. George • Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208016, India, and Radiation Laboratory and Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556, USA. Document No. NDRL-2817 from the Notre Dame Radiation Laboratory.

In this review, more emphasis is placed on the synthetic applications of nickel peroxide oxidations, and much of the information is summarized in the form of tables. An attempt has been made to present only selected examples in these tables, and hence they are by no means exhaustive. This tabular survey parallels the text, but within each table no specific ordering has been followed. In some of the tables, a dash (—) in the column "Ratio of NiO_2 to reactant" indicates that the active oxygen content of nickel peroxide has not been estimated.

2. MECHANISM OF OXIDATION

Mechanistic details of nickel peroxide oxidation of several classes of organic compounds are not yet fully understood. It appears that more definitive studies have to be carried out before we have a comprehensive picture of the several individual steps involved in such oxidations. However, it has been generally accepted at present that nickel peroxide oxidations, in most cases, proceed through pathways involving free radical intermediates.[6–19] Isotopic labeling and ESR studies using radical scavengers support this view.

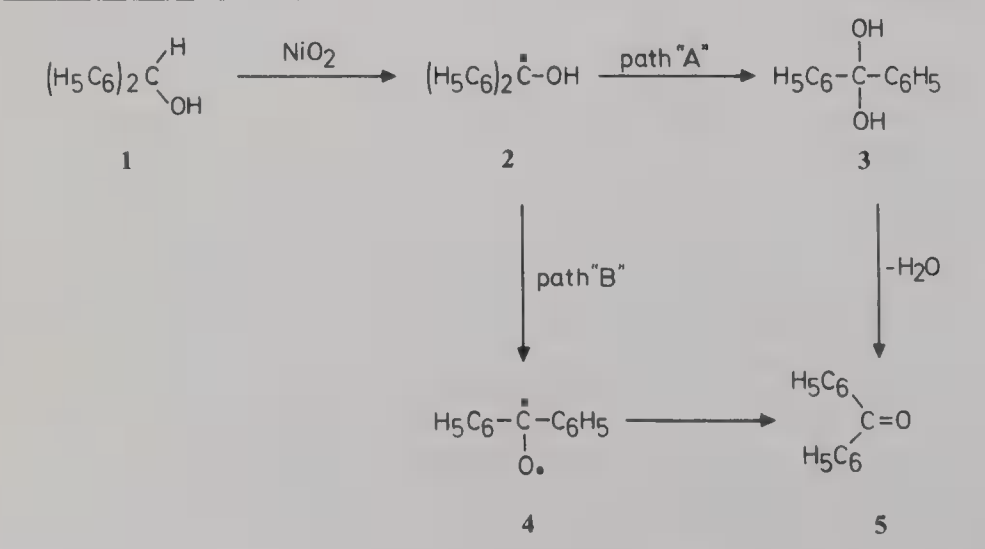
Primary alcohols are generally oxidized to the corresponding carboxylic acids by nickel peroxide in aqueous alkaline medium [Eq. (1)], whereas in organic solvents the oxidation stops with the initial formation of the corresponding carbonyl compounds [Eq. (2)].

$$RCH_2OH \xrightarrow[\text{base}]{NiO_2} RCO_2H \qquad (1)$$

$$RCH_2OH \xrightarrow[C_6H_6,\text{ether}]{NiO_2} RCHO \qquad (2)$$

Konaka *et al.*[11] have suggested that the nickel peroxide oxidation of alcohols involves the initial abstraction of the α-hydrogen atom, followed by hydrogen atom abstraction from the hydroxyl group, as against the alternative possibility of an initial hydrogen atom abstraction from the hydroxyl group. The appreciable difference in the rates of oxidation of $(C_6H_5)_2CHOH$ and $(C_6H_5)_2CDOH$ ($k_H/k_D = 7.4$) has been cited in support of this view. However, it may be pointed out that the mere observation of a kinetic effect does not necessarily signify that the C–H bond cleavage is the initial process. Two mechanistic possibilities, for example, are to be considered for the formation of benzophenone (**5**) from the radical species **2**, formed after the initial abstraction of a hydrogen atom from diphenyl carbinol (**1**), as shown in Scheme 1. The radical **2** can combine with a hydroxyl radical from

SCHEME 1



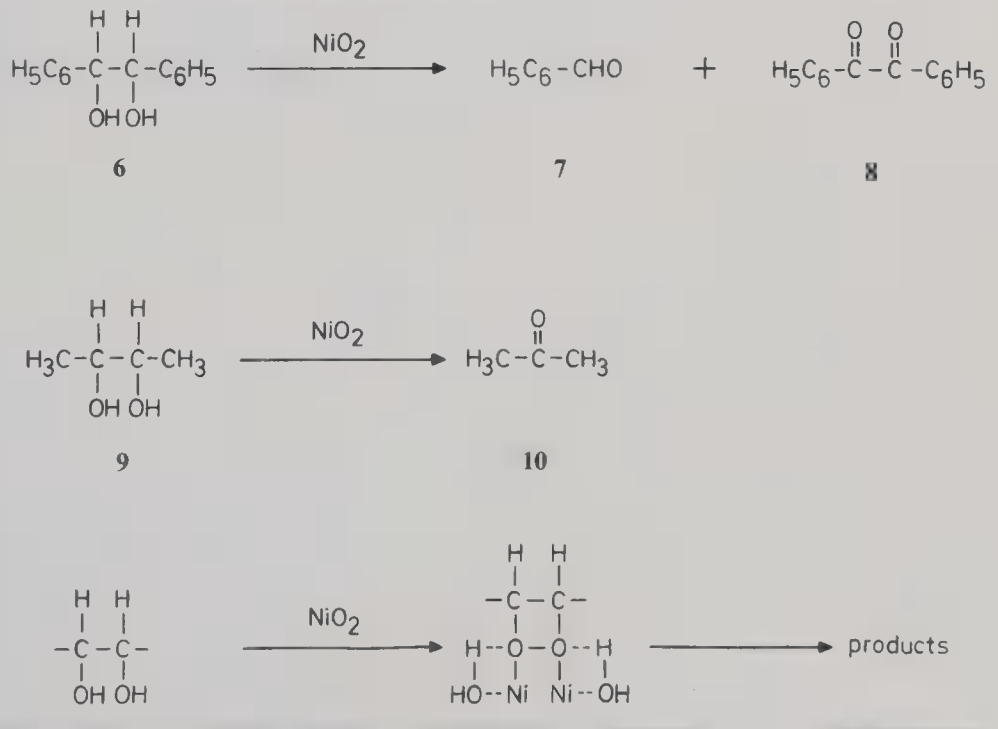
1 **2** **3** **4** **5**

nickel peroxide to give the dihydroxy intermediate **3**, which can subsequently lead to benzophenone, through the loss of a molecule of water (path A). An alternative pathway (path B) involves the formation of the diradical intermediate **4**, which can then lead to benzophenone. Using diphenylcarbinol with $^{18}0$ label, it has been possible to show that path B is actually followed in this oxidation.

The oxidation of 1,2-diols with nickel peroxide gives rise to 1,2-dicarbonyl compounds, as well as oxidative fragmentation products.[17] Thus, the oxidation of *meso*-hydrobenzoin (**6**) with nickel peroxide gives mainly benzaldehyde (**7**) and a small amount of benzil (**8**), whereas pinacol (**9**) gives acetone (**10**) (Scheme 2). An inverse isotope effect has been observed in the oxidation of *meso*-1,2-diphenylethane-1,2-diol and *meso*-1,2-dideuterio-1,2-diphenylethane-1,2-diol ($k_H/k_D = 0.8$). A similar observation has been made in the oxidations of *meso*-butane-2,3-doil and *meso*-2,3-dideuteriobutane-2,3-diol ($k_H/k_D = 0.75$). It has been suggested that these oxidations may be taking place through concerted processes, occurring on the surface of the oxidant (Scheme 2). However, the formation of any cyclic complex, as in the case of lead tetraacetate oxidation,[18] has been ruled out, since no appreciable difference in the rates of oxidations of *cis*- and *trans*-cyclopentane-1,2-diols has been observed ($k_{cis}/k_{trans} = 2.1$).[13]

Phenols generally undergo oxidation with nickel peroxide to give quinone derivatives in addition to oligomeric and polymeric products. Thus, *p*-cresol (**11**) on treatment with nickel peroxide, for example, gives a mixture of products consisting of the ketonic product **12**, the dimer **13**, the trimer **14**, and polymeric products (Scheme 3).[20] In a fairly detailed study of nickel peroxide oxidations, using ESR techniques, Konaka *et al.*[11] have shown that radical intermediates are actually involved in these reactions. Thus, in the oxidation of 2,6-di-*tert*-butyl-4-methylphenol in benzene, the presence of 2,6-di-*tert*-butyl-4-methylphenoxyl radical has been detected. In a recent investigation, ESR spin trapping technique using nitrosobenzene has been employed to show the involvement of phenoxyl radicals in these reactions.[15,16] Thus, in the oxidation of phenol (**15**) with nickel peroxide in the presence of nitrosobenzene, for example, the formation of the phenoxazine-*N*-oxyl radical (**23**) has been inferred through ESR studies. In addition, the *N*-oxide **24**, arising through the reaction of the initially formed phenoxyl radical with nitrosobenzene, has been isolated (Scheme 4).

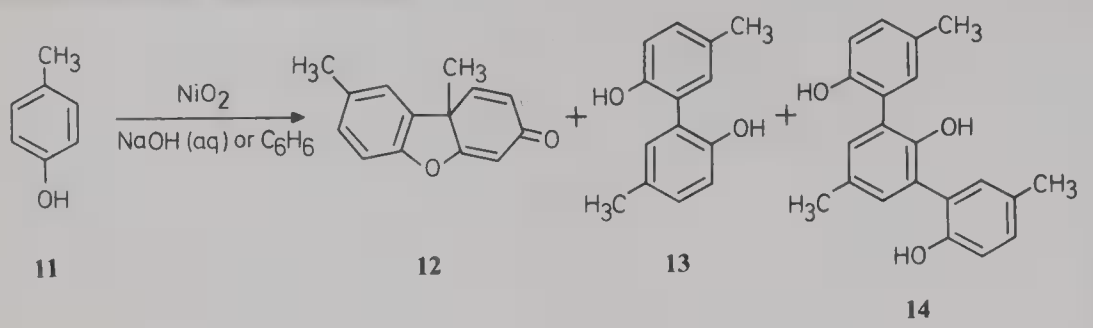
SCHEME 2



6 **7** **8**

9 **10**

SCHEME 3



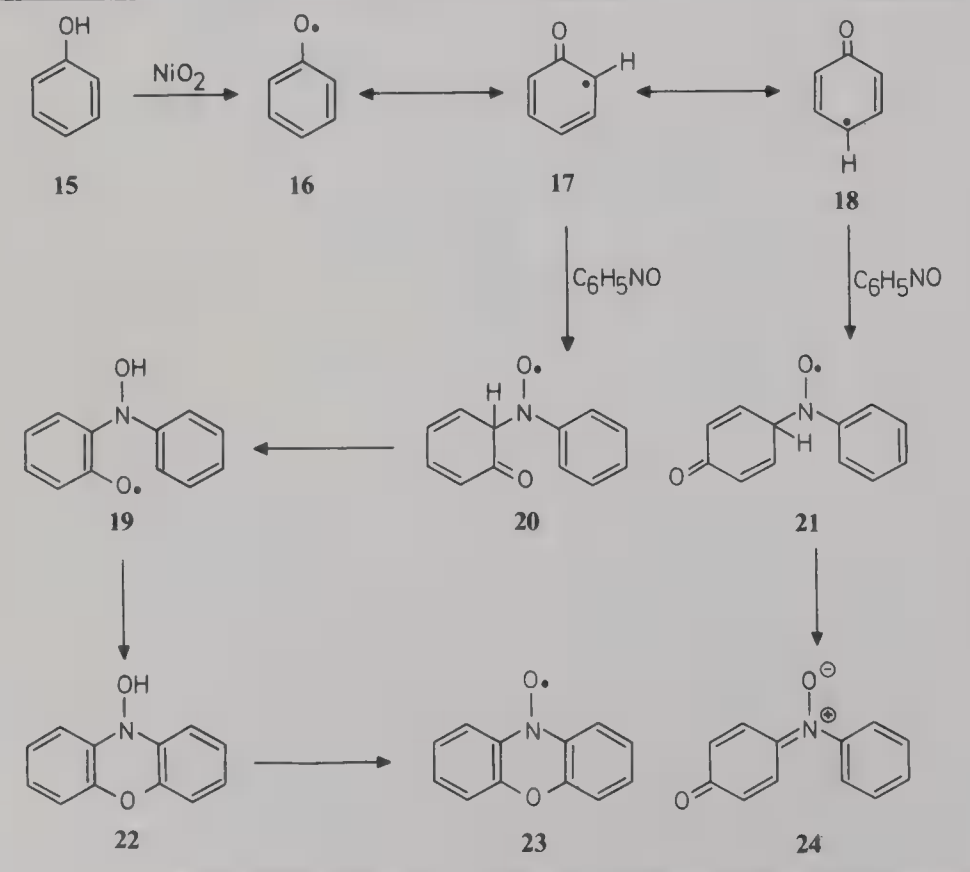
11 12 13 14

+ polymer

Nickel peroxide oxidation of hydrocarbons containing activated C–H bonds gives rise to the corresponding oxygenated compounds. Thus, toluene is oxidized to benzoic acid and diphenylmethane to benzophenone.[11] It has been suggested that these reactions proceed through pathways involving benzylic radicals, formed through the abstraction of the benzylic hydrogen atoms. The intermediacy of benzylic radicals in the nickel peroxide oxidation of aromatic hydrocarbons like $ArCHR_2$ and Ar_2CHR has been demonstrated through ESR spin trapping techniques.[16]

Although the mechanistic details of the nickel peroxide oxidation of several other classes of organic compounds have not been well studied, some tentative suggestions have been advanced in some of these cases. Thus, for example, free radical intermediates, formed through the abstraction of aldehydic hydrogen atoms, have been suggested to be the inter-

SCHEME 4

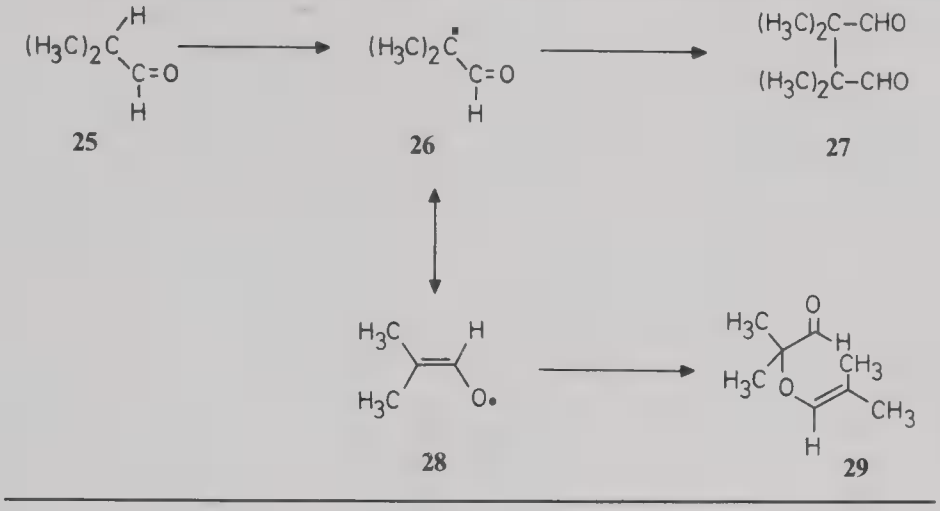


15 16 17 18

19 20 21

22 23 24

SCHEME 5



mediates in the nickel peroxide oxidation of aldehydes to the corresponding carboxylic acids. Similar radical species may be involved in the oxidative dimerizations of isobutyraldehyde (**25**), leading to both C–C and C–O dimers (**27** and **29**) (Scheme 5).[21] Aromatic primary amines are reported to undergo oxidation to give rise to diazo compounds, and these reactions may be proceeding through the dimerization of the initially formed nitrene intermediates. The oxidative dimerization reactions of secondary amines, leading to hydrazine derivatives, may be proceeding through free radical intermediates. Thus, the nickel peroxide oxidation of diphenylamine to tetraphenylhydrazine may involve the diphenylamine radical, formed through the initial abstraction of the NH hydrogen atom by the oxidant.[22] Aldehyde phenylhydrazones and chalcone phenylhydrazones are reported to undergo analogous C–C coupling reactions.[23,24] Aromatic hydroxylamines are oxidized by nickel peroxide to the corresponding azoxy compounds [Eq. (3)].[25] It has been assumed that the nitroso com-

$$\mathrm{ArNHOH} \xrightarrow{\mathrm{NiO_2}} \mathrm{Ar-\overset{\oplus}{N}(-O^{\ominus})=N-Ar} \qquad (3)$$

pounds formed initially on the surface of the oxidant react further with hydroxylamine to give the azoxy compounds.

3. SCOPE AND LIMITATIONS

An important feature of a substrate undergoing nickel peroxide oxidation is that it contains active hydrogen atoms, which are attached to hetero atoms such as oxygen, nitrogen, and sulfur or carbon atoms bearing electronegative groups. Thus, substrates such as alcohols, phenols, polyhydroxy compounds, carbonyl compounds, etc. are excellent candidates for nickel peroxide oxidation. Other types of reactions that are commonly encountered include dehydrogenation reactions of hydrocarbons and heterocycles, telomerization and polymerization reactions, and free radical addition reactions.

3.1. Alcohols

The oxidation of alcohols by nickel peroxide is affected by the alkalinity of the solvent medium and also the reaction conditions.[17] Whereas the oxidation of alcohols in organic

solvents such as benzene and petroleum ether gives the corresponding carbonyl compounds, primary alcohols in aqueous alkaline medium are further oxidized to the corresponding carboxylic acids.

3.1.1. Oxidation in Aqueous Alkaline Medium

Saturated aliphatic primary alcohols are readily converted to the corresponding carboxylic acids, on treatment with nickel peroxide in alkaline medium.[6] In general, the oxidation of straight-chain alcohols proceeds more readily than that of the corresponding branched chain isomers [Eqs. (4), (5)].

$$CH_3(CH_2)_2CH_2OH \xrightarrow[H_2O,\,3h,\,30°C]{NiO_2} CH_3(CH_2)_2CO_2H \quad (94\%) \tag{4}$$

$$(CH_3)_2CHCH_2OH \xrightarrow[H_2O,\,5h,\,30°C]{NiO_2} (CH_3)_2CHCO_2H \quad (85\%) \tag{5}$$

Unsaturated alcohols, on the other hand, undergo oxidative cleavage in some cases. Allyl alcohol, for example, gives a mixture of acrylic acid, formic acid, and carbon dioxide, on treatment with nickel peroxide in alkaline medium [Eq. (6)].[6] The oxidation of

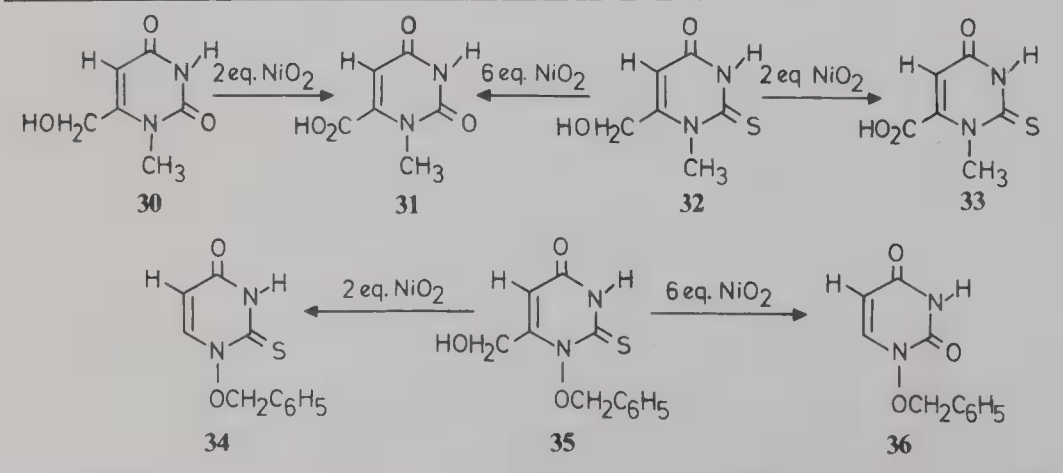
$$CH_2{=}CHCH_2OH \xrightarrow{NiO_2} CH_2{=}CHCO_2H + HCO_2H + CO_2 \tag{6}$$

propargyl alcohol, however, gives mainly propiolic acid, whereas cinnamyl alcohol undergoes smooth conversion to cinnamic acid.

In the case of alcohols possessing active methylene groups, the methylene groups, in part, are simultaneously oxidized at room temperature. However, at lower temperatures, only the hydroxylic function is affected. Thus, the oxidation of 3-phenyl-1-propanol at 0°C gives mainly 3-phenylpropionic acid along with traces of benzoic acid, whereas at 30°C, a much higher yield of benzoic acid is obtained.[6] Benzylic alcohols are easily oxidized to the corresponding carboxylic acids. The oxidation of α-furfuryl alcohol likewise is reported to give α-furoic acid.[6]

Nickel peroxide has been found to be a selective oxidizing agent for bringing about transformations in the pyrimidine series. Thus, it has been observed that 6-hydroxymethyluracil (**30**) is converted to orotic acid (**31**) on treatment with nickel peroxide, and in this reaction, the hydroxymethyl group is selectively oxidized to a carboxylic acid functionality (Scheme 6). In contrast, the oxidation of the 2-thiouracil (**32**) with excess of nickel peroxide leads to orotic acid, involving both the oxidation of the hydroxymethyl

SCHEME 6



group and also the oxidative desulfurization of the thiocarbonyl group (Scheme 6). It has been observed that in the presence of excess of nickel peroxide, further decarboxylation also occurs. Thus, treatment of **35** with two equivalents of nickel peroxide results in the decarboxylated product **34**, whereas treatment with six equivalents of nickel peroxide results in the decarboxylated and desulfurized product **36** (Scheme 6).[7]

The oxidation reactions of several alcohols in aqueous alkaline medium are summarized in Table I.

3.1.2. Oxidation in Organic Solvents

Alcohols are readily converted to the corresponding carbonyl derivatives, when treated with nickel peroxide in organic solvents such as benzene and petroleum ether. The oxidation of saturated aliphatic alcohols, employing equivalent amounts of the oxide and alcohol, gives poor yields of the products, as most of the available oxygen in the oxidizing agent is lost as oxygen.[6] Benzylic alcohols and their α-substituted analogs have been oxidized to the corresponding carbonyl derivatives. Because of its mild nature, nickel peroxide could be successfully used in the conversion of heterocyclic alcohols such as furfuryl alcohol to give the corresponding aldehydes.[6]

Nickel peroxide has been found to be an excellent reagent for the oxidation of allylic alcohols. Thus, allyl and cinnamyl alcohols have been oxidized to the corresponding aldehydes in good yields.[6] It may be pointed out here that manganese dioxide also brings about these oxidations.[26] However, these reactions take a much longer time for completion as compared to the corresponding nickel peroxide oxidations. Geraniol, on oxidation with nickel peroxide, for example, is reported to give an 81% yield of citral in 6 h.[6] The oxidation of geraniol in the presence of manganese dioxide, however, gives 61%–79% yield of citral after 96 h.[27a] Similarly, the oxidation of vitamin A with nickel peroxide[6] gives an 83% yield of retinal in 1 h as compared to the manganese dioxide oxidation,[27b] which requires 18 h to give comparable yields.

It has been observed recently that acetylenic alcohols[28] and α-ketoalcohols[29] give the corresponding carbonyl compounds, as well as cyclized products, on treatment with nickel peroxide. Thus, the acetylenic diol **37** is oxidized to the furan derivative **38** (Scheme 7).

α-Allenic aldehydes, ketones, and amides are easily prepared from 1,1-disubstituted α-allenic alcohols through nickel peroxide oxidation.[30] This method of obtaining the aldehyde or ketone is even superior to the oxidation of allenic alcohols by pyridinium chlorochromate.[31] Thus, for example, the nickel peroxide oxidation of 4-methylpent-2,3-diene-1-ol in ether at 20°C gives a 90% yield of the corresponding aldehyde [Eq. (7)].[30] On

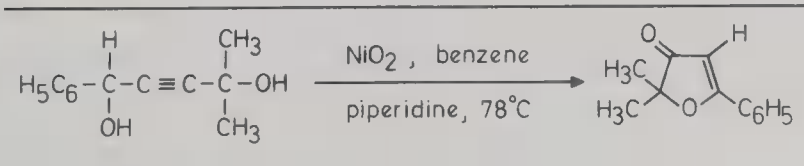
$$(CH_3)_2C{=}C{=}C(H)CH_2OH \xrightarrow{NiO_2} (CH_3)_2C{=}C{=}C(H)CHO \qquad (7)$$

the other hand, amides are obtained through the treatment of the α-allenic alcohols with ammonia in ether in the presence of nickel peroxide at lower temperatures. Thus, the reaction of 4-methylpent-2,3-diene-1-ol at −20°C gives the corresponding amide in a 60% yield [Eq. (8)].[30]

$$(CH_3)_2C{=}C{=}C(H)CH_2OH \xrightarrow[NH_3,\,-20°C]{NiO_2,\,ether} (CH_3)_2C{=}C{=}C(H)CONH_2 \qquad (8)$$

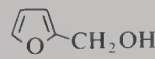
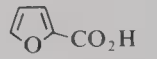
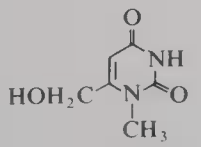
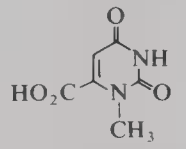
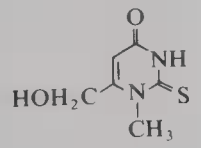
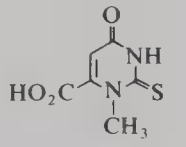
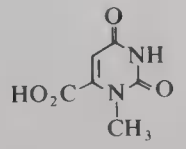
The oxidation reactions of several alcohols in organic solvents are summarized in Table II.

SCHEME 7



37 **38**

TABLE I. Oxidation of Alcohols in Aqueous Alkaline Medium

Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
CH_3CH_2OH	1.5	Water/30°C/3 h	CH_3CO_2H	97	6
	1.5	Water/30°C/5 h	CH_3CO_2H	99	6
$HC\equiv CCH_2OH$	1.1	Water/5°C/0.5 h	$HC\equiv CCO_2H$	50	6
$C_6H_5CH=CHCH_2OH$	2.0	Water/50°C/6 h	$C_6H_5CH=CHCO_2H$	81	6
$C_6H_5CH_2CH_2CH_2OH$	1.5	Water/30°C/10 h	$C_6H_5CH_2CH_2CO_2H$	57	6
			$+C_6H_5CO_2H$	18	
$C_6H_5CH_2OH$	1.1	Water/30°C/3 h	$C_6H_5CO_2H$	93	6
	1.5	Water/30°C/3 h	$C_6H_5CO_2H$	97	6
o-$CH_3C_6H_4CH_2OH$	1.1	Water/30°C/3 h	*o*-$CH_3C_6H_4CO_2H$	92	6
	1.5	Water/30°C/3 h	*o*-$CH_3C_6H_4CO_2H$	97	6
	1.5	Water/30°C/3 h		90	6
	2.0	AqNaOH/room temperature/24 h		73	7
	2.0	AqNaOH/room temperature/3.5 h		72	7
	Excess	AqNaOH/room temperature/24 h		67	7

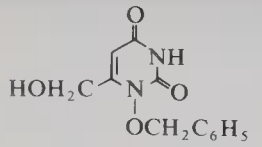
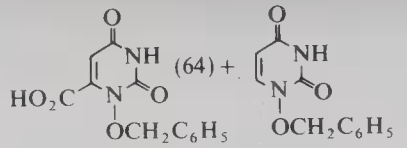
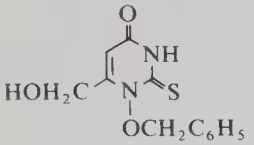
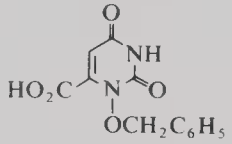
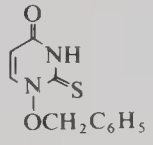
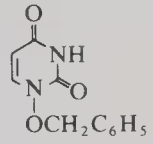
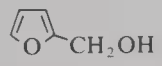
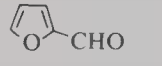
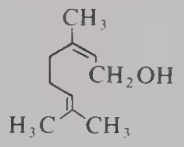
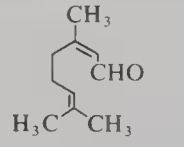
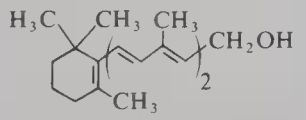
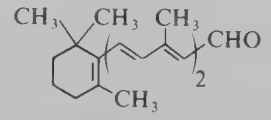
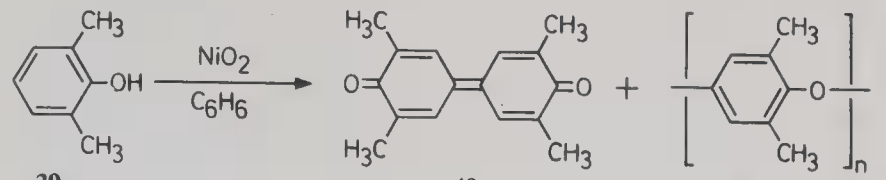
	—	AqNaOH/room temperature/6 h	 (64) +	24	7
	Excess	AqNaOH/room temperature/18 h		77	7
	2.0	AqNaOH/room temperature/1 h		76	7
	6.0	AqNaOH/room temperature/22 h		74	7
$R^1R^2C=C=CR^3CH(OH)R^4$	4.0	Ether/20°C	$R^1R^2C=CR^3(COR^4)$		30
R^1 R^2 R^3 R^4					
CH_3 CH_3 H H				90	
C_2H_5 CH_3 H H				88	
C_6H_5 CH_3 H H				60	
$(CH_2)_5$ H H				75	
$(CH_2)_5$ H CH_3				74	
CH_3 CH_3 H CH_3				89	
C_2H_5 CH_3 H CH_3				85	
$R^1R^2C=C=CHCH_2OH$	4.0	Ether/NH_3/−20°C/4 h	$R^1R^2C=C=CHCONH_2$		30
$R^1=R^2=CH_3$				60	
$R^1=C_2H_5$, $R^2=CH_3$				68	
R^1, $R^2=(CH_2)_5$				55	

TABLE II. Oxidation of Alcohols in Organic Solvents

Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
$C_6H_5CH_2OH$	1.2	C_6H_6/50°C/3 h	C_6H_5CHO	91	6
$C_6H_5CH(OH)CH_3$	1.2	C_6H_6/50°C/3 h	$C_6H_5COCH_3$	51	6
$CH_2=CHCH_2OH$	1.2	C_6H_6/50°C	$CH_2=CHCHO$	79	6
$C_6H_5CH=CHCH_2OH$	1.2	C_6H_6/50°C/1 h	$C_6H_5CH=CHCHO$	86	6
$C_6H_5COCH(OH)C_6H_5$	1.2	C_6H_6/50°C/5 h	$C_6H_5COCOC_6H_5$	98	6
$C_6H_5COCH(OH)C_6H_5$	1.2	Ether/30°C/3 h	$C_6H_5COCOC_6H_5$	98	29
$C_6H_5CH(OH)C_6H_5$	1.2	C_6H_6/50°C/6 h	$C_6H_5COC_6H_5$	98	6
o-$CH_3C_6H_4CH_2OH$	1.0	C_6H_6/50°C/3 h	*o*-$CH_3C_6H_4CHO$	76	6
m-$CH_3C_6H_4CH_2OH$	1.0	C_6H_6/50°C/3 h	*m*-$CH_3C_6H_4CHO$	58	6
p-$CH_3C_6H_4CH_2OH$	1.0	C_6H_6/50°C/3 h	*p*-$CH_3C_6H_4CHO$	65	6
	2.0	C_6H_6/50°C/3 h	*p*-$CH_3C_6H_4CHO$	81	6
	1.2	C_6H_6/30°C/10 h		78	6
$C_6H_5CH_2CH_2OH$	1.2	C_6H_6/30°C/1 h	$C_6H_5CH_2CHO$	13	6
$C_6H_5CH_2CH_2CH_2OH$	1.2	C_6H_6/50°C/4 h	$C_6H_5CH_2CH_2CHO$	12	6
	1.2	C_6H_6/50°C/6 h		81	6
	1.2	Petroleum ether/ 30°C/1 h		83	6
$(CH_3)_2C=C=C(H)CH_2OH$	—	—	$(CH_3)_2C=C=C(H)CHO$	90	30
	—	Ether/NH_3/−20°C	$(CH_3)_2C=C=C(H)CONH_2$	60	30

SCHEME 8



39 40 41

3.2. Phenols

Phenol is reported to undergo oxidation with nickel peroxide to give polymeric products.[32] 2,6-Xylenol (**39**), on the other hand, is known to give a mixture of products consisting of poly-2,6-dimethyl-1,4-phenylene ether (**41**) and a small amount of 3,3′,5,5′-tetramethyl-4,4′-diphenoquinone (**40**) (Scheme 8).[20,33] However, only polymeric materials are formed when the reaction is carried out in aqueous alkaline medium. Catechol (**42**) reacts with nickel peroxide to give *cis,cis*-muconic acid (**43**), arising through the cleavage of the aromatic ring (Scheme 9).

An unusual oxidative dealkylation has been reported in the case of 2,6-di-*tert*-butyl-4-methylphenol (**44**). Thus, the treatment of **44** with nickel peroxide in benzene at room temperature gives a mixture of several products consisting of **45–51** (Scheme 10).[34]

4-Cyanocatechol (**52**) is oxidized by nickel peroxide to give an *o*-quinone intermediate which has been trapped with 2,3-dimethylbutadiene (**53**) to give the adduct **54** (Scheme 11).[35]

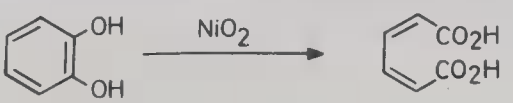
Nickel peroxide has been found to be a useful reagent in the synthesis of fuchsones from 4-hydroxytriphenylmethane, which in turn could be obtained through the acid-catalyzed condensation of benzhydrol with substituted phenols.[36] Thus, the treatment of 3,5-dimethyl-4-hydroxytriphenylmethane (**55**) with nickel peroxide in benzene has been reported to give an 84% yield of the corresponding fuchsone (**56**) (Scheme 12). It has been found that 3,5-disubstitution of the 4-hydroxytriphenylmethane is essential for their smooth oxidation to give fuchsones. A substrate such as 4-hydroxy-3-phenyltriphenylmethane, for example, undergoes oxidation to give only dimeric and polymeric products.[36] It may be mentioned in this connection that attempts to prepare the sterically hindered 2,3,5,6-tetramethylfuchsone have been unsuccessful. It may be noted here that manganese dioxide has also been reported to effect the oxidation of 3,5-disubstituted-4-hydroxytriphenylmethanes to the corresponding fuchsone derivatives.[36]

The oxidation reactions of several phenols are summarized in Table III.

3.3. Hydroxy Compounds Containing Other Functionalities

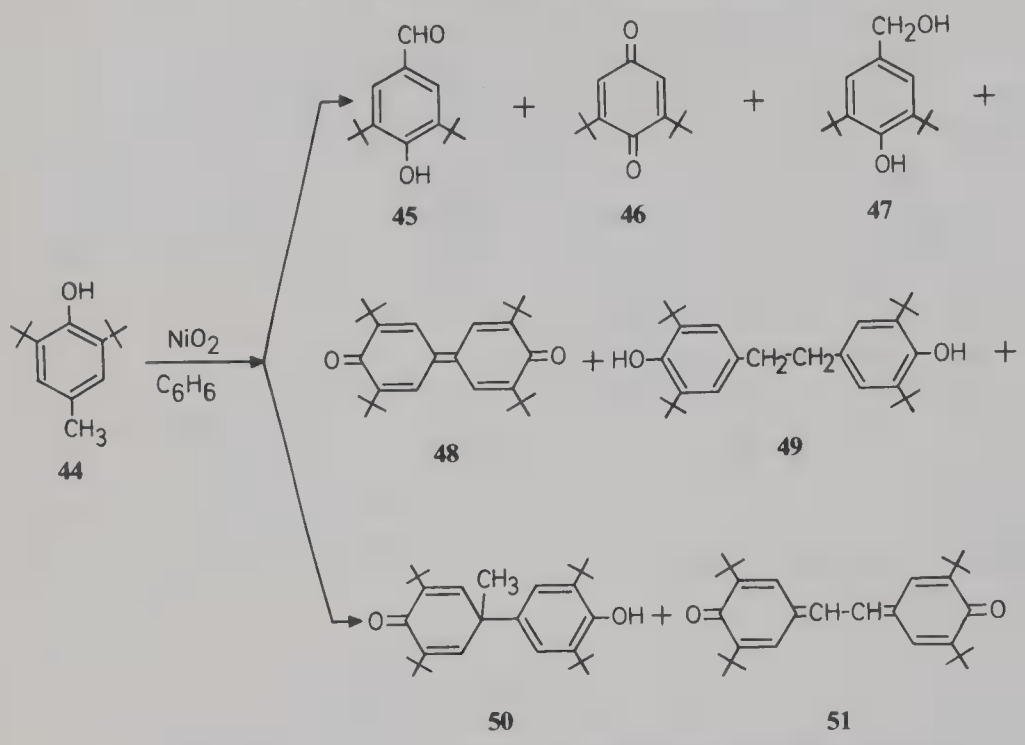
Lead tetraacetate and periodic acid are commonly employed in the cleavage of α-glycols. It has been shown that nickel peroxide also brings about the oxidation of a wide variety of hydroxy compounds such as glycols, α-hydroxy acids, α-oxo alcohols, and α-oxo acids

SCHEME 9



42 43

SCHEME 10



(Table IV).[17] It is interesting to note that oxidative fragmentation products have been observed when the reactions are carried out in organic solvents. Thus, for example, phenylethylene glycol, on oxidation with nickel peroxide in benzene, gives benzaldehyde, whereas benzoic acid is the only product formed when the oxidation is carried out in aqueous medium. Similarly, *cis*-cyclohexane-1,2-diol gives adipaldehyde in benzene medium.

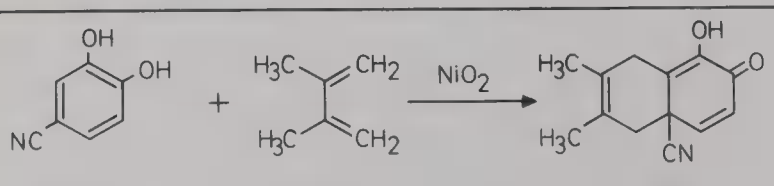
α-Hydroxy acids undergo oxidative decarboxylation on treatment with nickel peroxide. Mandelic acid, for example, has been reported to give a 78% yield of benzaldehyde on oxidation with nickel peroxide in benzene. In aqueous medium, however, the product formed in benzoic acid.

3.4. Carbonyl Compounds

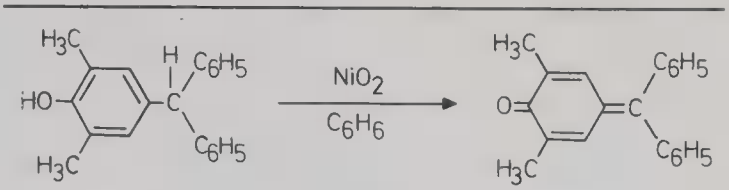
Oxidation of aldehydes with nickel peroxide in alkaline medium gives rise to carboxylic acids.[6] Thus, benzaldehyde is smoothly converted to benzoic acid. Similarly, furfural is oxidized to furoic acid.

Aldehydes containing α-hydrogen atoms, on the other hand, are reported to give aldol condensation products, and the alkalinity of the medium may be responsible for this type of reaction.

SCHEME 11



SCHEME 12



55 **56**

Nickel peroxide has been shown to be a useful reagent for the synthesis of 1,4-dicarbonyl compounds, through the dehydrodimerization of the corresponding carbonyl compounds.[21,37] Thus, isobutyraldehyde (**25**) on treatment with nickel peroxide gives the 1,4-dialdehyde **27**, in addition to the enol ether **29**, formed through a C–O coupling reaction (Scheme 5).[21] Similar dimerizations have been observed in the cases of 2-methylbutyraldehyde and 2-ethylbutyraldehyde. With monocyclic ketones, however, the reactions have been found to be rapid and exothermic. Thus, the reaction of cyclohexanone with nickel peroxide in acetonitrile for 0.5 h, for example, leads to a 73% yield of bicyclohexyl-2,2′-dione. The oxidation of a mixture of cyclopentanone and cyclohexanone, on the other hand, gives a mixture of bicyclohexyl-2,2′-dione, bicyclopentyl-2,2′-dione, and cyclohexylcyclopentyl-2,2′-dione. Similar reactions occur with acyclic ketones, though less readily. On the basis of ESR studies, employing spin traps, it has been possible to show that the dehydrodimerization of aldehydes in presence of nickel peroxide involves free radical intermediates.[37]

It has been shown that alcohols and aldehydes can be directly converted to the corresponding amides by their treatment with nickel peroxide in ether solution, containing ammonia, at temperatures below $-20°C$.[38,39] At higher temperatures, however, the yields of amides decrease and nitriles become the major products, under these conditions. Thus, *p*-chlorobenzaldehyde, for example, could be converted to *p*-chlorobenzamide in a 92% yield by carrying out the reaction with nickel peroxide in ether at $-25°C$, whereas when the reaction is carried out at 35°C, a mixture of *p*-chlorobenzamide (5%), *p*-chlorobenzoic acid (15%), and *p*-chlorobenzonitrile (34%) are formed along with the recovery of some unchanged starting material (42%).

Nickel peroxide oxidations of several carbonyl compounds are summarized in Table V.

3.5. Amines

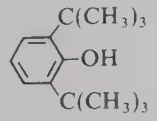
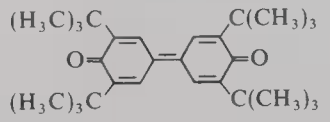
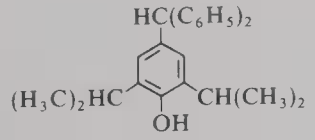
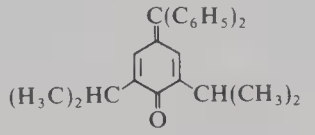
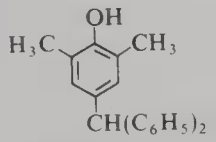
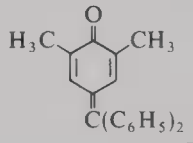
3.5.1. Primary Amines

Aromatic primary amines are readily converted to the corresponding azo compounds on oxidation with nickel peroxide.[40] Aniline, for example, on treatment with nickel peroxide in benzene, gives azobenzene (44%). The yields of the products in these reactions, however, depend on the nature of the substituents present in the aromatic ring. Thus, it has been observed that nitroanilines give better yields of the corresponding azo compounds, on treatment with nickel peroxide,[40] as compared to the oxidations employing manganese dioxide.[41] However, the situation is reversed in the cases of chloroanilines, anisidines, and toluidines.

Nickel peroxide oxidation of *o*-phenylenediamine (**57**) results in the cleavage of the aromatic ring to give the dinitrile **58** (Scheme 13).[42] It may be mentioned here that the manganese dioxide oxidation of **57**, on the other hand, gives the diazo compound **59** (Scheme 13).[43] However, the analogous dinitrile is not formed in the nickel peroxide oxidation of 2,3-diaminonaphthalene.

Aliphatic primary amines, on the other hand, give rise to the corresponding nitriles. Thus, benzylamine on oxidation with nickel peroxide in benzene at 60°C for 1.5 h, for exam-

TABLE III. Oxidation of Phenols

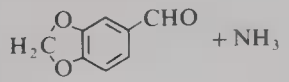
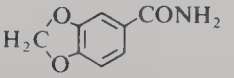
Reactant	NiO_2 used[a]	Conditions	Product(s)	Yield (%)	References
C_6H_5OH	0.0532	AqNaOH/60°C/2 h	Polymer (soluble in C_2H_5OH) + polymer (insoluble in C_2H_5OH)	61 29	20
	0.0532	C_6H_6/50°C/5 h		99	20
		C_6H_6/room temperature/3 h		94	36
		C_6H_6		84	36

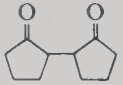
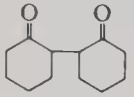
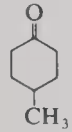
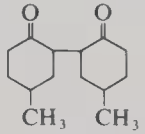
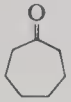
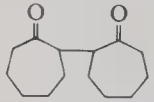
[a] Effective oxygen/total nickel peroxide.

TABLE IV. Oxidation of Hydroxy Compounds Containing Other Functionalities

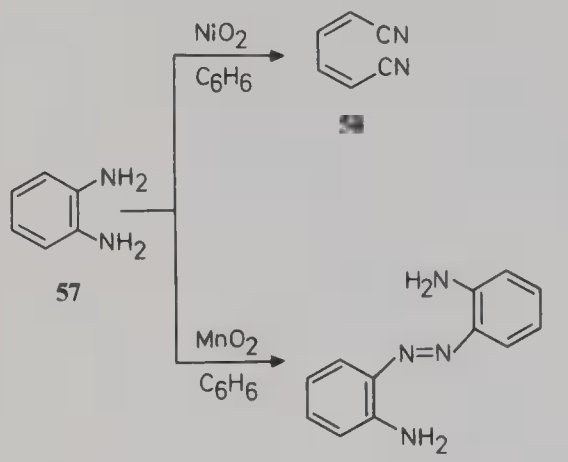
Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
$C_6H_5CH(OH)CH(OH)C_6H_5$	1.1	C_6H_6/50°C/1 h	C_6H_5CHO	85	17
	1.1	C_6H_6/50°C/5 h	C_6H_5CHO	81	17
	1.1	Ether/35°C/0.5 h	C_6H_5CHO	90	17
	1.1	AqNaOH/50°C/8 h	$C_6H_5CO_2H$	97	17
$C_6H_5CH(OH)CH_2OH$	1.1	C_6H_6/50°C/2 h	C_6H_5CHO	90	17
	1.1	AqNaOH/50°C/5 h	$C_6H_5CO_2H + CO_2$	92	17
$(CH_3)_2C(OH)C(OH)(CH_3)_2$	1.1	C_6H_6/70°C/3 h	CH_3COCH_3	61	17
	1.1	C_6H_6/30°C/1 h	CH_3COCH_3	70	17
	1.1	AqNaOH/30°C/24 h	$CH_3COCH_3 + CO_2$	10	17
$C_6H_5CH(OH)CO_2H$	1.1	C_6H_6/50°C/1.5 h	C_6H_5CHO	78	17
	1.1	Water/10°C/7 h	C_6H_5CHO	51	17
	1.1	AqNaOH/50°C/5 h	$C_6H_5CO_2H$	90	17
$C_6H_5CH(OH)CO_2C_6H_5$	—	AqNaOH/50°C/5 h	$C_6H_5CO_2H$	99	17
	—	AqNaOH/30°C/8 h	$C_6H_5CO_2H$	95	17
RCH(OH)COR R = β-furyl	—	AqNaOH/30°C/5 h	RCO_2H	91	17
$C_6H_5COCO_2H$	—	AqNaOH/50°C/3 h	$C_6H_5CO_2H$	98	17

TABLE V. Oxidation of Carbonyl Compounds

Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
p-$ClC_6H_4CHO + NH_3$	1.3	Ether/$-25°C$/4 h	p-$ClC_6H_4CONH_2$	92	50
			+ p-$ClC_6H_4CO_2H$	5	
	1.3	Ether/0°C/4 h	p-$ClC_6H_4CONH_2$	72	50
			+ p-$ClC_6H_4CO_2H$	17	
p-$ClC_6H_4CHO + NH_3$	1.3	Ether/20°C/4 h	p-$ClC_6H_4CONH_2$	37	50
			+ p-$ClC_6H_4CO_2H$	28	
			+ p-ClC_6H_4CN	14	
			+ p-ClC_6H_4CHO	16	
	1.3	C_6H_6/80°C/4 h	p-$ClC_6H_4CONH_2$	9	50
			+ p-$ClC_6H_4CO_2H$	26	
			+ p-ClC_6H_4CN	51	
			+ p-ClC_6H_4CHO	10	
$C_6H_5CHO + NH_3$	1.3	Ether/$-20°C$/4 h	$C_6H_5CONH_2$	89	50
	1.3	Ether/$-20°C$/4 h		86	50
$C_6H_5CH=CHCHO + NH_3$	1.3	Ether/$-20°C$/4 h	$C_6H_5CH=CHCONH_2$	85	50

$RCHO + NH_3$ $R = \alpha$-furyl	1.3	Ether/−20°C/4 h	$RCONH_2$	86	50
	0.66	CH_3CN/60–65°C/0.5 h		80	37
	0.66	CH_3CN/45°C/0.5 h		73	37
	0.66	Ethyl acetate/45°C/0.5 h		72	37
	0.66	C_6H_5CN/45°C/0.5 h		71	37
	1.3	C_6H_6/45°C/2.5 h		70	37
	0.8	C_6H_5CN/65°C/0.25 h		72	37
	0.66	65°C		16	37
	0.8	Reflux/0.25 h		79	37
$CH_3COCH_2CH_3$	0.66	C_6H_6/78°C/2 h	$CH_3COCH(CH_3)CH(CH_3)COCH_3$ $+ CH_3COCH(CH_3)CH_2COCH_2CH_3$	38 15	37

SCHEME 13



ple, gives a 79% yield of benzonitrile. In contrast, phenylethylamine gives *trans*-α,α′-stilbenedicarbonitrile [Eq. (9)] under similar conditions.[3,4]

$$C_6H_5CH_2CH_2NH_2 \xrightarrow{NiO_2} C_6H_5(CN)C{=}C(CN)C_6H_5 \qquad (9)$$

The oxidation reactions of several primary amines are summarized in Table VI.

3.5.2. *Secondary Amines*

Secondary amines undergo oxidative dimerization to yield tetrasubstituted hydrazines. Polymers also are formed in some of these reactions. Thus, the nickel peroxide oxidation of diphenylamine (**60**) gives tetraphenylhydrazine (**62**) as the major product, along with a small amount of polydiphenylamine (**63**) (Scheme 14).[22] However, in the case of benzylanilines, in addition to the dimeric products, appreciable amounts of Schiff bases are also formed through dehydrogenation reactions [Eq. (10)].[23] *p*-Tolylphenylamine (**64**), under analogous

$$C_6H_5CH_2NHAr \xrightarrow{NiO_2} C_6H_5CH_2(Ar)NN(Ar)CH_2C_6H_5 + CH_6H_5CH{=}NAr \qquad (10)$$

conditions, gives the corresponding hydrazine derivative (**65**) and *N*-(*p*-tolyl)-*p*-benzoquinone monoimine (**66**) (Scheme 15). Similarly, the oxidation of carbazole gives 9,9′-bicarbazole and 9,3′,9′,9″-tetracarbazole and some amount of polymeric materials.[44]

Manganese dioxide oxidation of *N*-benzylanilines has been reported to give rise to the corresponding benzylidineanilines.[46] On the contrary, nickel peroxide oxidation gives two types of oxidative dimers, in addition to benzylidineanilines. Thus, *N*-benzylaniline on treat-

SCHEME 14

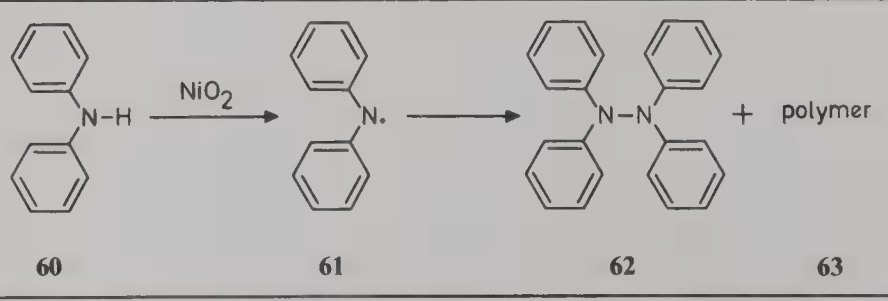
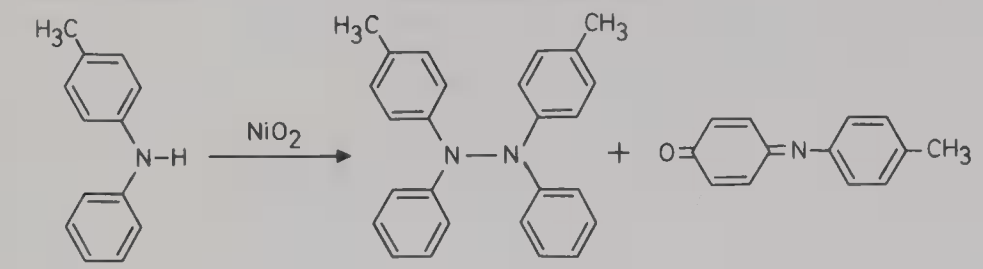


TABLE VI. Oxidation of Primary Amines

Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
$C_6H_5NH_2$	1.5	C_6H_6/80°C/6 h	$C_6H_5N=NC_6H_5$	44	40
p-$NO_2C_6H_4NH_2$	1.5	C_6H_6/80°C/6 h	*p*-$NO_2C_6H_4N=NC_6H_4NO_2$-*p*	64	40
$C_6H_5CH_2NH_2$	1.5	C_6H_6/60°C/1.5 h	C_6H_5CN	79	40
p-$CH_3OC_6H_4CH_2NH_2$	1.5	C_6H_6/60°C/1.5 h	*p*-$CH_3OC_6H_4CN$	88	40
p-$CH_3C_6H_4CH_2NH_2$	1.5	C_6H_6/60°C/1.5 h	*p*-$CH_3C_6H_4CN$	75	40
m-$CH_3C_6H_4CH_2NH_2$	1.5	C_6H_6/60°C/1.5 h	*m*-$CH_3C_6H_4CN$	79	40
o-$CH_3C_6H_4CH_2NH_2$	1.5	C_6H_6/60°C/1.5 h	*o*-$CH_3C_6H_4CN$	77	40
p-$NO_2C_6H_4CH_2NH_2$	1.5	C_6H_6/60°C/1.5 h	*p*-$NO_2C_6H_4CN$	56	40
o-$NO_2C_6H_4CH_2NH_2$	1.5	C_6H_6/60°C/1.5 h	*o*-$NO_2C_6H_4CN$	87	40
p-$ClC_6H_4CH_2NH_2$	1.5	C_6H_6/60°C/1.5 h	*p*-ClC_6H_4CN	73	40
m-$ClC_6H_4CH_2NH_2$	1.5	C_6H_6/60°C/1.5 h	*m*-ClC_6H_4CN	70	40
o-$ClC_6H_4CH_2NH_2$	1.5	C_6H_6/60°C/1.5 h	*o*-ClC_6H_4CN	87	40
RCH_2NH_2			RCN		
R = α-furyl	1.5	C_6H_6/5°C/0.5 h		63	40
R = α-naphthyl	1.5	C_6H_6/60°C/1.5 h		91	40
$CH_3(CH_2)_{10}CH_2NH_2$	1.5	C_6H_6/80°C/1.5 h	$CH_3(CH_2)_{10}CN$	81	40
	2.0	C_6H_6/room temperature		14	42

SCHEME 15



64 65 66

ment with nickel peroxide gives a mixture of benzylidineaniline (**69**) and *N*-benzyl-*N*-phenyl-*N'*-benzylidine-*p*-phenylenediamine (**68**) (Scheme 16).[23]

Tertiary amines have so far not been oxidized by nickel peroxide, whereas numerous reports have appeared in the literature dealing with the oxidation of these compounds with manganese dioxide.[45]

The oxidation reactions of several secondary amines are summarized in Table VII.

3.6. Hydrazines

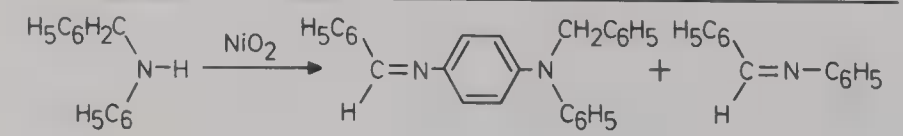
Phenylhydrazine is known to undergo oxidation with nickel peroxide to give a variety of products, depending upon the nature of the solvent employed in these reactions.[48] Thus, the oxidation in cyclohexane, for example, gives a mixture of benzene and biphenyl, whereas in carbon tetrachloride, the products formed include chlorobenzene, benzene, biphenyl, and hexachloroethane. On the other hand, when the reaction is carried out in benzene, biphenyl, traces of phenol, and 1,4-dihydrobiphenyl are formed. In contrast to the nickel peroxide oxidation, manganese dioxide oxidation of phenylhydrazine in benzene gives biphenyl and azobenzene.[43]

It has been reported recently that 2-hydrazinobenzothiazole (**70**) is oxidized by nickel peroxide in benzene medium to give a mixture of 2-phenylbenzothiazole (**71**) and benzothiazole (**72**), whereas in toluene both benzothiazole (**72**) and 2,2'-benzothiazolyl (**73**) are formed.[49] However, when the reaction is carried out in chloroform, a mixture of benzothiazole (**72**) and 2.2'-azobenzothiazole (**74**) is formed (Scheme 17).[49]

3.7. Hydroxylamines

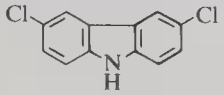
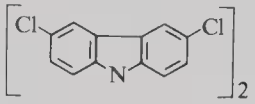
Aromatic hydroxylamines are oxidized to the corresponding azoxy compounds by nickel peroxide.[25] Table VIII summarizes the results of the oxidation of several hydroxylamines. Thus, the oxidation of phenylhydroxylamine, for example, gives a 90% yield of azoxybenzene. Oxidation of *N*-benzylhydroxylamine, on the other hand, gives only a trace of the

SCHEME 16

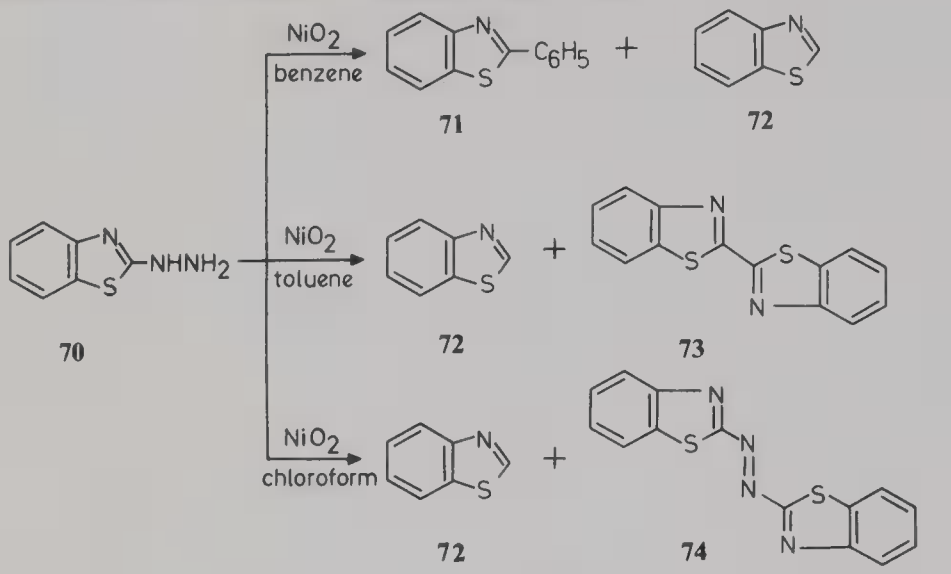


67 68 69

TABLE VII. Oxidation of Secondary Amines

Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
$(C_6H_5)_2NH$	1.3	C_6H_6/4 h	$(C_6H_5)_2NN(C_6H_5)_2$	52	22
			+ polymer	12	
p-$CH_3C_6H_4NHC_6H_5$	1.3	C_6H_6/4 h	$[(C_6H_5)(C_6H_4CH_3$-$p)N]_2$	46	22
			+ p-$CH_3C_6H_4N$=⟨⟩=O	23	
	1.5	Ether		90	44
$C_6H_5CH_2NHC_6H_4CH_3$-p	—	C_6H_6/room temperature/2 h	$[(p$-$CH_3C_6H_4)(C_6H_5CH_2)N]_2$	64	23
			+ C_6H_5CH=$NC_6H_4CH_3$-p	24	
$C_6H_5CH_2NHC_6H_4OCH_3$-p	—	C_6H_6/room temperature/2 h	$[(p$-$CH_3OC_6H_4)(C_6H_5CH_2)N]_2$	50	23
			+ C_6H_5CH=$NC_6H_4OCH_3$-p	37	
$C_6H_5CH_2NHCH_2C_6H_5$	—	C_6H_6/80°C/6 h	$C_6H_5CH_2N$=CHC_6H_5	43	23
			+ C_6H_5CHO(48) + CH_3CN	40	

SCHEME 17



corresponding azoxy compound, whereas the major product formed is α-nitrosotoluene (35%). In contrast, the oxidation of benzoylhydroxylamine gives a 58% yield of *N,O*-dibenzoylhydroxylamine [Eq. (11)]. Similarly, the oxidation of *N*-benzoyl-*N*-phenylhydroxylamine with nickel peroxide gives benzanilide, along with a small amount of *N,O*-dibenzoyl-*N*-phenylhydroxylamine.

$$C_6H_5CONHOH \xrightarrow{NiO_2} C_6H_5CONHOCOC_6H_5 \qquad (11)$$

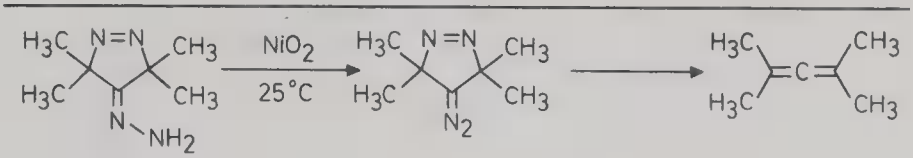
3.8. Hydrazones, Phenylhydrazones, Benzoylhydrazones, and Oximes

Aldehyde and ketone monohydrazones are oxidized by nickel peroxide to the corresponding diazo compounds in excellent yields.[50] Benzophenone hydrazone, for example, is reported to give a 99% yield of diphenyldiazomethane. It may be mentioned in this con-

TABLE VIII. Oxidation of Hydroxylamines

Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
C_6H_5NHOH	—	—	$C_6H_5\overset{\oplus}{N}(O^{\ominus})=NC_6H_5$	90	25
p-ClC_6H_4NHOH	—	—	*p*-$ClC_6H_4\overset{\oplus}{N}(O^{\ominus})=NC_6H_4Cl$-*p*	97	25
p-$CH_3C_6H_4NHOH$	—	—	*p*-$CH_3C_6H_4\overset{\oplus}{N}(O^{\ominus})=NC_6H_4CH_3$-*p*	92	25
$C_6H_5CONHOH$	—	—	$C_6H_5CONHOCOC_6H_5$ + $C_6H_5CO_2H$	58 8	25

SCHEME 18



75 **76** **77**

nection that the manganese dioxide oxidation of benzophenone hydrazone also gives the same diazo compound, along with a small amount of diphenylketazine.[51]

Oxidation of benzil monohydrazone with nickel peroxide at ca. 0°C is reported to give a nearly quantitative yield of the α-diazo ketone [Eq. (12)], whereas the oxidation at room temperature gives a mixture of benzophenone and diphenylketene.[3,4]

$$C_6H_5COC(NNH_2)C_6H_5 \xrightarrow{NiO_2} C_6H_5COC(N_2)C_6H_5 \qquad (12)$$

The oxidation of the pyrazolinone hydrazone **75** with nickel peroxide has been shown to give the allene **77**, presumably through the intermediacy of **76** (Scheme 18).[52]

Recent studies have shown that nickel peroxide oxidation of the hydrazones **78** would form a convenient procedure for the synthesis of the triazolopyridines, **79** (Scheme 19).[63]

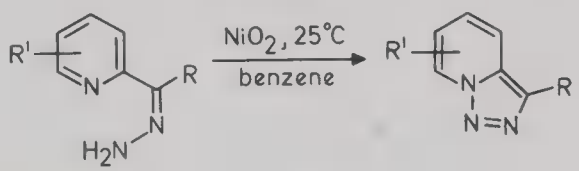
1,2-Diketone bishydrazones are oxidized to the corresponding alkynes, on treatment with nickel peroxide. Thus, benzil bishydrazone in oxidized to diphenylacetylene.[3,4] A similar oxidation of cyclohexane-1,2-dione bishydrazone with manganese dioxide is reported to give cyclohexyne.[54–56]

Oxidation of ketone and aldehyde phenylhydrazones gives various types of products. Thus, benzophenone phenylhydrazone, on oxidation with nickel peroxide, gives a mixture of benzophenone and biphenyl.[23] In contrast, the oxidation of benzaldehyde phenylhydrazone (**80**) gives the *C–C* coupling product **81**.[23] Manganese dioxide oxidation of benzaldehydrazone, however, gives rise to a mixture of products consisting of **81–85** (Scheme 20).[57]

Chalcone phenylhydrazones give pyrazoles on oxidation with manganese dioxide.[24] Nickel peroxide oxidation of chalcone phenylhydrazones, on the other hand, gives rise to bipyrazolines. Benzylideneacetone phenylhydrazone (**86**), for example, gives a *dl*-mixture of **87**, on oxidation with nickel peroxide (Scheme 21).[64]

Bisazoalkenes, triazoles, and azopyrazoles are the usual products in the nickel peroxide oxidation of 1,2-diketone bisphenylhydrazones. Thus, the oxidation of glyoxal bisphenylhydrazone (**88a**), for example, at room temperature, gives bisphenylazoethylene

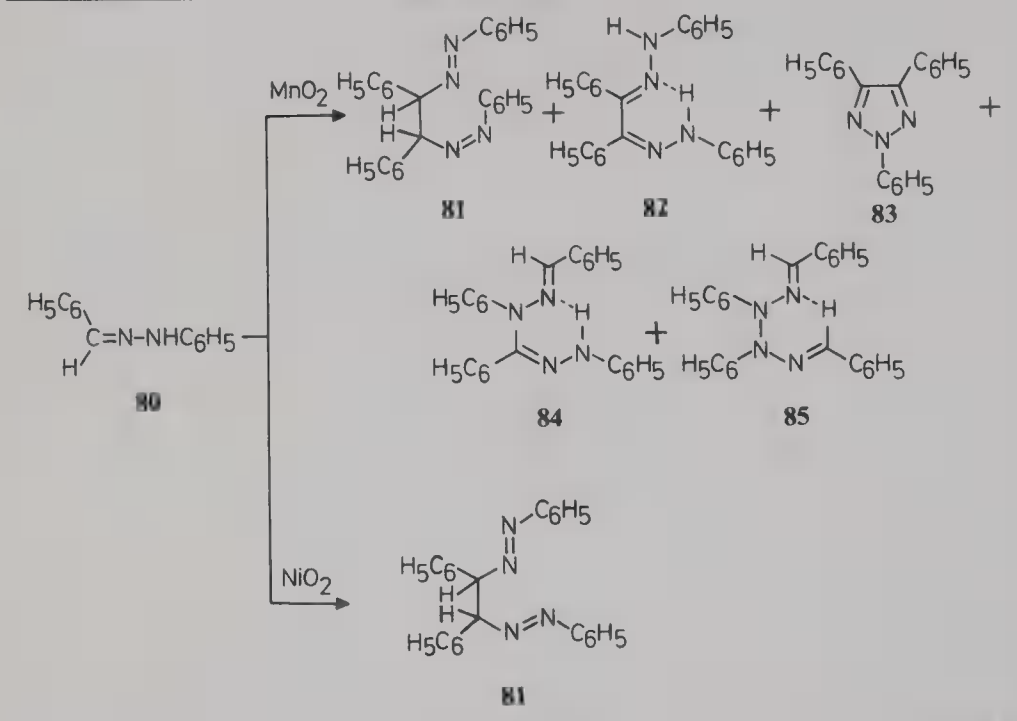
SCHEME 19



78 **79**

a) R = R' = H ; b) R = H ; R' = CH_3
c) R = CH_3 ; R' = H ; d) R = C_6H_5 ; R' = H
e) R = p-$CH_3C_6H_4$; R' = H
f) R = p-$CH_3OC_6H_4$; R' = H
g) R = p-ClC_6H_4 ; R' = H
h) R = o-ClC_6H_4 ; R' = H
i) R = 2-pyridyl ; R' = H

SCHEME 20



(**89a**) (Scheme 22).[58] Oxidation of the bishydrazones **88b–88d** gives the triazoles **91b–91d**, presumably arising through a pathway involving the zwitterionic intermediates, **90b–90d** (Scheme 22).[58–60]

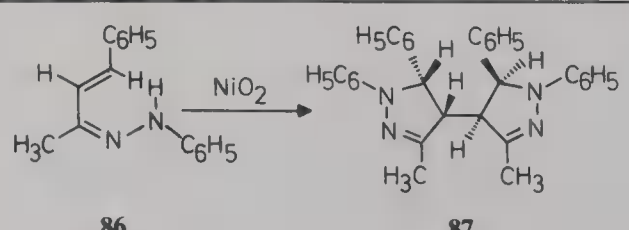
The oxidation of methylglyoxal bisphenylhydrazone (**92a**) at room temperature is reported to give exclusively 1,2-bisphenylazopropylene (**94a**), whereas in refluxing benzene, a mixture of **94a** and **98** is formed (Scheme 23). Similar results have been obtained in the case of **92b**, whereas **92c** gives the pyrazole **98c**, both at room temperature and under refluxing conditions (Scheme 23).[58]

The room-temperature oxidation of benzylmethylglyoxal bisphenylhydrazone (**99**) gives a mixture of 3-phenylazo-3-buten-2-one phenylhydrazone (**100**) and 1,5-diphenyl-3-methyl-4-phenylazopyrazole (**101**). Under refluxing conditions in benzene, the oxidation of **99** gives a mixture of the phenylazopyrazole **101** and 1-phenyl-3-benzoyl-4-phenylazopyrazole (**102**). (Scheme 24).[58]

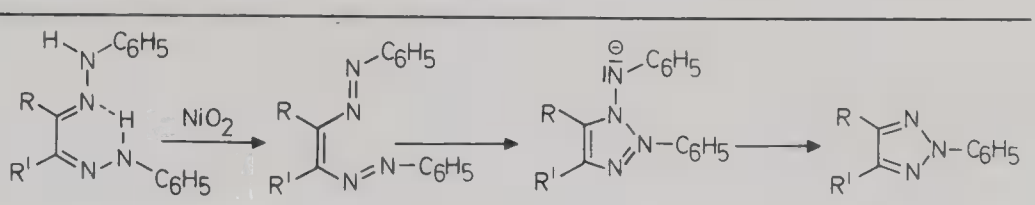
The oxidation of phenylglyoxal bisphenylhydrazone (**103**) has been shown to give a mixture of the triazole **104**, and **105** (Scheme 25).[58]

Benzoylhydrazones of aldehydes, ketones, and 1,2-diketones are known to undergo nickel peroxide oxidation to give a variety of products.[61] Benzaldehyde benzoylhydrazone (**106a**), for example, gives a mixture of the oxadiazole **107a** and the nickel complex **108a**. Similar results have been obtained with **106b–106d** (Scheme 26).[61]

SCHEME 21



SCHEME 22



88 **89** **90** **91**

a) R = R' = H ; b) R = R' = C_6H_5

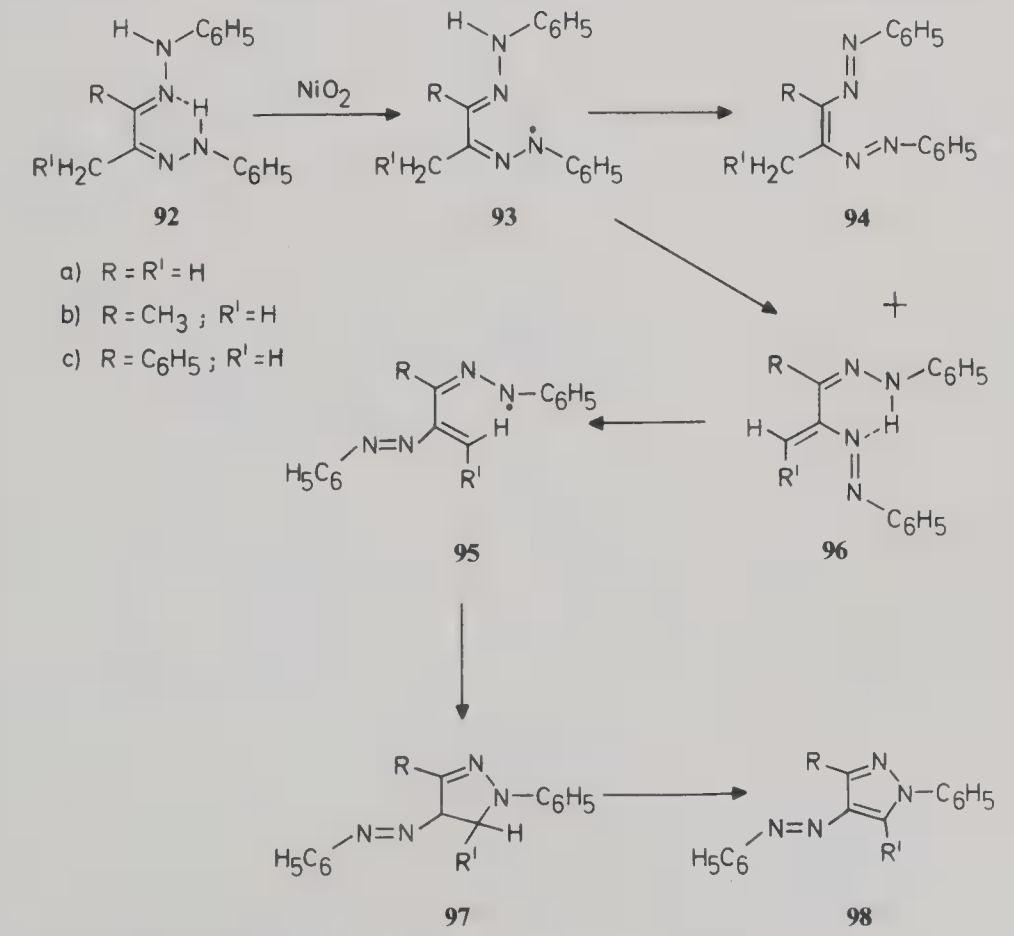
c) R = R' = p-CH_3O-C_6H_4 ; d) R = R' = p-Cl-C_6H_4

Acetophenone benzoylhydrazone (**109a**) gives, on oxidation with nickel peroxide, a mixture of acetophenone (**110a**) and **111a**. Similar results have been obtained with the benzoylhydrazones **109b**, **109c** (Scheme 27).[61]

Biacetyl bisbenzoylhydrazone (**112a**) on oxidation with nickel peroxide in chloroform gives a mixture of the triazole **116a** and the nickel complex **115a** (Scheme 28). Similar results have been obtained in the oxidation of **112b**, **112c**.[61]

The oxidation of phenylglyoxal bisbenzoylhydrazone (**117a**) with nickel peroxide gives a mixture of the triazoles **118a** and **119a** and the nickel complex **120a**. Similar results have been obtained in the oxidation of 4-methoxyphenylglyoxal bisbenzoylhydrazone (**117b**) (Scheme 29).[61]

SCHEME 23



92 **93** **94**

a) R = R' = H

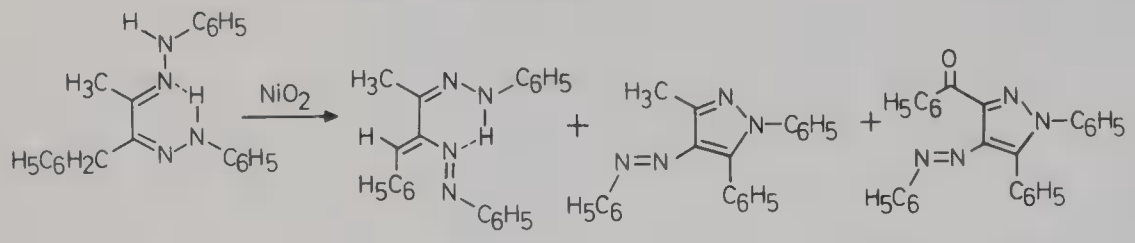
b) R = CH_3 ; R' = H

c) R = C_6H_5 ; R' = H

95 **96**

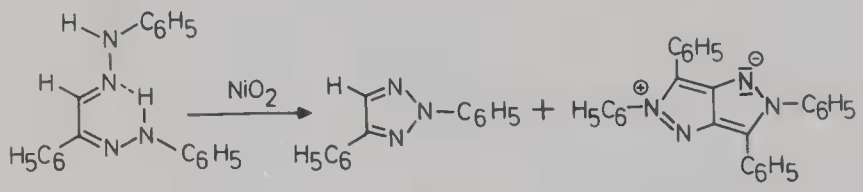
97 **98**

SCHEME 24



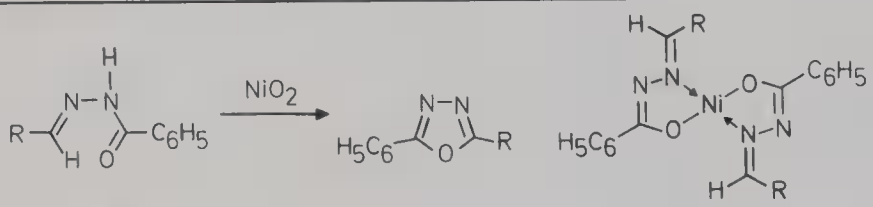
99 **100** **101** **102**

SCHEME 25



103 **104** **105**

SCHEME 26

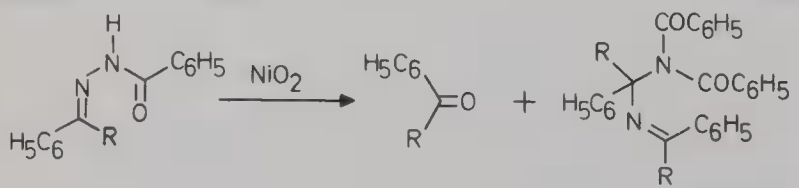


106 **107** **108**

a) R = C_6H_5 ; b) R = p-$CH_3C_6H_4$

c) R = o-$H_3COC_6H_4$; d) R = p-$H_3COC_6H_4$

SCHEME 27



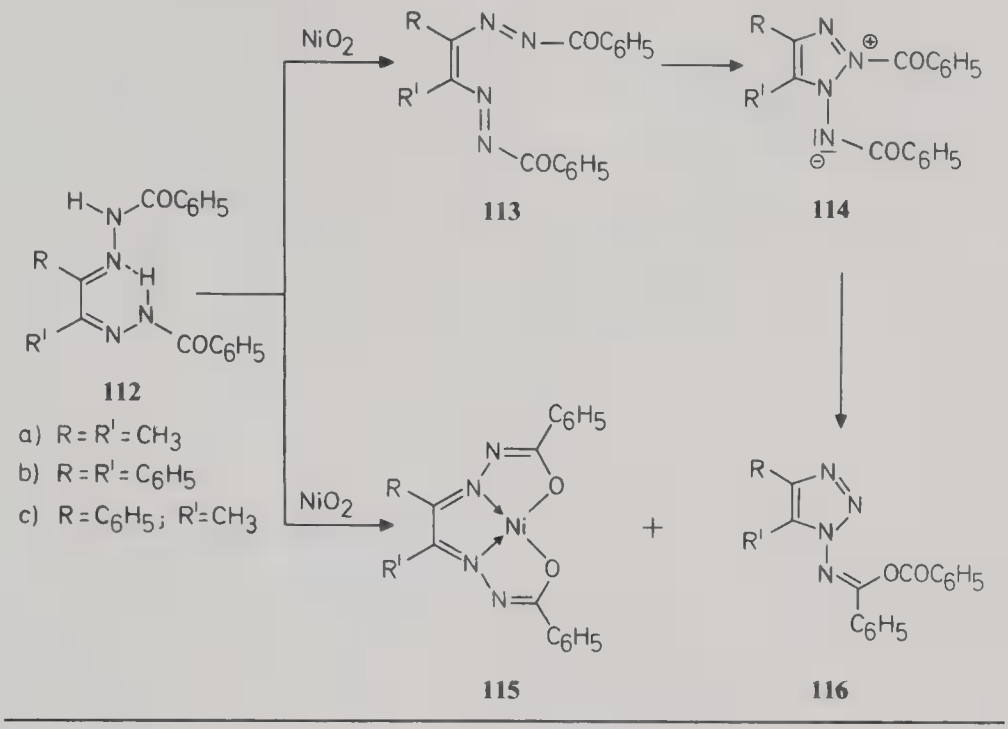
109 **110** **111**

a) R = CH_3

b) R = CH_2CH_3

c) R = C_6H_5

SCHEME 28



The oxidation of aldoximes with nickel peroxide gives aldazine bis-*N*-oxides as major products.

The reactions of several hydrazones, phenylhydrazones, benzoylhydrazones, and oximes are summarized in Table IX.

3.9. Schiff Bases

Several benzoxazoles have been prepared through the nickel peroxide oxidation of *o*-(benzylideneamino)phenols.[62] For example, *o*-(*p*-nitrobenzylidineamino)phenol on treatment

SCHEME 29

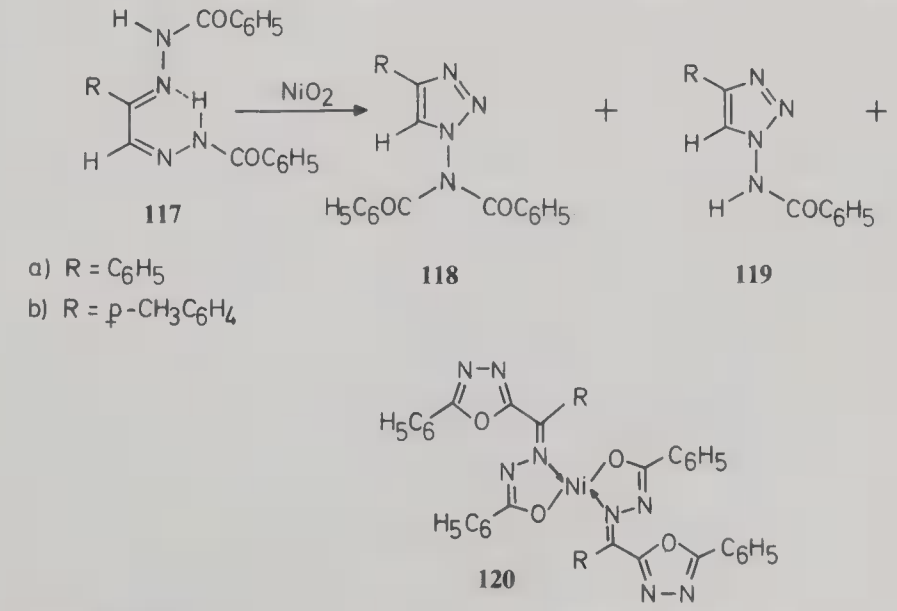
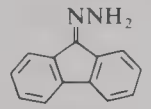
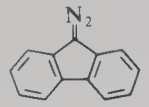
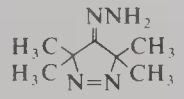
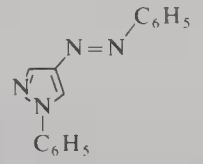


TABLE IX. Oxidation of Hydrazones, Phenylhydrazones, Benzoylhydrazones, and Oximes

Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
$(C_6H_5)_2C=NNH_2$	—	20°C/1 h	$(C_6H_5)_2CN_2$	99	50
$C_6H_5(CH_3)C=NNH_2$	—	0°C/1 h	$C_6H_5(CH_3)CN_2$	56	50
$C_6H_5COC(C_6H_5)NNH_2$	—	0°C	$C_6H_5COC(C_6H_5)N_2$	99	3,4
$C_6H_5(H)C=NNH_2$	—	0°C/1 h	$C_6H_5(H)CN_2$	68	50
	—	20°C/1 h		92	50
$(CO_2C_2H_5)_2C=NNH_2$	—	20°C/1 h	$(CO_2C_2H_5)_2CN_2$	89	50
	—	Ether/room temperature	$(H_3C)_2C=C=C(CH_3)_2$	87	54
$C_6H_5(H)C=NNHC_6H_5$	—	C_6H_6/room temperature/4 h	$C_6H_5CHN=NC_6H_5$ | $C_6H_5CHN=NC_6H_5$	65	23
$C_6H_5NHN=CHCH=NNHC_6H_5$	—	C_6H_6/room temperature/3 h	$C_6H_5N=NCH=CHN=NC_6H_5$	93	58
$C_6H_5NHN=C(H)C(CH_3)=NNHC_6H_5$	—	C_6H_6/room temperature/4 h	$C_6H_5N=NCH=C(CH_3)N=NC_6H_5$	90	58
		C_6H_6/room temperature/6 h	$C_6H_5C_6H_5$	3	
			$+ C_6H_5N=NCH=C(CH_3)N=NC_6H_5$	45	
			+ 	15	

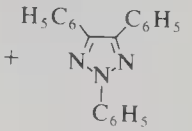
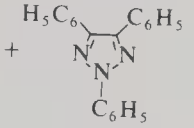
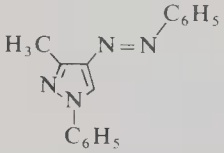
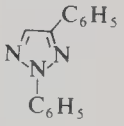
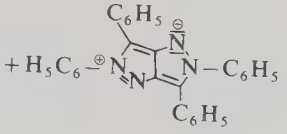
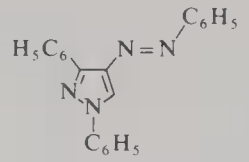
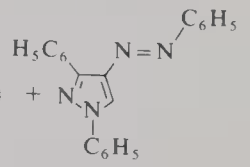
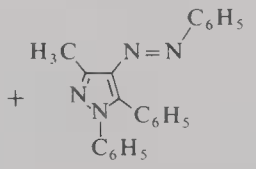
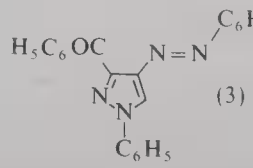
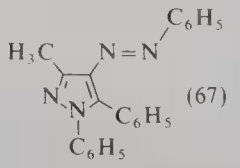
$C_6H_5NHN=C(C_6H_5)C(C_6H_5)=NNHC_6H_5$	—	C_6H_6/room temperature/3 h	$C_6H_5N=N(C_6H_5)C=C(C_6H_5)N=NC_6H_5$	60	58
				13	
	—	C_6H_6/reflux/3 h	$C_6H_5N=N(C_6H_5)C=C(C_6H_5)N=NC_6H_5$	66	58
				16	
$C_6H_5NHN=C(CH_3)(CH_3)C=NNHC_6H_5$	—	C_6H_6/room temperature/4 h	$C_6H_5N=N(CH_3)C=C(CH_3)N=NC_6H_5$	85	58
$C_6H_5NHN=C(CH_3)(CH_3)C=NNHC_6H_5$	—	C_6H_6/reflux/5 h		52	58
			$+C_6H_5C_6H_5$	6	
$HC=NNHC_6H_5$ $H_5C_6C=NNHC_6H_5$	—	C_6H_6/reflux/4 h	$C_6H_5C_6H_5$(20) + 	19	58
				18	

Table continued

TABLE IX. *Continued*

Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
$H_5C_6C=NNHC_6H_5$ $H_3CC=NNHC_6H_5$	—	C_6H_6/room temperature/4 h		76	58
	—	C_6H_6/reflux/4 h	$C_6H_5C_6H_5$(21) + 	58	
$H_3CC=NNHC_6H_5$ $H_5C_6H_2CC=NNHC_6H_5$	—	C_6H_6/room temperature/2 h	$H_3CC=NNHC_6H_5$ $H_5C_6HC=C-N=NC_6H_5$	19	58
			+ 	50	
	—	C_6H_6/reflux/2.5 h	$C_6H_5C_6H_5$(3) + $H_3CC=NNHC_6H_5$(14) $H_5C_6HC=C-N=NC_6H_5$		58
			 (3) +  (67)		

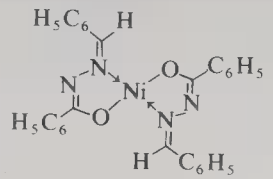
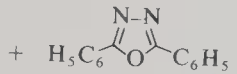
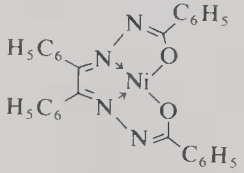
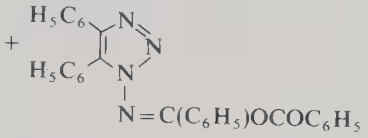
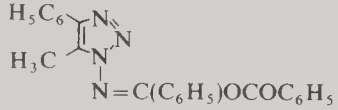
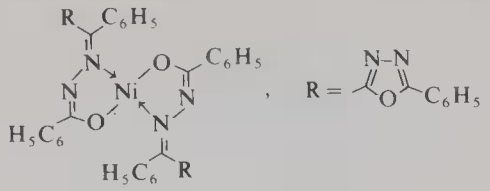
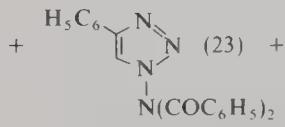
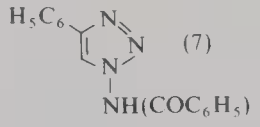
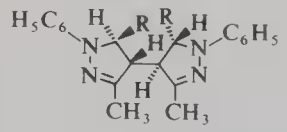
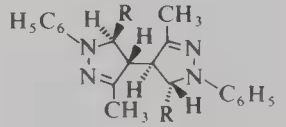
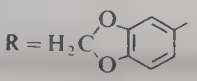
$C_6H_5CH=NNHCOC_6H_5$	—	$CHCl_3$/reflux/4 h		47	61
				30	
$C_6H_5(CH_3)C=NNHCOC_6H_5$	—	C_6H_6/reflux/4 h	$C_6H_5COCH_3$	36	61
			$+C_6H_5(CH_3)C=NC(CH_3)(C_6H_5)$ $\lvert$ $N(COC_6H_5)_2$	11	
$(C_6H_5)_2C=NNHCOC_6H_5$	—	C_6H_6/reflux/4 h	$(C_6H_5)_2CO$	50	61
			$+(H_5C_6)_2C=NC(C_6H_5)_2N(COC_6H_5)_2$	16	
$H_5C_6C=NNHCOC_6H_5$ $\lvert$ $H_5C_6C=NNHCOC_6H_5$	—	$CHCl_3$/reflux/4 h		22	61
				26	61
$H_5C_6C=NNHCOC_6H_5$ $\lvert$ $H_3CC=NNHCOC_6H_5$	—	$CHCl_3$/reflux/4 h		25	61

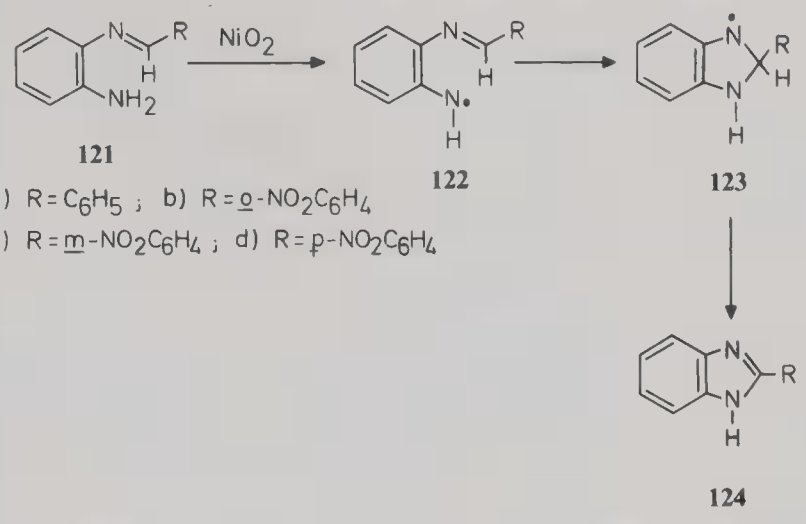
Table continued

TABLE IX. *Continued*

Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
$H_5C_6C=NNHCOC_6H_5$ $HC=NNHCOC_6H_5$	—	$CHCl_3$/reflux/3 h	 +  (23) +  (7)	31	61
$RC(H)=C(H)(CH_3)C=NNHC_6H_5$	—	—	 (A) +  (B) + $C_6H_5C_6H_5$ (C)		64

			A	*B*	*C*
$R=C_6H_5$	—	C_6H_6/room temperature/4 h	70	0	0
$R=p\text{-}CH_3C_6H_4$	—	C_6H_6/room temperature/4 h	0	40	0
$R=o\text{-}ClC_6H_4$	—	C_6H_6/room temperature/4 h	0	18	6
	—	C_6H_6/room temperature/5 h	14	30	7

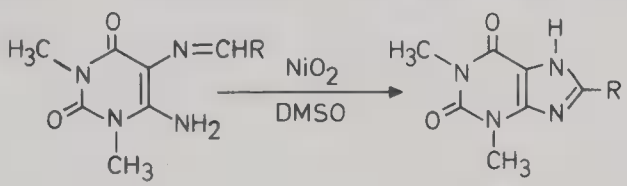
SCHEME 30



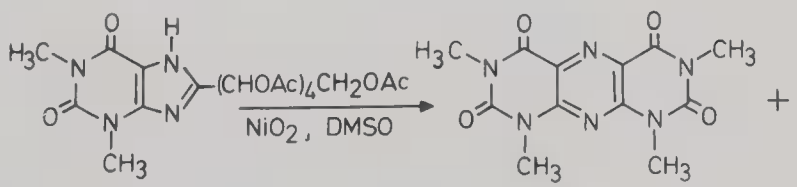
with nickel peroxide in benzene at 15°C for 1 h gives 2-(*p*-nitrophenyl)benzoxazole, in good yields. Similarly, the oxidation of *N*-benzylidine-*o*-phenylenediamines **121a–121d**, with nickel peroxide gives good yields of 2-substituted benzimidazoles **124a–124d** (Scheme 30).[49] Similar oxidative cyclizations have been employed in the preparation of substituted triazolopyridines.[63]

Mineo *et al.* have reported the synthesis of the theophyllines, **126a–126e** through the nickel peroxide oxidation of the uracils **125a–125e** in dimethylsulfoxide (Scheme 31).[53]

SCHEME 31

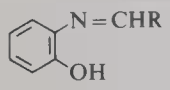
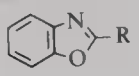
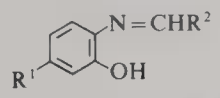
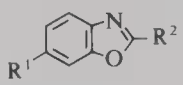
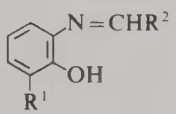
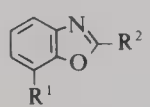
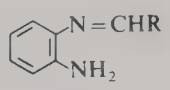
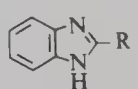
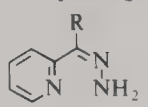
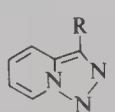


a) R = C_6H_5
b) R = p-CH_3O-C_6H_4-
c) R = p-ClC_6H_4-
d) R = p-$NO_2C_6H_4$-
e) R = 2-pyridyl



penta-O-acetyl gluconic acid
+
$(CH_3)_2SO_2$

TABLE X. Oxidation of Schiff Bases

Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
					
R = C_6H_5	—	C_6H_6/15°C/1 h		72	62
R = *o*-$NO_2C_6H_4$	—	C_6H_6/15°C/1 h		61	62
R = *m*-$NO_2C_6H_4$	—	C_6H_6/15°C/1 h		77	62
R = *p*-$NO_2C_6H_4$	—	C_6H_6/15°C/1 h		73	62
R = *p*-CNC_6H_4	—	C_6H_6/15°C/1 h		69	62
R = *p*-$(CH_3)_2NC_6H_4$	—	C_6H_6/15°C/1 h		66	62
R = *p*-$CH_3C_6H_4$	—	C_6H_6/15°C/1 h		73	62
R = *p*-$CH_3OC_6H_4$	—	C_6H_6/15°C/1 h		72	62
R = *p*-ClC_6H_4	—	C_6H_6/15°C/1 h		71	62
					
R^1 = NO_2, R^2 = C_6H_5	—	C_6H_6/15°C/1 h		72	62
R^1 = NO_2, R^2 = *p*-$NO_2C_6H_4$	—	C_6H_6/15°C/1 h		73	62
R^1 = NO_2, R^2 = *p*-$CH_3OC_6H_4$	—	C_6H_6/15°C/1 h		73	62
R^1 = NO_2, R^2 = *p*-ClC_6H_4	—	C_6H_6/15°C/1 h		65	62
R^1 = Cl, R^2 = C_6H_5	—	C_6H_6/15°C/1 h		70	62
R^1 = Cl, R^2 = *p*-$NO_2C_6H_4$	—	C_6H_6/15°C/1 h		64	62
R^1 = Cl, R^2 = *p*-ClC_6H_4	—	C_6H_6/15°C/1 h		74	62
R^1 = CH_3, R^2 = *p*-ClC_6H_4	—	C_6H_6/15°C/1 h		76	62
					
R^1 = Cl, R^2 = *p*-ClC_6H_4	—	C_6H_6/15°C/1 h		48	62
R^1 = NO_2, R^2 = *p*-$NO_2C_6H_4$	—	C_6H_6/15°C/1 h		78	62
R^1 = H, R^2 = CH=CHC_6H_5	—	C_6H_6/15°C/1 h		61	62
					
R = C_6H_5	2.0	C_6H_6/30°C/3 h		71	49
R = *p*-$NO_2C_6H_4$	2.5	C_6H_6/30°C/3 h		57	49
					
R = H	—	C_6H_6/30°C		65	63
R = CH_3	—	C_6H_6/30°C		79	63
R = C_6H_5	—	C_6H_6/30°C		95	63

Nickel peroxide oxidation of the Schiff base acetate **127** is known to give the pyrimidopteridinetetrone **128**[53]

The oxidation reactions of several Schiff bases are summarized in Table X.

3.10. Compounds Containing Activated C–H Bonds

Nickel peroxide oxidation of hydrocarbons containing activated C–H bonds is extremely slow under mild conditions, while under drastic conditions these substrates are oxidized to the corresponding carboxylic acids. In the oxidation of toluene, for example, it has been reported that further addition of nickel peroxide after 8 h of reaction time results in increased yields of benzoic acid. Manganese dioxide, on the other hand, does not oxidize simple hydrocarbons such as toluene, xylene, and ethylbenzene.

Oxidation of diphenylmethane using nickel peroxide in refluxing benzene gives a 56% yield of benzophenone. However, in the absence of any solvent, and at 110°C, the yield of benzophenone is increased to 79%.[23]

A reported procedure for the α-fluorination of alkylbenzenes involves their treatment with fluoride in presence of nickel peroxide at low temperatures (−30°C).[65] *p*-Nitrotoluene, for example, gives a 44% yield of *p*-fluoromethylnitrobenzene and a 20% yield of *p*-difluoromethylnitrobenzene under these conditions [Eq. (13)].[8,9]

$$p\text{-}NO_2C_6H_4CH_3 \xrightarrow[HF,\,25°C,\,17\,h]{NiO_2} p\text{-}NO_2C_6H_4CH_2F + p\text{-}NO_2C_6H_4CHF_2 \qquad (13)$$

Phenylacetonitrile (**129**) on oxidation with nickel peroxide gives a variety of products consisting of *meso*-2,3-diphenylsuccinonitrile (**130**) *cis*- and *trans*-dicyanostilbenes (**131**, **132**), benzoic acid (**133**) and polymeric products (Scheme 32).[66] The nitrile **130** itself undergoes oxidation with nickel peroxide to give a mixture of **131** and **132**, along with polymeric materials.[66]

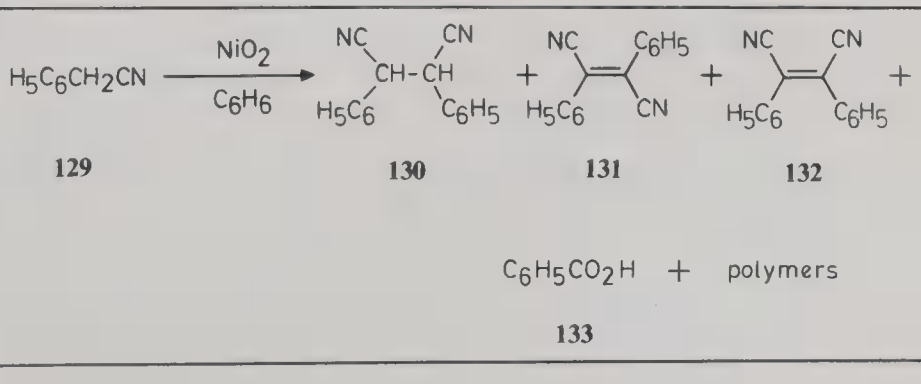
An interesting coupling reaction has been observed in the case of the oxazolidine **134**, which on treatment with nickel peroxide gives rise to the cyclopropane **135** (Scheme 33).[47]

The nickel peroxide oxidation reactions of several compounds containing activated C–H bonds are summarized in Table XI.

3.11. Sulfur Compounds

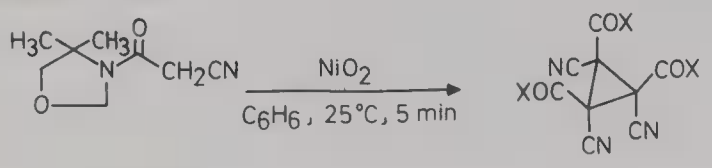
Oxidative dimers are obtained in the oxidation of thiols with nickel peroxide.[67] Thiophenol, for example, is oxidized to diphenyldisulfide in a 95% yield. Ethyl mercaptan, similarly, gives a 87% yield of diethyldisulfide, on oxidation with nickel peroxide at 30°C for 2 h. On the other hand, the oxidation of sulfides to sulfones with nickel peroxide proceeds

SCHEME 32



129 **130** **131** **132** **133**

SCHEME 33



134 135

X = oxazolidinyl

very slowly. Thus, diphenyl sulfide on oxidation with nickel peroxide at 80°C gives only a 48% yield of diphenylsulfone, even after 10 h of reaction time [Eq. (14)].

$$C_6H_5SC_6H_5 \xrightarrow{NiO_2} C_6H_5SO_2C_6H_5 \tag{14}$$

Sugita and Tsujino have examined the nickel peroxide oxidation of several phenothiazines.[68] Mixtures of products consisting of oxidative dimers, dehydrogenated products, sulfones, sulfoxides, and polymeric materials have been observed in these reactions.

The oxidation of thiosemicarbazides is known to give different types of products, depending on the substituents present in these compounds.[69] For example, the oxidation of 1-(2-pyridyl)-4-methylthiosemicarbazide (**136**) gives the triazolopyridine **137**, on treatment with nickel peroxide (Scheme 34), whereas phenyl-4-methylthiosemicarbazide, under analogous conditions gives the corresponding azo compound [Eq. (15)]. In contrast, the oxidation of the semicarbazide **138** results in decomposition products only (Scheme 34).

$$C_6H_5NHNHCSNHCH_3 \xrightarrow{NiO_2} C_6H_5N{=}NC(S)NHCH_3 \tag{15}$$

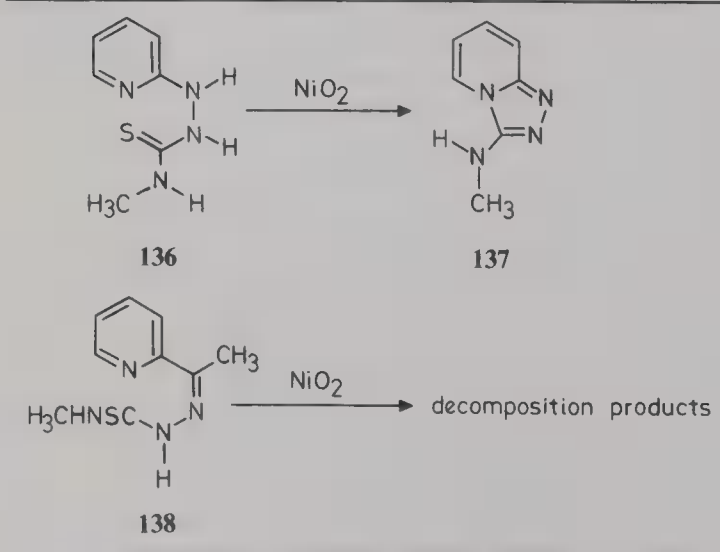
The oxidation reactions of several sulfur compounds are summarized in Table XII.

3.12. Miscellaneous Reactions

3.12.1. Dehydrogenation and Other Reactions of Heterocycles

Nickel peroxide is a useful reagent in the dehydrogenation of heterocycles such as pyrazolines, oxazolines, and thiazolines. Thus, the pyrazoline **139**, on treatment with nickel

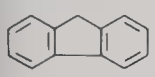
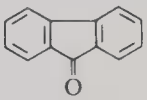
SCHEME 34



136 137

138

TABLE XI. Oxidation of Compounds Containing Activated C–H Bonds

Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
p-$NO_2C_6H_4CH_3$	3.2	HF/25°C/17 h	p-$NO_2C_6H_4CH_2F$ + p-$NO_2C_6H_4CHF_2$	44 20	8, 9
	2.4	Poly(chlorotrifluoroethylene)/ −30 to 80°C/17 h	p-$NO_2C_6H_4CH_2F$ + p-$NO_2C_6H_4CHF_2$	21 71	65
$C_6H_5CH_2C_6H_5$	—	C_6H_6/80°C/5 h	$C_6H_5COC_6H_5$	56	3, 4
$C_6H_5CH_2C_6H_5$	—	110°C/5 h	$C_6H_5COC_6H_5$	79	3, 4
	—	110°C/5 h		66	23
$(C_6H_5)_3CC(C_6H_5)_3$	0.6	C_6H_6/55°C/10 h	$(C_6H_5)_3COH$	90	11
$C_6H_5N{=}NC(C_6H_5)_3$	1.1	C_6H_6/65°C	$(C_6H_5)_3COH$ + $(C_6H_5)_3CH$ + $C_6H_5C_6H_5$	56 48 79	11
$(C_6H_5)_2CHCN$	—	C_6H_6/25°C/1 h	$(C_6H_5)_2CCN$ | $NCC(C_6H_5)_2$	99	3, 4, 11

peroxide in benzene at 80°C for 3 h, gives a 95% yield of the pyrazole **140** (Scheme 35).[23] Similarly, the oxazoline **141** gives a 69% yield of the oxazole **142** (Scheme 35).[70] The thiazoline **143**, on treatment with nickel peroxide at 25°C for 72 h, undergoes dehydrogenation to give the thiazole **144** (Scheme 35).[70] Mention may be made here of the dehydrogenation of the naturally occurring phleomycin A_2 to give bleomycin A_2 in a 83% yield, on treatment with nickel peroxide.[70]

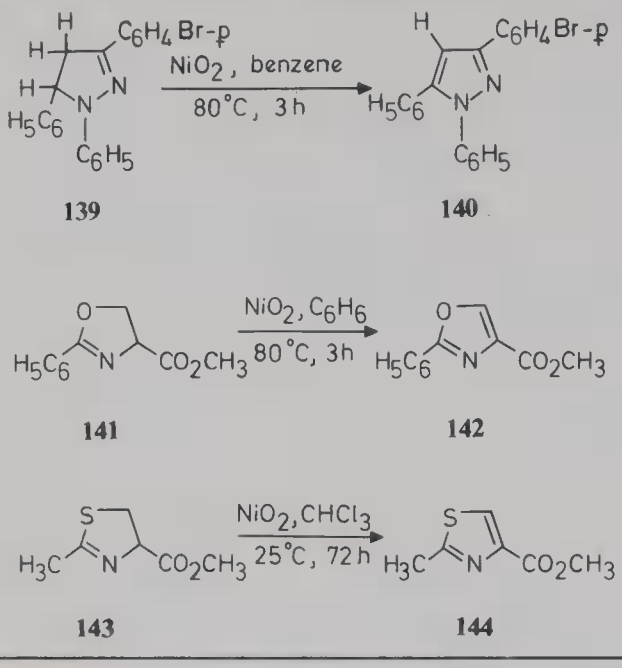
Dicarbonyl azo compounds can be prepared through the dehydrogenation of the corresponding diacyl hydrazides by treatment with nickel peroxide.[71] Thus, the treatment of maleic hydrazide (**145**) with nickel peroxide at room temperature gives 3,6-dioxopyridazine (**146**). Similarly, the oxidation of **148** gives rise to the diazanaphthaquinone **149** (Scheme 36). When these oxidation reactions are carried out in the presence of dienes, the corresponding Diels–Alder adducts are isolated. Thus, the oxidation of **145** and **148** with nickel peroxide in the presence of *trans,trans*-1,4-diphenyl-1,3-butadiene, for example, gives rise to the adducts **147** and **150**, respectively (Scheme 36).[71]

Nickel peroxide could be used for generation of benzyne through the oxidation of 1-aminobenzotriazole (**151**).[72] In the absence of benzyne trapping agents, however, the oxidation of **151** gives rise to a mixture of products consisting of biphenylene (**153**), azobenzene (**154**), and 1-phenylbenzotriazole (**155**) (Scheme 37). It has been suggested that the nitrene **152** is a probable intermediate in this reaction. On the other hand, the oxidation of

TABLE XII. Oxidation of Sulfur Compounds

Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
C_6H_5SH	—	1 h	$C_6H_5SSC_6H_5$	95	67
CH_3CH_2SH	—	30°C/2 h	$CH_3CH_2SSCH_2CH_3$	87	67
$C_6H_5SC_6H_5$	—	80°C/10 h	$C_6H_5(SO_2)C_6H_5$	48	67

SCHEME 35



139 140 141 142 143 144

151 in the presence of a benzyne trapping agent such as tetracyclone gives the naphthalene derivative **159** (45%), presumably formed through the loss of carbon monoxide from the initially formed adduct **157** (Scheme 38).[72] Similarly, the nickel peroxide oxidation of **151** in the presence of anthracene gives rise to triptycene (**158**, 4%) (Scheme 38).[72]

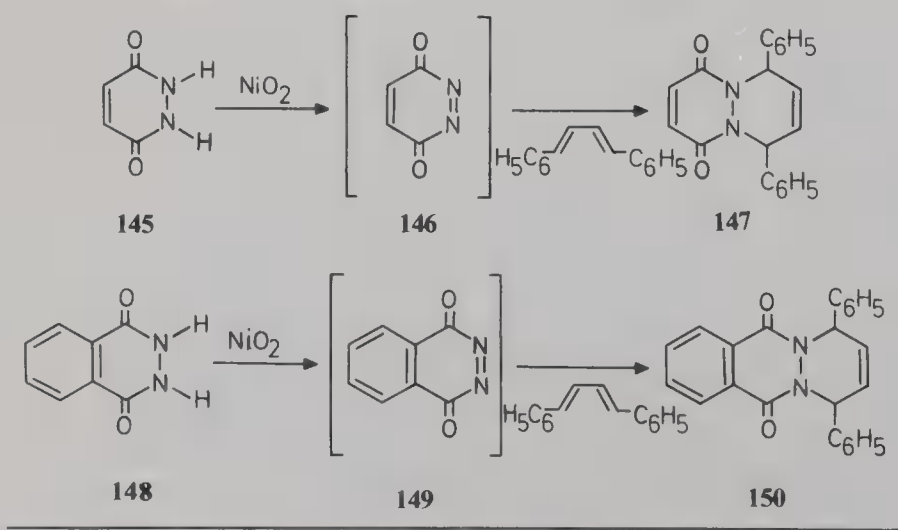
The reactions of several heterocycles with nickel peroxide are summarized in Table XIII.

3.12.2. Telomerization and Polymerization Reactions

It has been observed that chloroform is converted to hexachloroethane in a 72% yield, on treatment with nickel peroxide, and this reaction is assumed to proceed through the intermediacy of trichloromethyl radicals.[6] Such halogenated alkyl radicals formed in similar oxidation reactions have been made use of in different telomerization and polymerization reactions.[73,74]

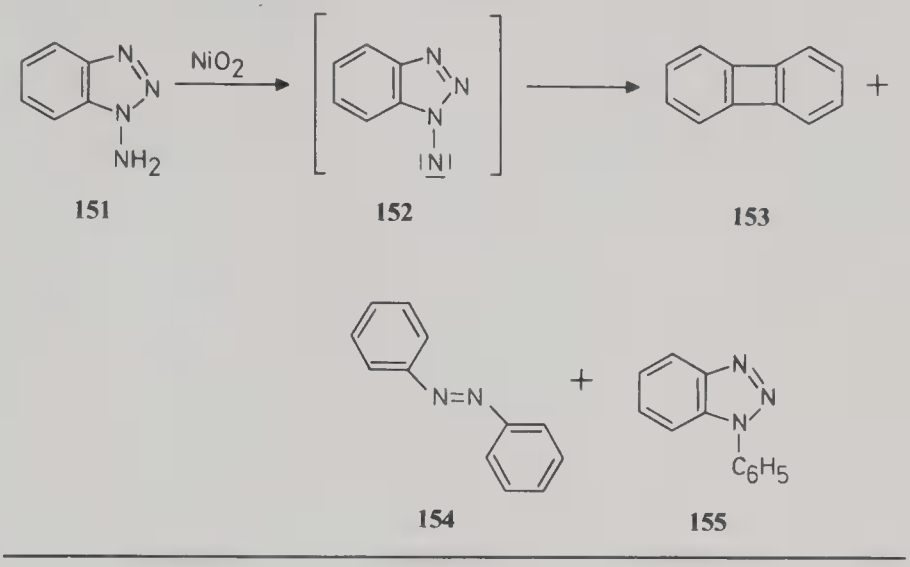
Thus, it has been observed that in the reaction of 1-octene with bromoform in the

SCHEME 36



145 146 147 148 149 150

SCHEME 37

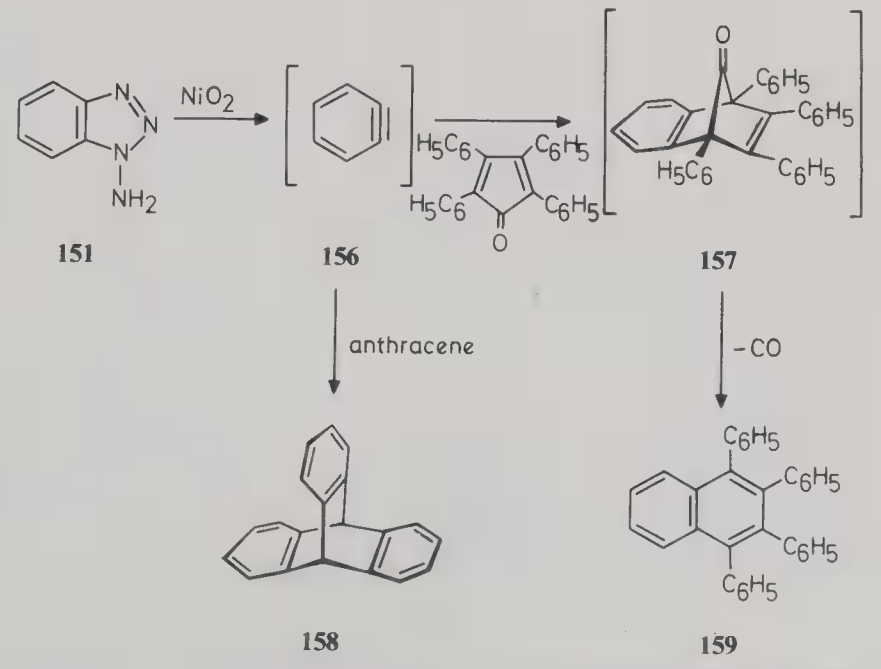


151 152 153 154 155

presence of nickel peroxide, for example, a 1:1 addition product is formed. However, styrene in the presence of chloroform yields products with a higher degree of polymerization. Under analogous conditions, tetrabromoethane, gives a 1:1 adduct in nearly quantitative yield. The reaction of a mixture of chloroform and bromoform with nickel peroxide in carbon tetrachloride is reported to give a mixture of 1,1,1-tribromo-2,2,2-trichloroethane, hexachloroethane, hexabromoethane, and tetrabromoethylene through telomerization reactions.[75]

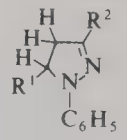
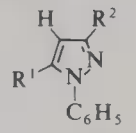
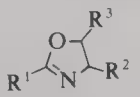
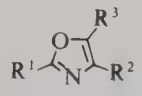
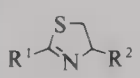
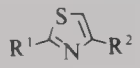
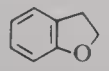
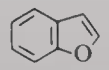
Several terpenes such as α-terpineol, linalool, myrcene, and dipentene have been synthesized through the telomerization of isoprene and prenyl chloride, using nickel peroxide as the initiator.[76] Mention may also be made that several stereospecific polymers have been synthesized through the use of nickel peroxide as initiator.[77–87]

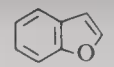
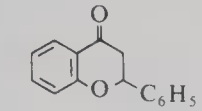
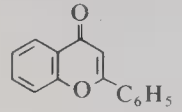
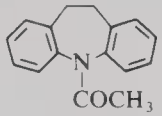
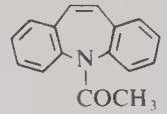
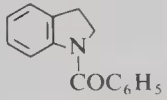
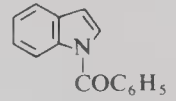
SCHEME 38



151 156 157 158 159

TABLE XIII. Dehydrogenation and Other Reactions of Heterocycles

Reactant	Ratio of NiO_2 to reactant	Conditions	Product(s)	Yield (%)	References
					
$R^1 = C_6H_5$, $R^2 = CH{=}CHC_6H_5$	—	C_6H_6/80°C/3 h		76	23
$R^1 = C_6H_5$, $R^2 = p$-BrC_6H_4	—	C_6H_6/80°C/3 h		95	23
R^1 = -thiofuryl, $R^2 = C_6H_5$	—	C_6H_6/80°C/3 h		93	23
					
$R^1 = CH$, $R^2 = CO_2C_2H_5$, $R^3 = H$	1.5	Hexane/reflux/16 h		53	70
$R^1 = C_3H_7$-n, $R^2 = CO_2CH_3$, $R^3 = H$	3.8	C_6H_6/reflux/40 h		58	70
$R^1 = C_6H_5$, $R^2 = CO_2CH_3$, $R^3 = H$	1.5	Cyclohexane/reflux/6 h		69	70
					
$R^1 = CH_3$, $R^2 = CO_2CH_3$	2.0	$CHCl_3$/25°C/72 h		81	70
$R^1 = SCH_3$, $R^2 = H$	2.4	CH_2Cl_2/25°C/24 h		43	70
	3.7	C_6H_6/reflux/4 h		60	70
$R^1 = SH$, $R^2 = H$	1.0	$CHCl_3$/25°C/12 h		88	70
$R^1 = CH_3CONH(CH_2)_2$, $R^2 = CO_2C_2H_5$	2.6	C_6H_6/reflux/3.5 h		56	70
	1.4	C_6H_6/reflux/6.5 h		32	70
			+ Starting material	40	

	2.2	C_6H_6/reflux/11 h		52	70
	1.6	C_6H_6/reflux/4 h		71	70
	1.7	C_6H_6/reflux/4 h		73	70
	1.3	C_6H_6/reflux/18 h		37	70
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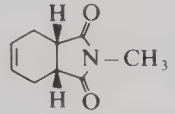
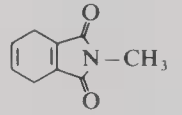
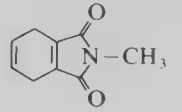
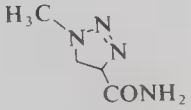
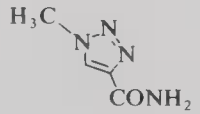
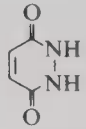
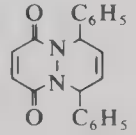
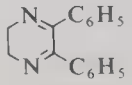
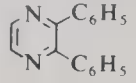
	2.2	C_6H_6/reflux/1.5 h		30	70
	2.3	C_6H_6/reflux/7 h		62	70
	1.7	C_6H_6/reflux/4 h		41	70
	1.2–2.0	CH_2Cl_2/*trans*, *trans*-1,4-diphenylbutadiene		63	71
	1.7	C_6H_6/reflux/4 h		92	70

Nickel peroxide could also be used in the alkylation of compounds containing activated methylene groups with terminal alkenes. Thus, the reaction of ethyl cyanoacetate with 1-hexene in the presence of nickel peroxide, for example, gives rise to ethyl α-cyanooctanoate.[88]

4. EXPERIMENTAL CONSIDERATIONS

Nickel peroxide oxidations are relatively simple to carry out; however, the reaction conditions have to be carefully optimized for better results. There have been only very few studies detailing the effects of variables such as proportions of reactants, solvents, time, temperature, presence of other materials, workup procedures, etc. in nickel peroxide oxidations of organic substrates.

4.1. Nickel Peroxide

Nickel peroxide is the name used to designate the black amorphous, hydrous and higher oxides of nickel, formed by the reaction of nickel (II) salts with a strong oxidizing agent such as sodium hypochlorite. It has a larger surface area when compared to manganese dioxide and is a more effective oxidizing agent. It is insoluble in organic solvents and water which are commonly used for oxidation reactions.

In practice, the amount of nickel peroxide needed for any oxidation is determined on the basis of its available oxygen. It has been observed that one equivalent of available oxygen converts one mole of an alcohol to the corresponding carbonyl compound, or corresponds to the generation of two radical species.[11] The amount of available oxygen in a given sample of nickel peroxide is estimated iodometrically and a typical experimental procedure is outlined in Section 4.4.

A sample of nickel peroxide loses a considerable portion of its available oxygen, on heating. However, it can be stored at room temperature, under protection against atmospheric moisture, for a long time without losing its activity.[6]

Although nickel peroxide is commercially available today, a brief discussion on the methods of its preparation and purification may not be out of place. Most procedures reported in the literature indicate that freshly prepared nickel peroxide has been employed as the oxidizing agent. Although the need for the use of freshly prepared nickel peroxide in some cases is questionable, it has been reported that aged samples of nickel peroxide may give results different from those obtained with freshly prepared samples of the oxidant.

The commonly employed method for the preparation of nickel peroxide is that of Nakagawa,[6] which is outlined under Section 4.4.

It has also been reported that nickel peroxide is formed in the electrolysis of nickel hydroxide pulp with a high current efficiency in the presence of sodium chloride and sulfate.[89] Sodium hypochlorite is assumed to be formed in this reaction under electrolytic conditions which then converts the nickel salt to nickel peroxide.

For large-scale oxidations, nickel peroxide supported on graphite can be employed, and it is prepared by treating nickel oxide on powdered graphite in aqueous solution with sodium hypochlorite.[90,91]

It may be mentioned in this connection that the nickel peroxide that has been used in reactions can be reactivated by oxidizing it with sodium hypochlorite solution.[6,92] A typical reactivation procedure is outlined in Section 4.4.

4.2. Reaction Conditions

Factors such as the nature of the solvent, temperature, reaction time, and stoichiometry of the reactants influence nickel peroxide oxidations appreciably. An important example of

the effect of solvents, for example, in nickel peroxide oxidations is that of alcohols. Thus, when alcohols are oxidized in aqueous alkaline medium, carboxylic acids are generally formed, whereas when the reaction is carried out in organic solvents, the oxidation stops with the initial formation of carbonyl compounds. The most commonly employed solvents in nickel peroxide oxidation are benzene, ether, petroleum ether, and water. In a few cases, combinations of some of these solvents have also been used. It may be noted that solvents with active hydrogens such as alcohol and chloroform should be avoided because they may themselves be oxidized and thereby interfere with the main reaction. Also, in general, solvents which can stabilize radical intermediates are preferred in nickel peroxide oxidations. Other solvents that have been employed include tetrahydrofuran, acetic acid, *n*-hexane, cyclohexane, methylcyclohexane, methylene chloride, and dimethyl sulfoxide.

Nickel peroxide oxidation of aldehydes in the presence of ammonia gives rise to amides or nitriles, depending on the reaction temperature. Thus, at lower temperatures amides are formed as the major products, whereas at higher temperatures nitriles predominate. Similarly, the reaction time and also the stoichiometry of the reactants influence the course of nickel peroxide oxidations. Thus, in the oxidation of 6-hydroxymethyl-2-thiouracils, for example, the use of two equivalents of nickel peroxide brings about selective oxidation of the hydroxymethyl group to a carboxyl group, whereas, when excess of nickel peroxide is used, the oxidative desulfurization of the thiocarbonyl group also takes place, along with the conversion of the hydroxymethyl group to the carbonyl group.[7]

4.3. Workup Procedures

Nickel peroxide oxidations are very clean and easy to carry out. After the reaction is over, the excess of nickel peroxide and other inorganic material can be easily removed by filtration. Removal of the solvent from the filtrate under reduced pressure gives the product mixture, which can be purified usually by fractional crystallization in the case of solids or by chromatography over alumina or silica gel.

4.4. Model Experimental Procedures

4.4.1. Preparation of Nickel Peroxide[6]

A mixture of 300 ml of 6% sodium hypochlorite solution and 42 g of sodium hydroxide is added, dropwise, to a solution of 130 g nickel sulfate hydrate in 300 ml of water and stirred for 0.5 h at 20°C. The black nickel peroxide that is formed is filtered and washed several times with water to remove all water-soluble salts. The solid cake that results is crushed to powder and dried over anhydrous calcium chloride, preferably under reduced pressure.

4.4.2. Determination of Available Oxygen in Nickel Peroxide[6]

About 0.2 g of nickel peroxide is accurately weighed and added to 20 ml of 36% acetic acid containing 2% – 3% of potassium iodide in a stoppered flask. After complete dissolution of the oxidant, the solution is allowed to stand for 10 min and the liberated iodine is titrated against 0.1 *N* sodium thiosulfate solution. The available oxygen content is calculated as per the following equation:

$$\frac{Na_2S_2O_3\,(ml)}{1000 \times \text{peroxide (g)} \times 10 \times 2} = \text{gram atom oxygen/gram of nickel peroxide}$$

4.4.3. Reactivation of Nickel Peroxide[6]

Nickel peroxide that has been used earlier is reactivated by stirring in 6% sodium hypochlorite solution (about ten times the quantity of nickel peroxide) for 20 min. The activated oxide is washed several times with water and dried over anhydrous calcium chloride under vacuum.

4.4.4. Oxidation of Benzyl Alcohol in Aqueous Alkaline Medium[6]

To a solution of 2.16 g of benzyl alcohol and 1.0 g of sodium hydroxide in 50 ml of water, 16.0 g of nickel peroxide (1.5 times the theoretical amount) is added while stirring on a magnetic stirrer (0.5 h). The stirring is continued for 3 h at room temperature (30°C) and the mixture is filtered to remove the unchanged oxidant and other organic material. Acidification of the clear filtrate with dilute hydrochloric acid gives a white solid precipitate which is filtered and dried to give 2.1 g (88%) of benzoic acid, mp 122.5°C, after recrystallization from water. Workup of the aqueous filtrate by extraction with ether gives an additional amount of 0.26 g (11%) of benzoic acid, mp 122.5°C.

4.4.5. Oxidation of Benzyl Alcohol in Benzene[6]

A mixture of 5 g of benzyl alcohol and nickel peroxide (1.5 times the required amount, on the basis of available oxygen) in 45 ml of benzene is stirred in a flask equipped with a reflux condenser and the reaction temperature is maintained at 50°C, by heating on a hot plate. After stirring for 3 h, the reaction mixture is filtered to remove all the inorganic material. An aliquot portion of the filtrate, on treatment with 2,4-dinitrophenylhydrazine, gives the 2,4-dinitrophenylhydrazone of benzaldehyde. Based on this assay, a 73% yield of benzaldehyde is inferred, whereas gas chromatographic analysis indicates a 76% yield.

4.4.6. General Procedure for Oxidation of Phenols[36]

A mixture of the phenol and calculated amount of nickel peroxide based on the available oxygen content is stirred in benzene or ether at room temperature using a magnetic stirrer. The reaction mixture is filtered to remove all the inorganic material and the clear filtrate is worked up by the usual procedure (see Table III).

4.4.7. Oxidation of Benzoin[6]

A mixture of 5.0 g of benzoin and nickel peroxide (1.2 times the theoretical amount based on the available oxygen content) in 200 ml of benzene is heated at 50°C for 5 h. The reaction mixture is filtered and washed with benzene, and the crude product is obtained after removal of the solvent is recrystallized from aqueous alcohol to give 4.87 g (97%) of benzil, mp 94°C.

4.4.8. Oxidation of Vitamin A_1[6]

To a solution of 25 mg of vitamin A_1 (prepared from its palmitate) in 15 ml of petroleum ether is added 100 mg of nickel peroxide and the mixture is stirred at room temperature for 1 h. The reaction mixture is filtered and washed with petroleum ether. Removal of the solvent from the filtrate gives the oily retinal, which is dissolved in isopropanol and is assayed through electronic spectroscopy to indicate a 83% yield.

4.4.9. General Procedure for the Ammoxidation of Aldehydes[38]

A solution of the aldehyde (allylic or aromatic) in freshly distilled ether is stirred under nitrogen, and dry ammonia gas is introduced until the solution is saturated at −20°C. The

requisite amount of nickel peroxide is added in small amounts over 1 h and ammonia gas is bubbled through the reaction mixture for about 4 h at −20°C. The reaction mixture is filtered and the solid residue is washed with hot methanol. Removal of the solvent gives the crude amide, which is purified by standard procedures.

4.4.10. Oxidation of 4-Hydroxy-3-phenyltriphenylmethane[36]

A suspension of nickel peroxide (11.0 g) in a solution of 1.12 g of 4-hydroxy-3-phenyl triphenylmethane in 80 ml of benzene is shaken for 3.5 h in a stoppered flask. Filtration and washing of the residual metal oxide with benzene gives a brown-red filtrate, which yields a semisolid residue, on removal of the solvent under vacuum. It is triturated with a small amount of benzene, filtered, and recrystallized by dissolving in hot chloroform and adding benzene to give 0.195 g (19%) of 3-phenylfuchsone, mp 325–328°C.

4.4.11. Oxidation of Cyciohexanone[37]

Nickel peroxide (2.0 g, active oxygen equivalent 2.62) is added, portionwise, to a stirred mixture of 30 g of cyclohexanone and 30 ml of acetonitrile and the reaction temperature is maintained below 45°C during the course of addition. After stirring the mixture for a further period of 0.5 h, the inorganic materials are removed by filtration. Removal of the solvent and unchanged cyclohexanone under vacuum gives 4.6 g of a product, bp 160–200°C (at 15 mm). GLC analysis indicates that the mixture contains bicyclohexyl-2,2′-dione (*meso* and *dl* mixture, 73%), along with a small amount of cyclohexanone (12%).

4.4.12. Oxidation of o-Phenylenediamine[42]

To a solution of *o*-phenylenediamine in benzene or ether is slowly added nickel peroxide (twice the theoretical amount based on available oxygen content), with constant stirring, at room temperature (~30°C). The reaction proceeds very rapidly and the color of the solution turns red brown. Removal of the inorganic material by filtration and the solvent under vacuum gives a residual solid, which is chromatographed over alumina to give a 14% yield of *cis,cis*-1,4-dicyano-1,3-butanediene, mp 128–129°C, after recrystallization from carbon tetrachloride.

4.4.13. Oxidation of Benzophenone Hydrazone[50]

To a solution of benzophenone hydrazone in ether, nickel peroxide (1.1 times the theoretical amount based on the available oxygen content) is added gradually, while stirring on a magnetic stirrer. Stirring is continued for an additional period of 1 h at ca. 20°C and the unchanged nickel peroxide and other inorganic materials are removed by filtration. Removal of the solvent under vacuum gives a residual material which is assayed by treatment with benzoic acid in ether solution to give benzhydryl benzoate (97%), mp 87.5°C.

4.4.14. Oxidation of Benzil Bisphenylhydrazone[58]

A mixture of 2 g of benzil bisphenylhydrazone and 4 g of nickel peroxide is stirred in 150 ml of benzene at room temperature (30°C) for 3 h. Removal of the nickel salts by filtration and the solvent under vacuum gives a residual solid, which is recrystallized from a mixture (1:1) of benzene and petroleum ether to give 1.2 g (60%) of 1,2-bisphenylazostilbene, mp 179°C. The mother liquor obtained after removal of the solid, is concentrated under vacuum and the residual material is chromatographed over neutral alumina. Elution of the column with petroleum ether gives 0.2 g (13%) of 2,4,5-triphenyl-

1,2,3-triazole, mp 124°C. Further elution of the column using the same solvent gives an additional 0.2 g (11%) of 1,2-bisphenylazostilbene, mp 179°C.

4.4.15. Oxidation of o-(p-Nitrobenzylidineamino)phenol[62]

A suspension of 2.4 g of *o*-(*p*-nitrobenzylidineamino)phenol in 50 ml of benzene is treated with 3.6 g of nickel peroxide (available oxygen content 3.5 mg-atom/g) at 15°C. The reaction mixture is stirred for 1 h and worked up in the usual manner to give 1.8 g (75%) of 2-(*p*-nitrophenyl)benzoxazole, mp 211.5–212°C.

4.4.16. Oxidation of Chloroform[6]

A mixture of 100 g of chloroform and 13.3 g of nickel peroxide (available oxygen content 3.1 mg atom/g) is refluxed for 15 h. The inorganic material is removed by filtration and the solvent under vacuum to give a residual solid which is sublimed in a sealed tube to give 7.2 g (72%, calculated on the basis of available oxygen content of nickel peroxide) of hexachloroethane, mp 184–186°C.

4.4.17. Oxidation of Methyl 2-n-Propyloxazoline-4-carboxylate[70]

A solution of 0.5 g of methyl 2-*n*-propyloxazoline-4-carboxylate in 30 ml of cyclohexane is treated with 0.7 g of nickel peroxide in two portions, while the reaction mixture is heated under reflux for 40 h. Removal of the unchanged nickel peroxide and other inorganic material by filtration and the solvent under vacuum gives an oil which is purified using thin layer chromatography (developed twice with 10% acetone in hexane) to give 0.29 g (58%) of methyl 2-*n*-propyloxazole-4-carboxylate, as a pale yellow oil.

4.4.18. Oxidation of Phthalic Acid Hydrazide in the Presence of 1,3-Cyclooctadiene[71]

To a stirred mixture of phthalic acid hydrazide (0.01 mol) and 1,3-cyclooctadiene (0.01–0.03 mol) in 50 ml of methylene chloride, at room temperature, nickel peroxide (1.2–2.0 times the theoretical amount) is added portionwise, and the stirring is continued for an additional period of 20–40 h, at room temperature. The reaction mixture is filtered, and removal of the solvent under vacuum (40°C) gives a residual solid, which is recrystallized from a mixture of petroleum ether, *n*-hexane, and ethanol to give a 2.4 g (89%) of the adduct, mp 200.5–201°C.

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7

Oxidations of Organic Compounds Catalyzed by Copper– and Cobalt–Amine Complexes

C. R. H. I. de Jonge

1. INTRODUCTION

Selective oxidations of organic substrates catalyzed by transition metal complexes capable of activating oxygen have been of interest since Glaser observed[1] more than a hundred years ago that phenylacetylene underwent smooth aerial oxidation to diphenylacetylene when cuprous chloride in ammonia was used as a catalyst. This reaction has since been applied to a wide variety of organic compounds possessing the ethynyl grouping. The Glaser copper–amine system has been used in various modifications for many years up to the 1950s when two independant groups found a breakthrough in the oxidation of phenols using a copper–amine complex as a catalyst.[2]

Brackman and Havinga observed that naphthols were dimerized to dinaphthols (C–C coupling) using O_2 and copper–collidine or copper–pyridine complexes as catalysts, and Hay found that when the oxidation of a 2,6-disubstituted phenol is carried out at room temperature by merely passing oxygen through a solution of the phenol in an organic solvent containing pyridine and cuprous chloride as a catalyst, linear polyphenylene ethers are formed (C–O coupling) when the substituent groups are small, as in 2,6-dimethylphenol. With bulky ortho substituents, as in 2,6-di-*t*-butylphenol, C–C coupling occurs and the diphenoquinone is the sole product.

Since then, the use of the O_2/Cu^I/amine oxidation system has been extended to, e.g., C–C coupling of activated methine compounds,[3] oxidative cleavage reactions,[4] oxygenation reactions,[5] and N–N coupling.[6]

In contrast to copper–amine catalyzed oxidations of organic substrates, the cobalt–amine catalyzed oxidations have only a restricted, but valuable, synthetic potential.

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Whereas in copper–amine catalyzed oxidations in most cases, selective dehydrogenation occurs, oxygenation predominates in cobalt–amine catalyzed oxidations.

This is illustrated by the synthesis of *p*-benzoquinones from phenols using O_2 and Salcomine-(bis(salicylidene) ethylenediiminocobalt II) as a catalyst.[7] In most cases the *p*-benzoquinones were the main reaction products, although compounds originating from coupling of aryloxy radicals were also isolated.

High selectivity, viz., almost quantitative oxygenation, was found by de Jonge *et al.* when dimethylformamide was used as the solvent, which suggests that the Salcomine catalyst differs from that in other cases.[8]

From this time on Salcomine catalyzed oxidations become of interest for, e.g., vital steps in the sterospecific total synthesis of gibberellic acid.[9]

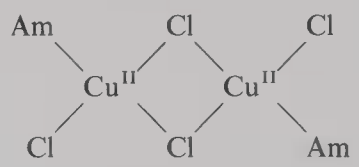
2. MECHANISM

In general, oxidations of organic substrates RH with copper–amine complexes as catalysts take place in three steps, viz., formation of an anion, oxidation to the corresponding radical, and radical coupling (dimerization or polymerization):

$$\underset{\mathbf{1}}{RH} \xrightarrow{-H^{\oplus}} \underset{\mathbf{2}}{R^{\ominus}} \xrightarrow{-e} \underset{\mathbf{3}}{R^{\cdot}} \longrightarrow \underset{\mathbf{4}}{\tfrac{1}{2}RR}$$

A generally adopted reaction scheme for the catalyst is as follows:

$$2CuCl_2 + 2Am \rightleftharpoons$$



Am = amine

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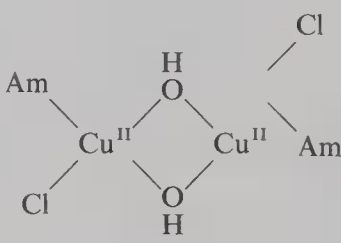
$$\mathbf{5} + H_2O \rightleftharpoons$$



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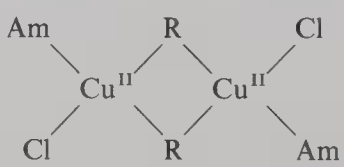
$$\mathbf{6} + 2(1) \rightleftharpoons$$



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$$\mathbf{7} \longrightarrow \mathbf{4} + 2AmCu^{I}Cl$$

$$2AmCu^{I}Cl + 2HCl + \tfrac{1}{2}O_2 \longrightarrow \mathbf{5} + H_2O$$

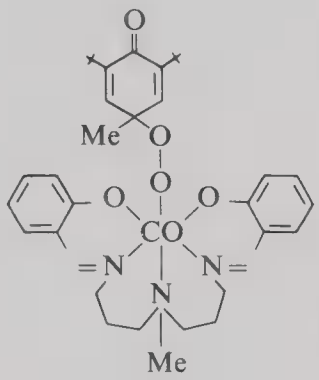
In copper–amine catalyzed oxidative coupling a substrate should fulfill conditions such as pK_a (substrate) < 20. Too high a pK_a or the use of aprotic solvents like dimethylsulfoxide

gives a fast oxygenation of the anion **2**[10]; R should stabilize the radical more than the anion; conversion of tertiary anions to tertiary radicals occurs more readily than conversion of secondary or primary anions to the corresponding radicals.[11]

The anion, the radical, and the dimerized product all should be relatively insensitive to oxygen; otherwise oxygenation of any of these intermediates or products will take place.

Along these lines the exclusive oxidative dimerization found with, e.g., *p*-tolylcyanoacetic methylester[3] can be understood.

The mechanism of cobalt–amine catalyzed oxidations has been studied by Matsuura *et al.*,[12] who found an interesting intermediate in the case of 4 alkyl-2,6-di-*t*-butylphenol.



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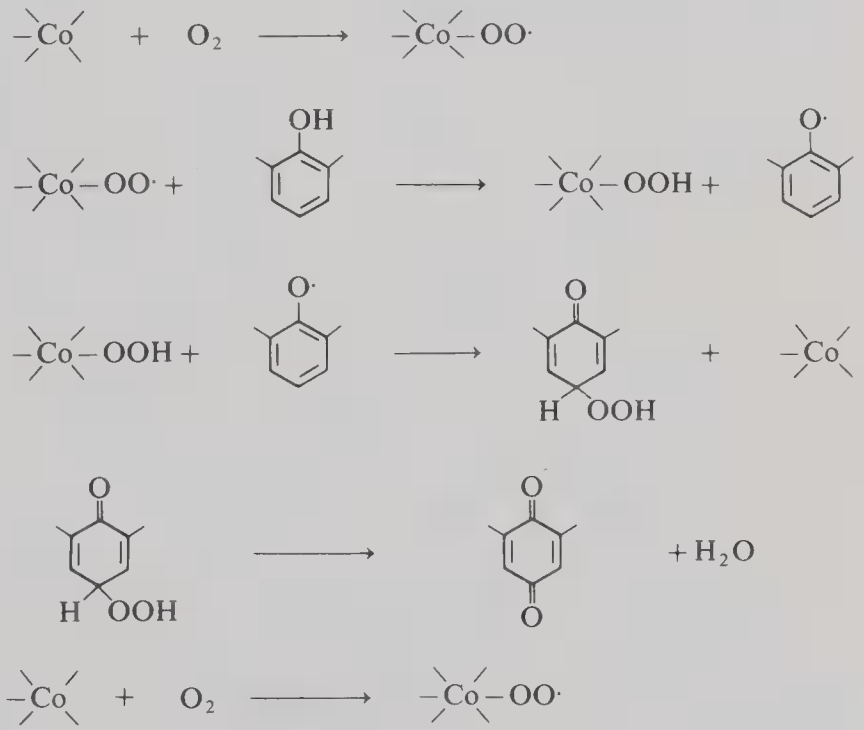
The formation of the peroxy-*p*-quinolato Co(III) complex (**8**) in the oxygenation of 4-alkyl-2,6-di-*t*-butylphenol with a Co(II) Schiff base can be rationalized by a mechanism involving hydrogen abstraction by a superoxo Co(III) species from the phenol producing a phenoxyl radical, electron transfer from the Co(III) complex to the phenoxyl radical, and oxygen incorporation into the phenolato Co(III) complex thus formed.



The high regioselectivity for the peroxy-*p*-quinolato Co(III) complexes may be due to the rapid phenolato Co(III) complex formation.

3. SCOPE AND LIMITATIONS

3.1. Copper–Amine-Catalyzed Oxidations

Catalytic oxidations of organic substrates with copper–amine complexes as catalysts are an attractive way to produce oxidation products. Generally, the reactions are carried out at ambient temperatures using oxygen or air as the oxidant. Laborious working up procedures can be avoided as, e.g., in the case of $K_3Fe(CN)_6$ $KMnO_4$, Ag_2O, MnO_2, and PbO_2 oxidations. On the other hand, the classes of organic substrates which are suited to be oxidized on a preparative scale (yields > 60%) are limited.

3.1.1. Acetylenes

The scope of the reaction, using Glaser's original procedure—i.e., an ethynyl compound dissolved in water or ethanol is added to a solution of cuprous chloride and ammonium chloride in water—is rather wide, and the coupling reaction can be applied to ethynyl-bearing carbinols,[13] aliphatic[14] and aromatic hydrocarbons,[15] thiophenes,[16] esters,[17] acids,[18] ethers,[19] thioethers,[19] nitriles,[20] enynes,[21] alleneynes,[22] α-diynes,[23] triynes,[24] and tetraynes.[25] These compounds bearing weakly acidic ethynyl groups couple more rapidly under acidic conditions. The reaction proceeds, although slowly in the presence of only catalytic quantities of cuprous chloride. A large excess (3 moles per mole ethynyl compound) has been recommended as the reaction then proceeds rapidly. The reaction is conducted in water or in mixtures of water with alcohol, acetone, dioxan or tetrahydrofuran. The oxidation proceeds smoothly over a wide range of pH and is thus adaptable for the coupling of acid or alkali-sensitive materials. Apart from the Glaser reagent CuCl/amine complexes can be used in the oxidative coupling of ethynyl compounds (Hay's method).[13] It was shown that the reactivity of Cu(I)Cl–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine ≫ Cu(I)Cl–pyridine > Cu(II) acetate–pyridine. Phenylacetylene couples faster than I-ethynylcyclohexanol, which couples faster than hexyne-I. It is seen that Cu(I)–diamine is the most effective catalyst for the C–C coupling of acetylenes. Advantages are that (a) the reaction can be carried out in a variety of organic solvents; (b) only catalytic amounts of Cu(I)Cl and the diamine are necessary; (c) the oxidative coupling reaction can be carried out under neutral conditions; (d) low temperatures can be used, due to the high activity of the catalyst. Comparing the Glaser conditions and the Hay conditions it is apparant that the limitations are found in the former method. Unsymmetrical coupling, for example, could be obtained with N-propargyl-glycine ethylester and trimethylsilylacetylene using the Hay conditions (Cu(I)Cl–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) to give *N*-acetyl-2-amino-7-(trimethylsilyl)-4,6-heptadiynoate in 57% yield.[26] Another example,[3] where the Glaser conditions failed and the Hay conditions could be successfully applied, is the oxidative coupling of heterocyclic acetylenes.[27]

Under Glaser conditions using too strongly acid conditions (pH = 1) coupling and an anionotropic rearrangement occur together:

$$\begin{array}{l} \qquad\qquad\qquad\qquad\quad CH_3{-}CH{=}CHCH(OH)C{\equiv}C{-}C{\equiv}C(OH)CHCH{=}CH{-}CH_3 \\ \qquad\qquad\qquad\quad \nearrow_{pH\ 6.5} \qquad\qquad\qquad\qquad 93\% \\ CH_3{-}CH{=}CHCH(OH)C{\equiv}CH \\ \qquad\qquad\qquad\quad \searrow_{pH\ 1} \\ \qquad\qquad\qquad\quad CH_3CH(OH)CH{=}CHC{\equiv}C{-}C{\equiv}CCH{=}CHCH(OH)CH_3 \\ \qquad\qquad\qquad\qquad\qquad\qquad 81\% \end{array}$$

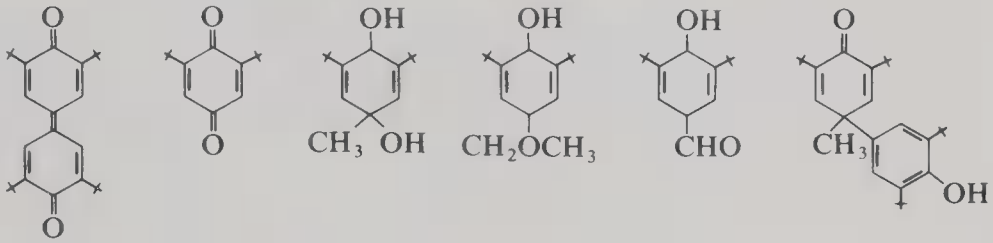
Too strongly acid conditions may give rise to other side reactions such as dehydration, hydrolysis, and Straus coupling,[28] which involves a dimerization as shown below:

$$2RC{\equiv}CH \longrightarrow RC{\equiv}C{-}CH{=}CHR$$

Also in the Glaser conditions the resulting diynes may be contaminated by enynes (Straus coupling).

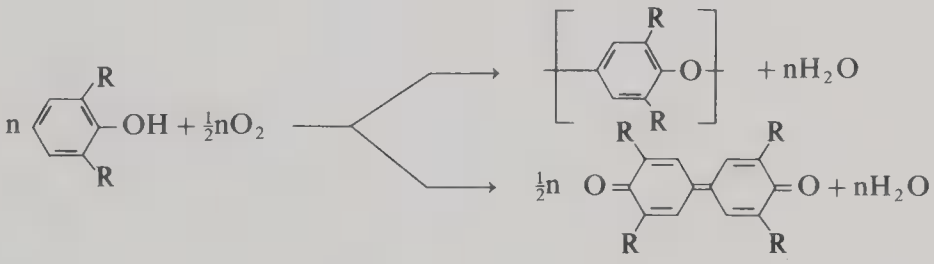
3.1.2. Phenols

Cu–amine catalyzed phenol oxidations have been studied extensively by a number of research groups. Most of the studies are especially important for elucidation of the mechanism. Only a few phenol oxidations are selective enough for preparative purposes. The number of reaction possibilities in phenol oxidation depending on the substituent pattern can be illustrated by the following set of reaction products obtained in the oxidation of 2,6-di-*t*-butyl-4-methylphenol in methanol[29]:



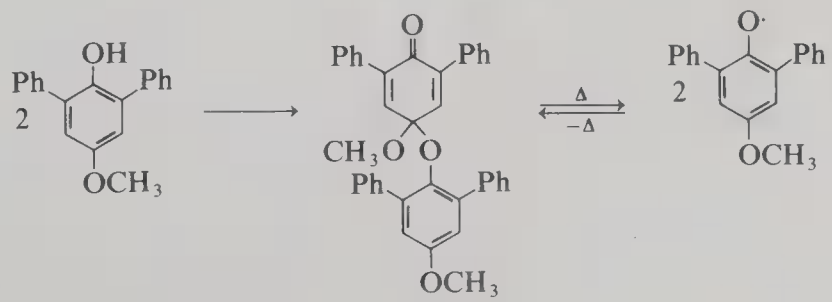
(5%) (27%) (14%) (14%) (12%) (28%)

Exceptional selectivity is found in the oxidative coupling of 2,6-disubstituted phenols, which give, depending on the size of the substituent groups, either poly-2,6-di-substituted-1,4-phenylene ethers (C–O coupling) or 3,3,5,5-tetrasubstituted diphenoquinones.[2]



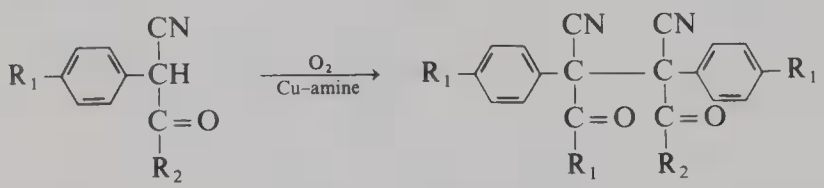
Another example of highly selective Cu–amine catalyzed oxidation is the synthesis of benzoquinones and hydroxylated benzoquinones starting from the corresponding hydroquinones. When *t*-butyl hydroquinone is oxidized using Cu(I)Cl–pyridine as a catalyst, *t*-butyl-*p*-benzoquinone is formed in high yield, whereas 2-*t*-butyl-6-hydroxy-*p*-benzoquinone is formed quantitatively when the oxidation of *t*-butyl-hydroquinone is carried out in the presence of Cu(I)Cl–secondary amine such as morpholine, piperidine, 2,6-dimethylpiperidine, and dipropylamine.[30]

An important factor determining selectivity in phenol dehydrogenation is the stability of the phenoxy radicals involved (see Section 2). Oxygenated by-products may result from phenoxyradical–O_2 reactions. The oxidation of 2,6-diphenyl-4-methoxyphenol, however, passes through an oxygen stable radical giving the corresponding ketal dimer in almost quantitative yield.[8]

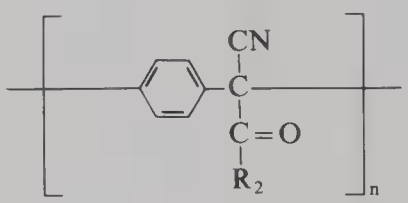


3.1.3. Activated Methine Compounds

Catalytic oxidative C–C coupling of compounds $R_1R_2R_3CH$ with Cu–amine–O_2 systems is limited to groups R_1–R_3 which enable the substrate to complex with the Cu catalyst. A first example in this field is the oxidative coupling of diphenylacetonitrile using $CuBr_2$–piperidine as a catalyst.[31] A high yield (95%) of tetraphenylsuccinonitrile was obtained. An extensive study of the scope and limitations of Cu–amine catalyzed oxidations of activated methine compounds has been made which resulted in exclusive C–C coupling depending on the nature of the groups R_1, R_2, and R_3 in $R_1R_2R_3CH$. Arylcyanoacetic esters, acylbenzylcyanides, and arylcyanoacetamides gave high yields of C–C dimers.[3] All those activated methine compounds have groups that can complex with the Cu catalyst. For instance, complexing of Cu compounds with nitrile groups is well documented in the literature.[32] In this respect it is interesting to note that arylmalonic esters mainly give a slow oxygenation to arylglyoxylic esters with the Cu–amine–O_2 system. High yields of C–C dimers, however, can be obtained with other oxidants.[33]



When, however, $R_1 = H$ the oxidative C–C coupling is accompanied by a fair amount of C–*para*–C coupling, which gives rise to oligomers as depicted below:

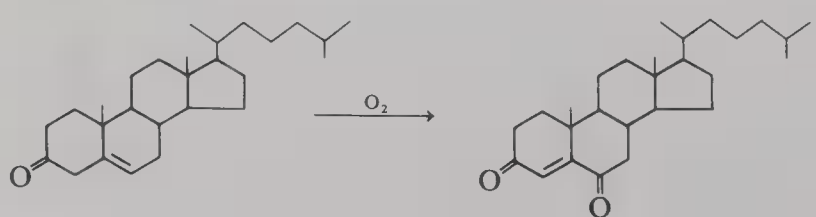


Substitution in the *para* position impedes this polymerization, and high yields (>80%) of pure C–C dimers are obtained.

3.1.4. Miscellaneous

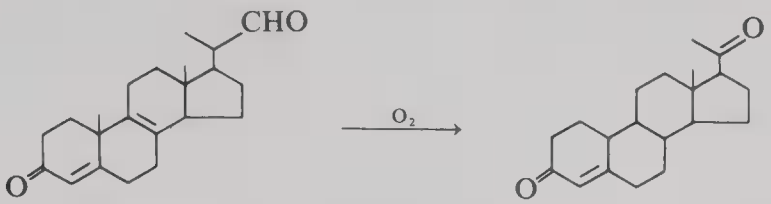
So far Cu–amine catalyzed oxidations have been described in which dehydrogenation predominates. In this section some oxidations are shown where oxygenation occurs, such as oxidation of a β, γ-unsaturated ketone, an aldehyde, and some oxidative cleavage reactions.

In the course of their studies into the copper-catalyzed oxidations of unsaturated carbonyl compounds Volger *et al.* found a simple and rapid synthesis of 3,6-diketo-Δ^4-steroids; e.g., Δ^5-cholestenone could be converted into Δ^4-cholestene-3,6-dione in 75% yield using copperacetate–pyridine as a catalyst.[5]



This reaction is not restricted to Δ^5-cholestenone but can be applied to a variety of α, β- and β, γ-unsaturated ketones and aldehydes. In most cases studied so far, oxygen is

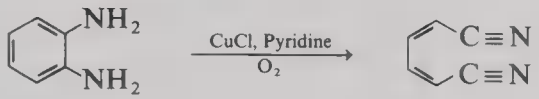
introduced in the γ position. An exception is the copper–amine catalyzed oxidation of 3-oxobisnor-4-cholen-22-al to progesterone in 90% yield.[34]



It was proven that in this case there was a negligible attack on the α, β-unsaturated ketone in the A-ring. This reaction principle has been applied to oxidative decarbonylations of aldehydes such as isobutyraldehyde, 2-phenyl-propionaldehyde, and diphenylacetaldehyde. The corresponding ketones, viz., acetophenone and benzophenone were formed in high yield (75%–94%).

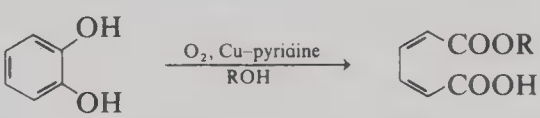
Another interesting application of the copper–amine system is the oxidative cleavage of *o*-phenylenediamine and catechol by Tsuji *et al.*

When *o*-phenylenediamine is oxidized with the Cu–pyridine–O_2 system *cis,cis*-muconononitrile is formed in high yield (>90%).[4]



Other *o*-phenylenediamine derivatives can be oxidized similarly provided that no electron-withdrawing group in the benzene ring is present. For instance 4,5-dimethyl-*o*-phenylenediamine gave the corresponding cis,cis-muconononitrile in 95% yield, whereas 4-nitro-*o*-phenylenediamine gave no nitrile at all.

For optimal muconononitrile formation the substrate/Cu ratio should be kept as low as possible to avoid an intermolecular reaction of the intermediate copper complex with *o*-phenylenediamine. When catechol is oxidized using the Cu–pyridine complex as a catalyst in an alcohol the monoester of cis,cis-muconic acid was formed in high yield (in methanol: 82%) at room temperature.[35]



The effect of substituents proved to be similar to the *o*-phenylenediamine oxidations. Catechols substituted by an electron donating group can be oxidized smoothly to give substituted muconates. 4-Methylcatechol was cleaved to give a mixture of monomethylmuconates in 79% yield. Similarly 3-methylcatechol was converted into a mixture of monoesters in 81% yield.

From 4-chlorocatechol a mixture of the corresponding monoester of chloromuconate was obtained in 37% yield. Nitrocatechol was not oxidized to muconate.

3.2. Cobalt–Amine-Catalyzed Oxidations

Synthetic use of cobalt–amine complexes as catalyst for selective oxidations is much more restricted than copper–amine complexes. Salcomine (Bis(salicylidene) ethylenediiminocobalt II) is an excellent catalyst for the preparation of *p*-benzoquinones from phenols in almost quantitative yields when the conditions are properly chosen.[8] Moreover cobalt–amine complexes are used as catalyst for the oxidative cleavage reactions of flavones[36] and indoles.[37]

3.2.1. Phenols

Phenols are catalytically oxidized to diphenoquinones, polyphenylene ethers, and benzoquinones by proper choice of catalyst, solvent, and starting materials. Using copper–amine complexes the main reaction is dehydrogenation, i.e., diphenoquinone and polyphenylene ether formation, whereas cobalt–amine complexes give oxygenated products, e.g., benzoquinones. When 4-alkyl-2,6-di-*t*-butylphenols are oxidized in the presence of Salcomine, quinolideperoxides (~50%) and *p*-benzoquinones (~30%) are formed.[38] However, when bis(3-salicylideneaminopropyl) amine cobalt II is used as a catalyst for the oxidation of, e.g., 4-methyl-2,6-di-*t*-butylphenol, 2,6-di-*t*-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone is obtained in 96% yield.[39]

p-Unsubstituted phenols give *p*-benzoquinones in high yield using Salcomine in dimethylformamide as a solvent.[8]

In the presence of quarterny ammonium alkoxides, 2,6-di-substituted phenols gave 3-alkoxy-2,6-disubstituted benzoquinones in high yield using Salcomine as a catalyst in alcohols.[40]

3.2.2. Oxidative Cleavage Reactions

Bis(salicylidene)ethylenediimino cobalt II (Salcomine) catalyzes the oxygenation of 3-substituted indoles giving rise to oxidative cleavage of the heterocyclic ring of the indoles selectively to give the corresponding *o*-formylaminoacetophenone derivatives.[37] The same procedure can also be applied to 3-hydroxyflavones to give the corresponding depsides.[36]

Both reactions proceed in excellent yields.

4. EXPERIMENTAL CONSIDERATIONS AND PROCEDURES

4.1. Copper–Amine Catalysts

In most cases this catalyst is made *in situ* by introduction of cuprous chloride and an amine in the reaction medium. However, in some cases it can be prepared separately as a crystalline material.

4.1.1. Copper–TMEDA Catalyst

Cuprous chloride (1 mol) and tetramethylethylenediamine (TMEDA, 2 mol) were shaken in 500 ml methanol and 27 ml of water in an oblong flask connected with a gas burette for oxygen uptake measurements. A total amount of 0.5 mol of oxygen was consumed within 30 min. The complex was removed by filtration, washed with acetone, and dried at 40°C (12 mm). There was obtained 424 g (90%) of purple powder decomposing at 138–139°C (heated from 120°C). Elemental analysis and molecular weight determinations suggest this compound to be $[Cu(OH)(TMEDA)]_2Cl_2$.[41]

Analysis: Calculated for $C_{12}H_{34}Cl_2Cu_2N_4O_2$: C,31.4; H,7.38; Cl,15.27; Cu,27.36; N,12.06; molecular weight 464.4. Found: C,31.0; H,7.3; Cl,15.2; Cu,27.2; N,11.9; molecular weight (ebullioscopic determination in boiling ethanol), 320 (apparently the complex is partly dissociated in boiling ethanol).

An identical purple copper complex has been prepared according to Wasson *et al.* by addition of four equivalents of TMEDA to a saturated aqueous $CuCl_2$ solution.[42] The complex showed an identical ir spectrum (KBr) and decomposition point (138–139°C, heated from 120°C). Both of the purple complexes can be converted into a hydrous, deep blue crystalline complex by dissolution in water followed by precipitation with acetone. The blue

complexes both show the same ir spectrum (KBr), visible spectrum (maximum at 625 nm), and decomposition point (142–143°C, after evaporation of the water, heated from 130°C).

Analysis: Calculated for $\{[Cu(OH)(TMEDA)]\ Cl.2H_2O\}_n$ (blue complex prepared from $CuCl_2$–TMEDA–H_2O): C,26.87; H,7.89; Cl,13.22; Cu,23.69; N,10.44. Found: C,26.6; H,7.8; Cl,13.3; Cu,24.0; N,10.2.

4.2. Cobalt–Amine Catalysts

Salcomine (Bis(salicylidene)ethylenediimino Cobalt II).[43] To a solution of salicylaldehyde (1.1 mol) in 100 ml of ethanol was added dropwise ethylenediamine (0.55 ml) in 40 ml of ethanol while stirring at room temperature. Immediately a yellow precipitate was formed. After completion stirring was prolonged for 0.5 h at 80°C (reflux). Then the reaction product was filtered, washed with cold ethanol, and dried. The Schiff base was obtained in 96% yield, mp. 125–125.5°C.

To a solution of the Schiff base (0.5 mol), sodium hydroxide (1 mol), and 2.5 g of sodium acetate in 1500 ml of boiling water there was added while stirring $CoCl_2 \cdot 6H_20$ (0.5 ml) in 250 ml of water. The reaction mixture was heated on a water bath and a red-brown precipitate was formed. The reaction product was filtered, washed 3 times with 250 ml portions of water and 2 times with ethanol, and dried *in vacuo* at 100°C. The Salcomine was obtained in 93% yield.

4.3. Copper–Amine-Catalyzed Oxidations of Organic Substrates

4.3.1. Ethynyl Compounds: Symmetrical Oxidative Coupling (Glaser Conditions)

Dimethyl Docosa-10,12-diynoate.[44]

$$CH_3OOC(CH_2)_8-C\equiv CH \xrightarrow[\text{air or } O_2]{CuCl,\ NH_4Cl} CH_3OOC(CH_2)_8(C\equiv C)_2(CH_2)_8COOCH_3$$

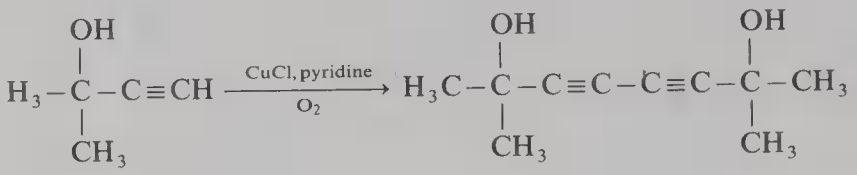
To a solution of cuprous chloride (12.8 g), ammonium chloride (22.4 g), and concentrated hydrochloric acid (2 drops) in water (120 ml) was added dropwise with constant stirring a solution of the ester (9.6 g) in 70 ml ethanol. The mixture was heated to 55–56°C and air bubbled through for five hours. The cold mixture was then poured into water and extracted with ether. The ether layer was filtered to remove insoluble copper salts, washed several times with water, dried, and evaporated. The resultant solid was crystallized from ether at −50°C to give pure dimethyl docosa-10,12-diynoate, m.p. 41–42°C, yield 8.0 g, 84%.

λ_{max} EtOH: 226, 239, and 254 mμ(ε464, 391, and 229, respectively).

1,1-Butadiynylenedicyclohexanol[13] *(Hay Conditions).*

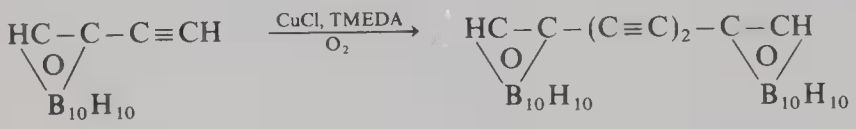
To a vigorously stirred solution (by means of a Vibromixer stirrer) of 1 g (0.01 mole) of cuprous chloride and 1.2 g (0.01 mole) of *N,N,N′,N′*-tetramethylethylenediamine in 135 ml of acetone was added over a period of 15 min, 25 g (0.20 mole) of 1-ethynylcyclohexanol. The temperature rose rapidly to 42°C. After the addition was complete, the reaction was continued for 20 min, then the acetone was evaporated and there was added 20 ml of water containing 1 ml of concentrated hydrochloric acid. The colorless product was filtered, washed with a small amount of water, and dried *in vacuo*. There was obtained 22.9 g (93% yield) of 1,1-butadiynylenedicyclohexanol, m.p. 177°C.

2,7-Dimethyl-3,5-octadiyne-2,7-diol.[45]



A mixture of 84 g (1 mole) of 2-methyl-3-butyn-2-ol, 20 g (0.25 mole) of pyridine, 1.2 g (0.012 mole) of cuprous chloride in 100 ml of methanol was stirred at 35°C for 2.5 h, while oxygen was passed through the solution at a rate of 10 liters/h. The oxygen absorption had ceased by this time (after 2.5 h) and a total of 7 liters (0.28 mole) of oxygen had been absorbed. The mixture was poured into 400 ml of a saturated ammonium chloride solution and extracted with ether. The extract was washed with a sodium carbonate solution, dried over magnesium sulfate, and evaporated to dryness. The crude diol (77 g) was crystallized from 1200 ml of benzene to afford 75 g (90% yield) of 2,7-dimethyl-3,5-octadiyne-2,7 diol, m.p 127–129°C.

1,4 Di(1'-1',2'-carboranyl)butadiyne.[46]

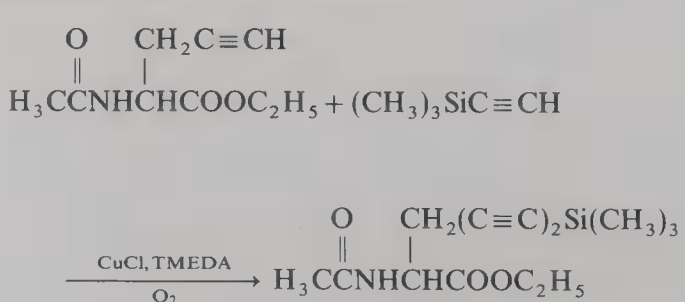


To a solution of 0.5 ml (3.9 mmol) of *N,N,N',N'*-tetramethylethylenediamine in 12 ml of acetone was added 1.0 g (10 mmol) of cuprous chloride while stirring, which was continued for 1 min. The resulting blue-green solution was decanted, the remaining solid was washed once with 5 ml of acetone, and the combined acetone fractions were diluted with an additional 10 ml of acetone and added to a 100-ml three-necked round-bottom flask equipped with a stirrer, reflux condenser, and a dropping funnel containing a solution of 2.14 g (12.7 mmol) of ethynylcarborane in 25 ml of acetone. A rapid stream of O_2 was bubbled through the solution as the ethynylcarborane solution was added dropwise over a period of 30 min. Oxygen was bubbled through the reaction mixture for an additional 2 h and then the contents of the flask was poured into 100 ml of ice-cold 3 *N* hydrochloric acid and extracted with four 100 ml portions of pentane. The pentane extracts were combined, dried over anhydrous magnesium sulfate, and evaporated to dryness. The resulting brown solid was chromatographed on a 1 × 10-in. silicagel column and eluted with hexane to afford 1.10 g (52% yield) of a white product, m.p. 315–317°C (dec).

Analysis: Calculated for $B_{20}C_8H_{22}$: B,64.69; C,28.72; H,6.58. Found: B,64.84. C,28.92; H,6.24.

4.3.2. Ethynyl Compounds: Unsymmetrical Oxidative Coupling (Hay Conditions)

Ethyl N-acetyl-2-amino-7-(trimethylsilyl)-4,6-heptadiynoate.[26]



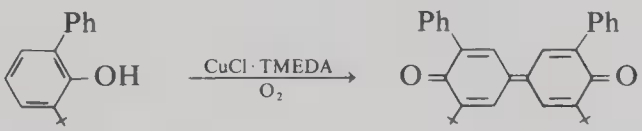
(Continued)

To a solution of 1.54 g of (trimethylsilyl)acetylene (15.6 mmol) and 1.0 g of DL-*N*-acetylpropargylglycine (5.46 mmol) in 25 ml of acetone was added 5 ml of a solution of cuprouschloride and *N,N,N′,N′*-tetramethylethylenediamine in acetone, prepared by the process of Eastmond *et al.*[47] The green solution was stirred vigorously for 20 h, while a thin stream of air was passed into it. The reaction mixture was poured onto ice and 2 *N* sulfuric acid and extracted twice with ethyl acetate. The ethyl acetate solution was washed with water, dried over anhydrous potassium carbonate, and evaporated to give 2.85 g of crude product mixture. This mixture was dissolved in a minimum amount of chloroform and chromatographed on silica gel 60 (E. Merck column, size B prepacked). The column was eluted first with hexane then with hexane-ethylacetate (1:1, v/v), followed by hexane-ethyl acetate (1:3, v/v). The by-product bis(trimethylsilyl) butadiyne was obtained first, 1.0 g, m.p. 108–109°C, followed by the protected amino acid, 0.85 g (57%) as a light oil. It was crystallized from ether-hexane, m.p. 47–49°C; NMR($CDCl_3$) δ, 6.5 (*d*, 1H, NH) 4.7 (*m*, 1H, $\alpha-H$) 4.25 (quartet, 2H, $J=7$, CH_2CH_3) 2.85 (*d*,2H,$J=5$, $\beta-CH_2$) 2.1 (*s*, 3H, $CH_3C=O$) 1.3 (*t*,3H, $J=7$, CH_2CH_3); IR ($CDCl_3$) 3400,2950,2250 (d), 2120,1740,1670,1500,1380,1340 cm^{-1} MS *m/e* 279.1 (M).

Analysis: Calculated for $C_{14}H_{21}NO_3Si$: C,60.16; H,7.58; N,5.01. Found: C,59.81; H,7.46; N,4.80.

4.3.3. Phenols

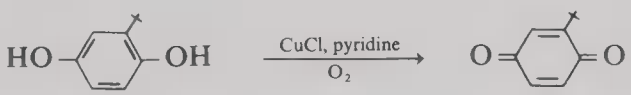
3,3′-Di-t-butyl-5,5′-diphenyldiphenoquinone.[48]



Through a vigorously stirred solution of 1.0 g of cuprous chloride, 2.3 g of *N,N,N′,N′*-tetramethylethylenediamine and 100 g (0.44 mole) of 2-*t*-butyl-6-phenylphenol in 500 ml of ethanol oxygen was passed. After 2 h, the reaction mixture was filtered and there was obtained 85.5 g (86% yield) of 3,3′-di-*t*-butyl-5,5′-diphenyldiphenoquinone, m.p. 213–214°C. Recrystallization from acetic acid gave red crystals, m.p. 214°C.

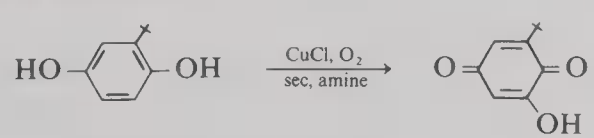
Analysis: Calculated for $C_{32}H_{32}O_2$: C,85.68; H,7.19. Found: C,85.58; H,7.21.

t-Butyl-p-benzoquinone.[30]



A solution of 10.05 g of *t*-butylhydroquinone and 0.227 g of CuCl in 40 ml of dry pyridine was shaken in an oxygen atmosphere. When no more oxygen was absorbed, the reaction mixture was acidified with 6 *N* HCl. Yellow needles of *t*-butyl-*p*-benzoquinone precipitated and were filtered off, washed with water and recrystallized from ethanol; m.p. 59–60°C. Yield 8.95 g (90%).

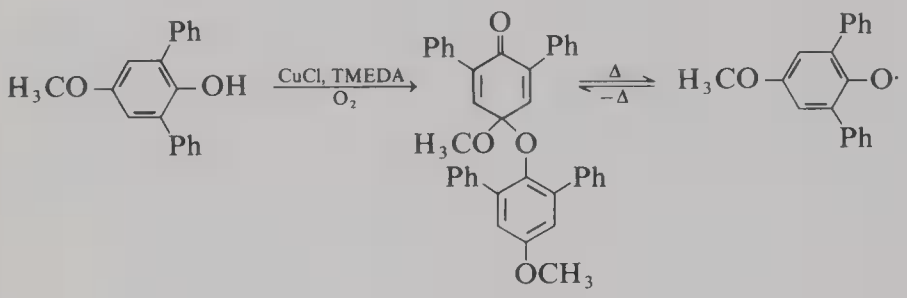
2-t-Butyl-6-hydroxy-p-benzoquinone.[30]



A solution of 5.0 g of *t*-butylhydroquinone and 0.113 g of CuCl, 5 ml of morpholine, piperidine, 2,6-dimethylpiperidine, or dipropylamine in 30 ml of methanol was shaken in an

oxygen atmosphere. The reaction mixture was acidified with 6 *N* HCl and yellow crystals of 2-*t*-butyl-6-hydroxy-*p*-benzoquinone were filtered off, washed with water, dried, and recrystallized from heptane, m.p. 128–130°C. Yield 4.9 g (99%).

4-Methoxy-2,6-diphenylphenoxyl.[8]

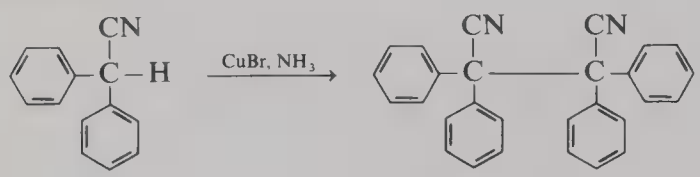


In a solution of 10 g of 4-methoxy-2,6-diphenylphenol, 0.1 g of cuprous chloride and 0.23 g of *N,N,N′,N′*-tetramethylethylenediamine in 100 ml of methanol oxygen was introduced at 0°C. After 1 h the reaction mixture was transferred to a separatory funnel containing 250 ml of toluene. After washing three times within 100 ml portions of water and drying over anhydrous potassium carbonate and evaporating the toluene, the reaction product was crystalized from hexane. 4-Methoxy-2,6-diphenylphenoxyl was obtained as its dimeric quinone acetal, m.p. 158.5–159.2°C (yield 96%).

Analysis: Calculated for $C_{38}H_{30}O_4$: C,82.9; H,5.3. Found: C,82.8; H,5.6. NMR ($CDCl_3$) δ, 7.10–7.80 (*m*,20H, arom), 6.97 (*s*, 2H,aliph), 6.45 (*s*,2H, arom *m*-H), 3.95 (*s*,3H, arom, O Me), 2.95 (*s*,3H,aliph O Me). IR ($CDCl_3$) 2830w, 1680s, 1650s and 700s cm^{-1}.

4.3.4. Activated Methine Compounds

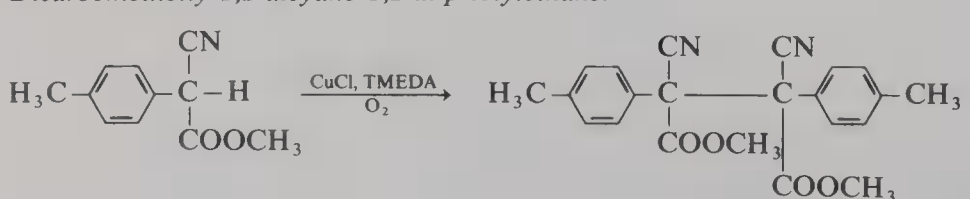
Tetraphenylsuccinonitrile.[31]



To a solution of 9.7 g (50 m mole) of diphenylacetonitrile in 150 ml of methanol was added a solution of 0.2 g (0.7 m mole) of cuprous bromide in 40 ml of concentrated ammonia. The mixture was stirred in an oxygen atmosphere and precipitation of tetraphenylsuccinontrile started immediately. When 600 ml (25 mmol) of oxygen had been absorbed the reaction mixture was acidified and 9 g of tetraphenylsuccinonitrile (yield 94%) was collected on a filter and washed with small portions of methanol and ether. The tetraphenylsuccinonitrile thus obtained melted at 222–224°C (dec).

Analysis: Calculated for $C_{28}H_{20}N_2$: C,87.47; H,5.24. Found: C,87.30; H,5.10.

1,2-Dicarbomethoxy-1,2-dicyano-1,2-di-p-tolylethane.[3]



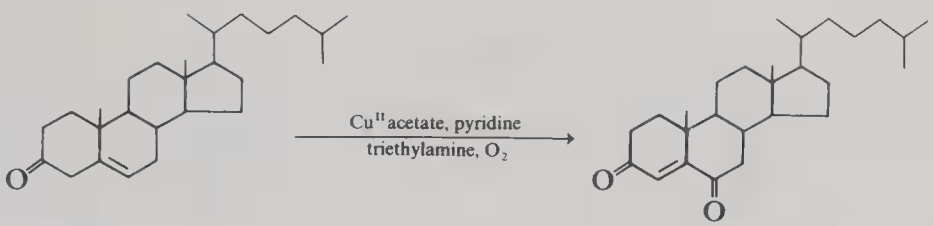
The oxidation was carried out in a 250-ml oblong double-walled flask with 7.5 g (40 mmol) of methyl-*p*-tolylcyanoacetate in 75 ml of methanol at 50°C with oxygen, using

1.0 g (2.2 mmol) of the crystalline CuCl–TMEDA catalyst (vide supra). Upon addition of methyl-*p*-tolylcyanoacetate to the catalyst solution, the color changed from blue to deep purple. The purple color did not change until the end of the reaction (2 min) and then suddenly turned blue again. When shaking was stopped at room temperature, the solution became colorless within a few seconds (Cu^{I} complex). During the reaction 1,2-di-carbomethoxy-1,2-dicyano-1,2-di-*p*-tolylethane precipitated. The reaction mixture was acidified with 5 ml of 2 *N* HCl and filtered and the product was washed twice with 10 ml of water and 10 ml of cold methanol. There was obtained 6.93 g (92%) of 1,2-dicarbomethoxy-1,2-dicyano-1,2-di-*p*-tolylethane, m.p. 217.5–219.1°C. Addition of 100 ml of water to the filtrate followed by chloroform extraction afforded a second crop of 0.57 g (7%) of the dimer, m.p. 214–216°C. The dimers obtained in these ways both consisted of an approximately 3:2 mixture of meso and dl isomers as shown by NMR.

Analysis: Calculated for $C_{22}H_{20}N_2O_4$: C,70.21, H,5.32, N,7.45. Found: C,69.9; H,5.3; N,7.7. NMR ($CDCl_3$) δ, 3.78 (*s*,3H,meso OCH_3), 3.92 (*s*,3H,dlOCH_3).

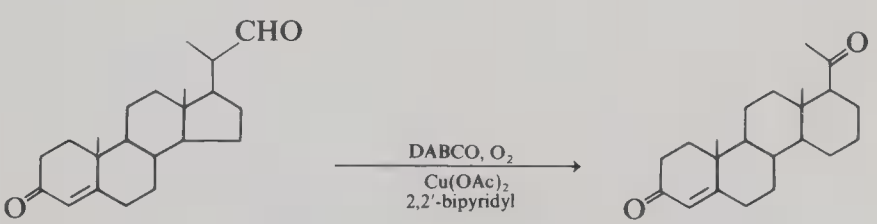
4.3.5. Miscellaneous

Oxygenation of a β, γ-unsaturated Ketone. Δ^4-Cholestene-3,6-dione.[5]



To a homogeneous solution containing 0.1 mmol of cupricacetate, 2.0 ml of pyridine and 0.5 ml of triethylamine in 7.5 ml of methanol was added a solution of 0.5 mmol of Δ^5-cholestenone in 20 ml of methanol at 0°C. The absorption of oxygen, which was stirred into the solution, was measured by means of a gas burette. Within 10 min 0.5 mmol of oxygen was consumed, after which the oxygen absorption stopped completely. The reaction mixture was neutralized with dilute nitric acid and Δ^4-cholestene-3,6-dione fully precipitated by further dilution with water. After recrystallization from methanol 75% of Δ^4-cholestene-3,6-dione was obtained, m.p. 120–123°C.

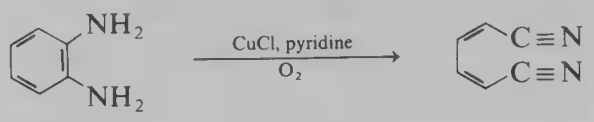
Oxygenation of Branched Aldehydes. Progesterone.[34]



Through a rapidly stirring mixture of 150 g (0.48 mole) of 3-oxobisnor-4-cholen-22-al, 30 g (0.27 mol) of 1.4-diazabicyclo [2.2.2] octane (DABCO) as base and 3.9 g of the cupric acetate-2,2′-bipyridylcomplex (1:1) in 300 ml of dimethylformamide air was bubbled for 20 h at 40°C. After dilution with water 90% of progesterone was obtained. (There was negligible attack on the $\alpha\beta$-unsaturated ketone in the A-ring during the reaction.)

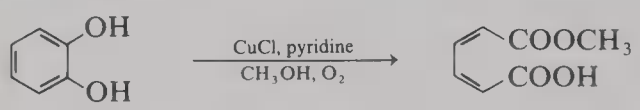
4.4. Oxidative Cleavage

Cis,cis-Muconononitrile.[4]



Oxygen was introduced into a vigorously stirred solution of 1.98 g (20 mmol) of cuprous chloride in 10 ml of pyridine. When the absorption of oxygen started, the color of the solution changed from yellow to dark green. When ~100 ml of oxygen was consumed the absorption ceased (10 min) and a solution of 1.08 g (10 mmol) of *o*-phenylenediamine in 10 ml of pyridine was added slowly. In 10 min 225 ml of oxygen was absorbed at 25°C. Then again 1.08 g (10 mmol) of *o*-phenylenediamine in 10 ml of pyridine was added slowly. This procedure was again repeated. After the reaction was over, pyridine was removed *in vacuo* and the residue was extracted with ether and recrystallized to give 2.97 g (95%) of *cis,cis*-muconononitrile, m.p. 128–129°C.

Monomethyl cis,cis-muconate.[35]



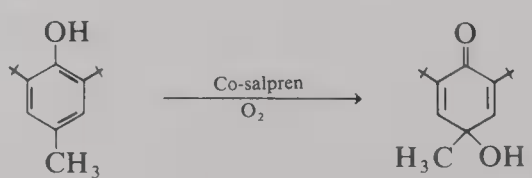
A yellow solution was obtained by mixing 0.79 g (8 mmol) of cuprous chloride, 0.4 ml of methanol and 20 ml of pyridine. The mixture was stirred in a flask connected with a gas burette containing oxygen. When 50 ml of oxygen was consumed the color of the solution turned to dark green. A solution of 0.44 g (4 mmol) of catechol in 20 ml of pyridine was added slowly in 2 h with efficient stirring. During the addition 100 ml of oxygen was absorbed. After the addition stirring was continued for 1 h. The mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of 3 *N* HCl and methylene chloride. The organic layer was separated and washed with water. Evaporation of the solvent gave monomethylmuconate, which was recrystallized from hexane to give 0.51 g of colorless needles of monomethyl *cis,cis*-muconate (82%) m.p. 80–81°C.

Analysis: Calculated for $C_7H_8O_4$: C,53.85; H,5.16. Found: C,53.78; H,5.22. NMR (CCl_4) δ,12.55 (*s*,1H), 8.3–8.65 (*m*,2H), 6.30–6.35 (*m*,2H), 4.17 (*s*,3H).

4.5. Cobalt–Amine-Catalyzed Oxidations of Organic Substrates

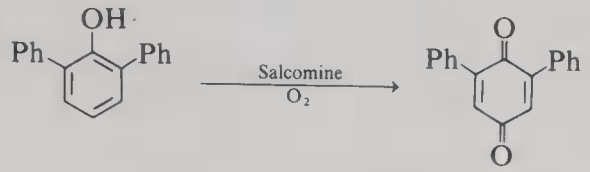
4.5.1. Phenols: Oxygenation

2,6-Di-t-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone.[39]



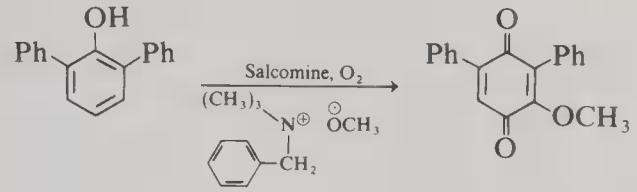
Through a solution of 8 mmol of 2,6-di-*t*-butyl-*p*-cresol and 3.6 mmol of di-(3-salicylideneaminopropyl) amine cobalt II in 300 ml of methanol oxygen was bubbled at room temperature for 20 h. The reaction mixture was then poured into ice water (800 ml). It was neutralized by addition of acetic acid and the pale yellow precipitate was collected on a filter and thoroughly washed with water and dried. Crystallization from hexane gave 96% of 2,6-di-*t*-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone, m.p. 111–112°C.

2,6-Diphenyl-p-benzoquinone.[8]



To a solution of 50 g (0.2 mole) of 2,6-diphenylphenol in 100 ml dimethylformamide, 2 g (6 mmol) of Salcomine was added and the flask was connected with a gas burette containing oxygen and placed on a shaking machine. The reaction was carried out at 40°C. After 3 h the oxygen uptake (4.8 liters) was complete. The mixture was poured onto crushed ice (600 ml) and 4 *N* HCl (30 ml). The red precipitate was filtered and washed three times with 150-ml portions of water. The crude 2,6-diphenyl-*p*-benzoquinone was recrystallized from *n*-butanol (93%), m.p. 136.2–136.8°C.

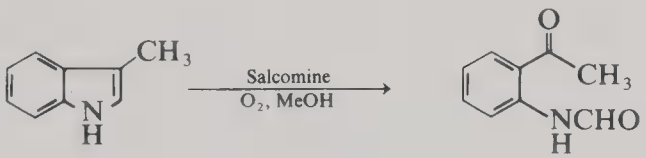
2,6-Diphenyl-3-methoxy-p-benzoquinone.[40]



The same procedure was followed as in the previous oxidation except for the solvent (in this case 500 ml of methanol) and the addition of 10.2 ml of a 40% solution of benzyltrimethylammoniummethoxide in methanol. After the usual working up procedure, 94% of 2,6-diphenyl-3-methoxy-*p*-benzoquinone was obtained, m.p. 142.1–143.3°C.

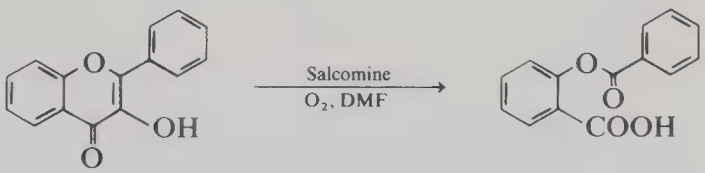
4.6. Oxidative Cleavage

o-Formylaminoacetophenone.[37]



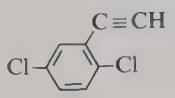
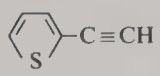
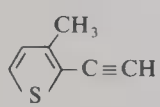
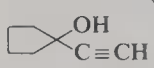
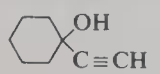
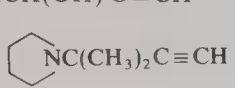
Oxygen was bubbled through a solution of 50 mmol of 3-methylindole and 10 mmol of Salcomine in 60 ml of methanol at room temperature. After 5 h the reaction mixture was evaporated and chromatographed on a silica gel column to give 70% of *o*-formylaminoacetophenone, m.p. 78–79°C. NMR ($CDCl_3$) δ, 6.95–8.80 (*m*,6H, ArH,NHCHO), 2.63 (*s*,3H,$COCH_3$).

o-Benzoyloxybenzoic acid.[36]



Oxygen was bubbled through a solution of 25 mmol of 3-hydroxyflavone and 5 mmol of Salcomine in 40 ml of dimethylformamide at ambient temperature. After 1 day the mixture was diluted with water and extracted with ether. Evaporation gave 97% of *o*-benzoylbenzoic acid, m.p. 130–131°C.

TABLE I. Oxidative Coupling of Acetylenes, $RC{\equiv}CH \longrightarrow R-C{\equiv}C-C{\equiv}C-R$, Glaser Conditions[a]

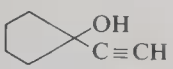
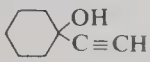
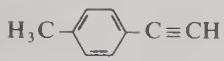
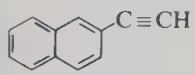
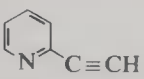
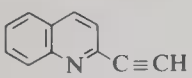
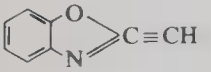
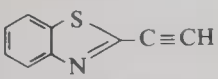
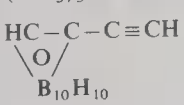
R−C≡CH	Yield dimer (%)	Comments	Reference
$HO(CH_2)_2C{\equiv}H$	87		49
$CH_3CH(OH)C{\equiv}CH$	94		49
$HOOCCH{=}CHC{\equiv}CH$	95	Acetone, 5°C	50
$CH_2{=}CHCH_2C{\equiv}CH$	86		51
$HOOC(CH_2)_2C{\equiv}CH$	99	0°C	52
$(CH_3)_2C(OH)C{\equiv}CH$	99		53
$HO(CH_2)_3C{\equiv}CH$	99		51
	85	Alcohol water	16
	95	Alcohol water	16
$CH_3CH(OH)(C{\equiv}C)_2H$	78	Alcohol water	23
$HOOCC(CH_3){=}CHC{\equiv}CH$	82	Alcohol water	54
$CH_3CH{=}CHCH(OH)C{\equiv}CH$	93		49
$HOCH_2C(CH_3){=}CHC{\equiv}CH$	80	Alcohol water	54
$CH_3CO(CH_2)_2C{\equiv}CH$	95		55
$CH_3(CH_2)_2CH(OH)C{\equiv}CH$	92	Alcohol water	56
	85	Alcohol water	16
$HOOCCH{=}CH(CH_2)_2{-}C{\equiv}CH$	99		57
	99		58
$(CH_3)_2C(OH)C(CH_3)(OH)C{\equiv}CH$	80		59
$CH_3COOCH_2CH{=}C(CH_3)C{\equiv}CH$	95	Methanol	60
$CH_3COCH(C_2H_5)CH_2C{\equiv}CH$	96		55
	99		58
$PhCH(OH)C{\equiv}CH$	88		49
	80	55°C	61
$CH_3OCH_2C{\equiv}C(CH_2)_4C{\equiv}CH$	80		62
o-$HOOCC_6H_4COOCH_2C{\equiv}CH$	83	*t*-$BuNH_2$ instead of NH_3	63

[a] Standard Glaser conditions, unless otherwise indicated (see Comments). The ethynyl compound is added to a solution of cuprous chloride (complex with NH_4Cl) in water (pH 6.5) and the mixture is stirred at room temperature in the presence of air or oxygen. The diyne is filtrated or extracted with ether.

5. TABULAR SURVEY OF OXIDATIONS OF ORGANIC COMPOUNDS CATALYZED BY COPPER– AND COBALT–AMINE COMPLEXES

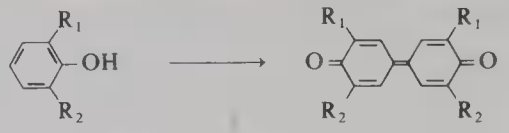
An attempt has been made to collect in the following tables examples of oxidation reactions in the presence of copper and cobalt amine complexes published before September 1984. Certain oxidations in the tables were prepared without the knowledge of optimal experimental conditions that is now available; some yields could certainly be improved by following one of the newer procedures for certain organic substrates.

TABLE II. Oxidative Coupling of Acetylenes, $RC{\equiv}CH \longrightarrow R-C{\equiv}C-C{\equiv}C-R$, Hay Conditions[a]

R–C≡CH	Yield dimer (%)	Comments	Reference
$HOCH_2C{\equiv}CH$	75	CuCl–pyridine	45
$CH_3C(OH)(CH_3)C{\equiv}CH$	87	CuCl–pyridine	13
$CH_3C(OH)(CH_3)C{\equiv}CH$	85		13
$CH_3CH{=}CH-CH(OH)C{\equiv}CH$	66	CuCl–pyridine	45
$CH_3CH_2C(OH)(CH_3)C{\equiv}CH$	82		13
	90		13
	93		13
	98		27
	97		27
$C_6Cl_5C{\equiv}CH$	84		64
	79		27
	64		27
	50		27
	90		27
$(CH_3)_3SiC{\equiv}C-CH{=}CHC{\equiv}CH$	70		65
	52		46

[a] Standard Hay conditions, unless otherwise stated (see Comments). The ethynyl compound is oxidatively coupled with oxygen in the presence of cuprous chloride and *N,N,N′,N′*-tetramethylethylendiamine.

TABLE III. Oxidative Coupling of 2,6-Disubstituted Phenols,



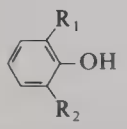
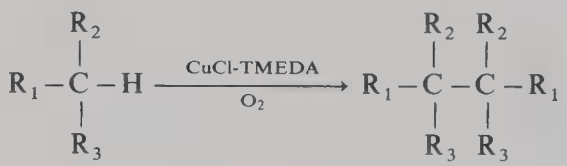
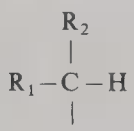
	Yield dipheno-quinone (%)	m.p. (°C)	Comments	Reference
$R_1 = R_2 = CH_3$	93	224	CuCl–CH_3CN	66
$R_1 = CH_3$, $R_2 = t$-Bu		217	CuCl–CH_3CN	66
$R_1 = R_2 = t$-Bu		246	CuCl–CH_3CN	66
$R_1 = R_2 = i$-Propyl		225	CuCl–CH_3CN	66
$R_1 = CH_3$, $R_2 = C_2H_5$		140	CuCl–CH_3CN	66
$R_1 = R_2 = OCH_3$		288	CuCl–CH_3CN	66
$R_1 = R_2 = Ph$		272	CuCl–CH_3CN	66
$R_1 = t$-Bu, $R_2 = Ph$	86	214	CuCl–TMEDA	48

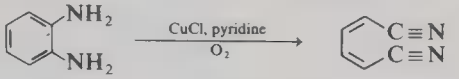
TABLE IV. Oxidative Coupling of Activated Methine Compounds,[a]



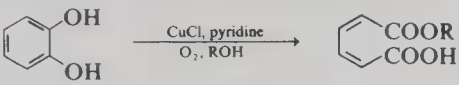
	Yield dimer (%)	m.p. (°C)	Comments	Reference
$R_1 = R_2 = Ph$, $R_3 = CN$	94	222–224 (dec)	CuBr, NH_3	31
$R_1 = Ph$, $R_2 = COOCH_3$, $R_3 = CN$	84	147–152[b]		3
$R_1 = Ph$, $R_2 = COOC_2H_5$, $R_3 = CN$	60	117–123[b]		3
$R_1 = p$-CH_3Ph, $R_2 = COOCH_3$, $R_3 = CN$	99	216.5–218[b]		3
$R_1 = p$-ClPh, $R_2 = COOCH_3$, $R_3 = CN$	91	207–213[b]		3
$R_1 = p$-CH_3OPh, $R_2 = COOCH_3$, $R_3 = CN$	87	195–196[b]		3
$R_1 = p$-NO_2Ph, $R_2 = COOCH_3$, $R_3 = CN$	49	220–226[b]		3
$R_1 = Ph$, $R_2 = COCH_3$, $R_3 = CN$	79	174.5–177[b]		3
$R_1 = p$-CH_3Ph, $R_2 = COCH_3$, $R_3 = CN$	83	168–181[b]		3
$R_1 = Ph$, $R_2 = COPh$, $R_3 = CN$	68	205–206.5[b]		3
$R_1 = p$-CH_3Ph, $R_2 = CONH_2$, $R_3 = CN$	74	218–220[b]		3
$R_1 = p$-CH_3Ph, $R_2 = CONHCH_3$, $R = CN$	68	192.5–193.5[b]		3
$R_1 = p$-CH_3Ph, $R_2 = CON\langle\bigcirc\rangle$, $R_3 = CN$	41	231–232[b]		3

[a] Yields are related to the procedure, where the oxidative coupling is carried out with oxygen in methanol using Cu(OH)Cl-TMEDA as a catalyst (except for example 1).
[b] All dimers were obtained as a mixture of two diastereoisomers.

TABLE V. Oxidative Cleavage of *o*-Phenylenediamines and Catechols,

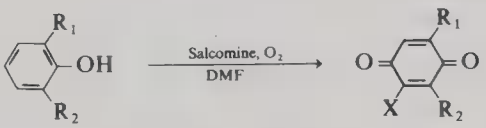


o-Phenylenediamine	Yield of corresponding *cis,cis*-mucono nitrile (%)	m.p. (°C)	Reference
o-Phenylenediamine	95	128–129	4
4-Methoxy-*o*-phenylenediamine	75	115–117	4
4,5-Dimethyl-*o*-phenylenediamine	95	106–108	4
4-Nitro-*o*-phenylenediamine	0	—	4
1,2-Diaminonaphthalene	72	68.5–69.5	4



Alcohol (ROH)	Yield of corresponding *cis,cis*-muconate (%)	m.p. (°C)	Reference
CH_3OH	82	80	35
C_2H_5OH	59	102	35
n-C_3H_7OH	45	74	35
i-C_3H_7OH	7	—	35
t-C_4H_9OH	0	—	35

TABLE VI. Oxygenation of Phenols to Benzoquinones,



Phenol		Yield of benzo-quinone (%)	m.p. (°C)	Comments	Reference
$R_1 = R_2 = CH_3$	X = H	88	73		67
$R_1 = R_2 = t$-Bu	X = H	83	66–67		8
$R_1 = R_2 = Ph$	X = H	86	136		8
$R_1 = R_2 = OCH_3$	X = H	91	252		8
$R_1 = OCH_3$, $R_2 = CH_2CH_2OCH_2Ph$	X = H	78	71–72		9
$R_1 = OCH_3$, $R_2 = CH(OCH_3)_2$	X = H	91	86–87		68
$R_1 = t$-Bu, $R_2 = Ph$	X = H	89	38		67
$R_1 = R_2 = Ph$	X = OCH_3	94	143	In the presence of trimethyl-benzylammonium methoxide	40

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8

RUTHENIUM TETROXIDE OXIDATIONS

JOHN L. COURTNEY

1. INTRODUCTION

The availability of a wide variety of selective reagents is important to the success of organic synthetic projects. Consequently, the search for new and more selective reagents is a never-ending process.

Osmium tetroxide's reactivity with organic compounds has been known since 1912[1] and its usefulness as a reagent has been well established since Criegee's[2] investigations in 1936. Since ruthenium and osmium are members of the same group of the Periodic Table the study of ruthenium tetroxide and its relationship to osmium tetroxide was obviously a worthwhile undertaking. Djerassi and Engle's[3] investigations were prompted by the desire to find a replacement for osmium tetroxide which is not only expensive but also very poisonous and dangerous to the eyes. It should be noted that very little is known about the toxicity of ruthenium tetroxide but it is regarded as being moderately dangerous.[4]

Ruthenium tetroxide and osmium tetroxide, as is to be expected, have very similar physical properties.[5] Both are low-melting, crystalline, volatile solids and both are extremely soluble in carbon tetrachloride. However, their chemical reactivities are markedly different. Whereas the usefulness of osmium tetroxide in organic chemistry is confined to its ability to react with olefins and ultimately produce *vic*-glycols, ruthenium tetroxide is a much more vigorous and versatile oxidant. Thus ruthenium tetroxide has been used to oxidize alcohols into ketones or aldehydes, aldehydes into acids, ethers into esters or lactones, amides into imides, and olefins into aldehydes and ketones.[6] It is also capable of reacting with and degrading aromatic systems. Other virtues of this reagent are that it may be used in neutral conditions and that it is capable of oxidizing sterically hindered groups where other oxidizing agents have been ineffective.

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2. THE MECHANISM OF RUTHENIUM TETROXIDE OXIDATIONS

In view of the versatility and usefulness of ruthenium tetroxide it is surprising that there has not been a great deal of research into the mechanism of its reactions. It has been proposed that this multipurpose oxidant may undergo reactions involving free radicals or ions and in some cases radical ions.

2.1. Ionic Reactions

2.1.1. Oxidation of Alcohols

Kinetic studies of the oxidation of 2-propanol by ruthenium tetroxide in aqueous perchloric acid solutions have revealed that different mechanisms operate at different levels of acidity.[7] In moderately acidic solutions (1–6.5 *M* $HClO_4$) the rate-determining step involves hydride abstraction, while at higher concentrations the rate-determining step involves carbonium ion formation. The strongly acidic conditions used (9–10.5 *M* $HClO_4$) would not normally be used in preparative chemistry so the results in these conditions are only of academic interest.

The mechanism proposed to account for the initial transfer of a hydride ion is

$$R-\overset{\overset{OH}{|}}{CH}-R' + RuO_4 \longrightarrow R-\overset{\overset{OH}{|}}{\underset{+}{C}}-R' + HRuO_4^-$$

$$R-\overset{\overset{OH}{|}}{\underset{+}{C}}-R' + HRuO_4^- \longrightarrow R-\overset{\overset{O}{\|}}{C}-R' + H_2RuO_4$$

The possibility that free radicals are involved was eliminated by the application of Roček's criterion. Roček and his co-workers[8–11] have shown that the oxidation of cyclobutanol can be used to determine whether the reagent acts as a one-electron or a two-electron oxidant. Thus two-electron oxidants convert cyclobutanol entirely into cyclobutanone where one-electron oxidants give rise to acyclic four-carbon compounds which appear to be derived from a primary free radical.

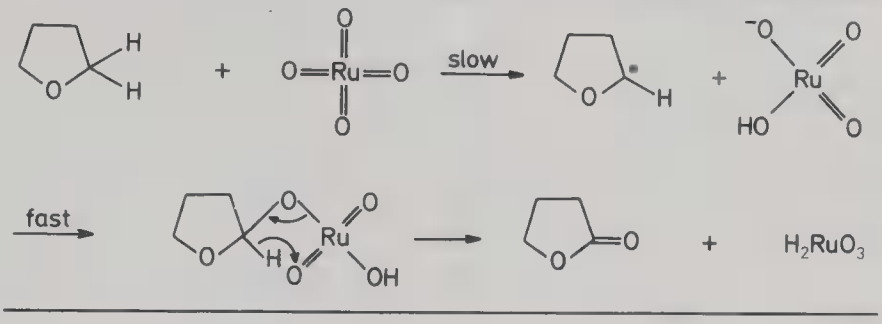
$$\text{Cyclobutanol} \xrightarrow[\text{oxidants}]{\text{one-electron}} \cdot CH_2-CH_2-CH_2-CHO$$

The only detectable product obtained by the oxidation of cyclobutanol with ruthenium tetroxide was cyclobutanone,[12] which indicates that ruthenium tetroxide acts as a two-electron transfer oxidant.

2.1.2. Oxidation of Ethers

The oxidation of acyclic and cyclic aliphatic ethers to the corresponding esters or lactones is most effectively accomplished by the use of ruthenium tetroxide. A kinetic study of the oxidation of tetrahydrofuran by ruthenium tetroxide in aqueous perchloric acid solutions led Lee and van den Engh[13] to propose a mechanism for the reaction. They found that the rate of reaction is directly dependent on the concentration of the oxidant and reductant but inversely dependent on the acidity of the medium. These results were considered to be consistent with a mechanism involving the transfer of a hydride ion to the oxidant in the rate-determining step. The fact that the rates of oxidation of tetrahydrofuran and 2-propanol in

SCHEME 1



similar conditions are comparable and that the activation parameters of the two reactions are almost identical lends support to the idea that both reactions involve hydride transfers.

The proposed mechanism is shown in Scheme 1.

2.1.3. Oxidation of N^6,N^6-Dialkyl Adenosines

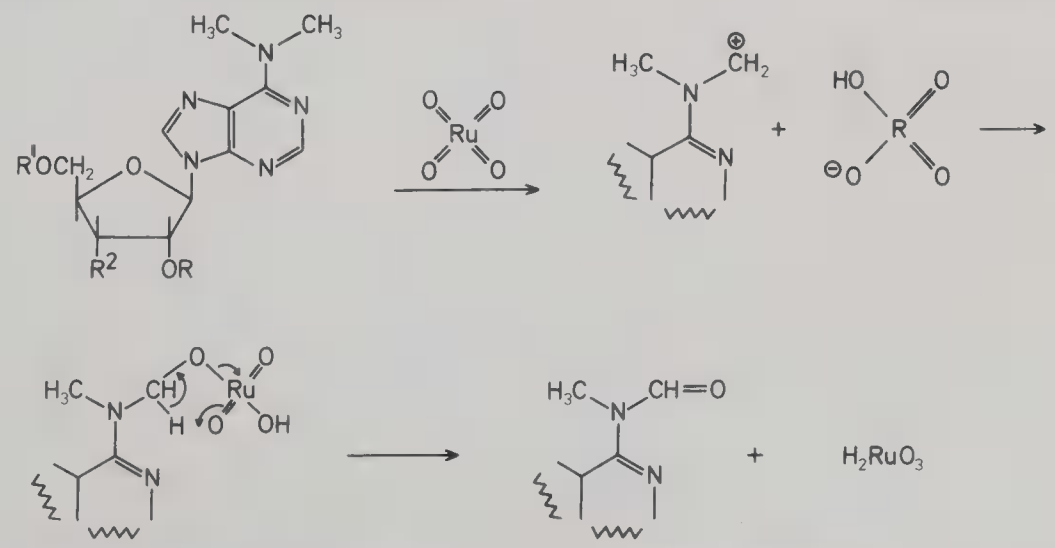
Endo and Žemlička[14] oxidized a number of N^6,N^6-dialkyl adenosines and showed that only one of the alkyl groups was converted to an amido derivative. On the basis of mechanisms proposed for the oxidation of alcohols and ethers by ruthenium tetroxide[7,13] Endo and Žemlička suggest that the mechanism in scheme 2 prevails.

2.1.4. Oxidation of Naphthalenes

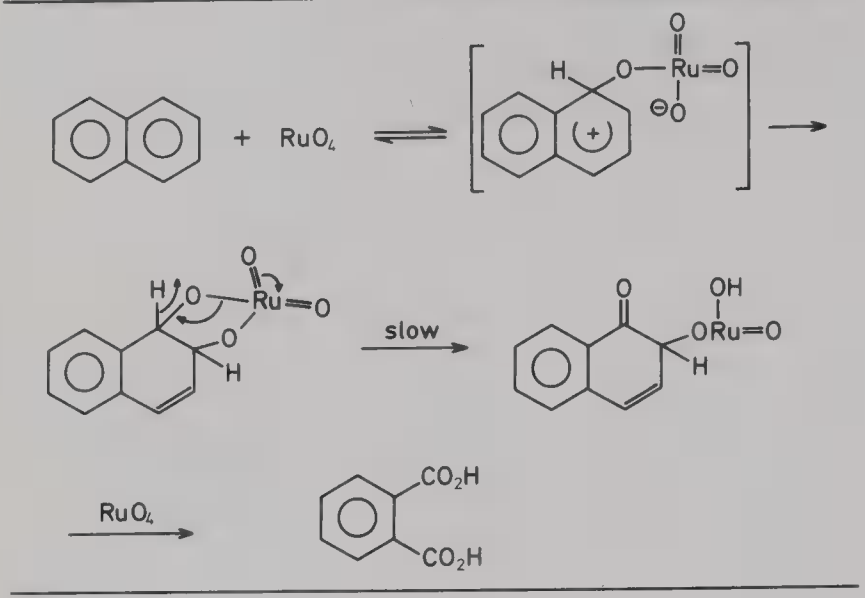
The oxidation of naphthalenes into the corresponding phthalic acids has been shown not to involve free radicals by ESR spectrometry. Kinetic studies[15] reveal that two processes occur; the first is a rapid second-order reaction yielding a ruthenium (VI) moiety and the second reaction is a slower first-order decomposition of this intermediate. The mechanism proposed for these oxidations is shown in Scheme 3.

Support for this mechanism was obtained in the following way: The reaction is an electrophilic aromatic substitution similar to sulfonation of aromatic compounds by sulfur trioxide. The activation parameters for the sulfonation of a variety of aromatic compounds in

SCHEME 2



SCHEME 3

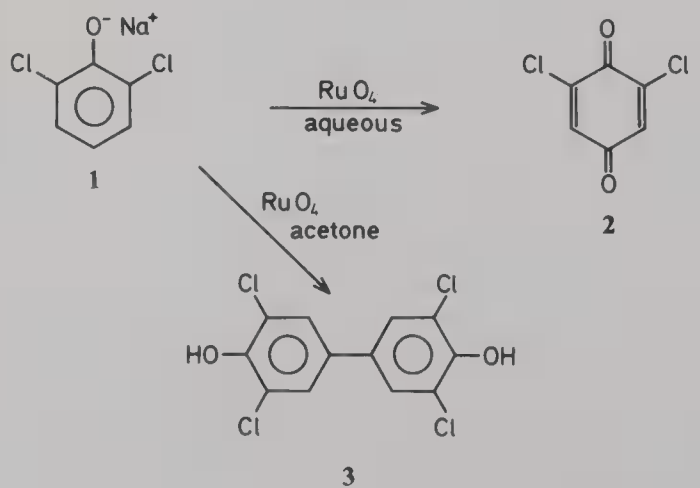


oleum were compared with the activation parameters of the reaction between ruthenium tetroxide and naphthalene and found to be similar.

2.2. Reactions Involving Free Radicals

2.2.1. Oxidation of Chlorophenols and Arylfurans

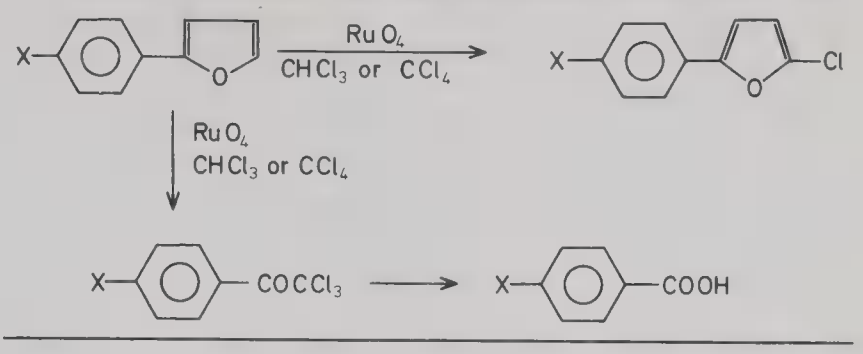
These reactions have been shown to proceed via free radical intermediates.[16] Evidence for this is based on ESR spectroscopy and on the nature of the products formed. Thus sodium 2,6-dichlorophenoxide (**1**) is oxidized in aqueous solution to 2,6-dichlorobenzoquinone (**2**), but in acetone solution it is converted into 3,3′,5,5′-tetrachloro-4,4′-dihydroxybiphenyl (**3**). When arylfurans are oxidized with ruthenium tetroxide in a two-



1 2 3

phase system of chloroform or carbon tetrachloride and aqueous hypochlorite the organic solvent participates in the reaction sequence. Thus either a chlorine atom or a trichlormethyl

SCHEME 4



radical becomes captured. See Scheme 4. It has been proposed that these oxidation products are formed through the intermediacy of a radical cation (**4**).

4

2.2.2. Oxidation of Alkenes

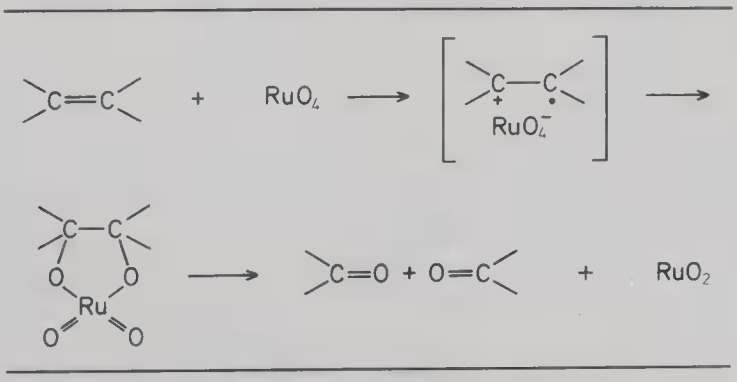
A kinetic study of the oxidation of a series of substituted methyl cinnamates indicated that the reaction proceeded in two distinct steps.[17] The first step involves the formation of a cyclic ruthenium (VI) diester intermediate, which is formed via a radical cation–perruthenium transition state. The cyclic ruthenium diester intermediate is analogous to that formed in osmium tetroxide oxidations but differs in the fact that it is too unstable to ever be isolated from the reaction. It should be noted that on occasions the cyclic osmate esters may react similarly and break down to give the corresponding carbonyl compounds.

The second step in the oxidation was found to be a slower first-order reaction which is compatible with the decomposition of a cyclic ruthenium diester intermediate into ruthenium dioxide and two carbonyl compounds. The proposed mechanism is illustrated in Scheme 5.

2.2.3. Oxidation of Cycloalkanes

Oxidation of cycloalkanes by ruthenium tetroxide affords the corresponding ketone plus the dicarboxylic acid resulting from ring fission.[18] The rates of oxidation of various cycloalkanes by ruthenium tetroxide, permanganate ion, and by hexavalent chromium have been compared and been found to be similar. On this basis it is suggested that the

SCHEME 5



mechanisms of oxidation for all three oxidants are similar. Moreover, it was assumed that these reactions are free radical in nature because the rates of acetolysis of tosylates of the corresponding cycloalkanols (reactions involving carbonium ion intermediates) are quite different with respect to the oxidation rates.

3. SCOPE AND LIMITATIONS

3.1. Oxidation of Alcohols

Ruthenium tetroxide effectively oxidizes primary alcohols to aldehydes and acids and secondary alcohols to ketones. The preparation of aldehydes from primary aliphatic alcohols is usually not practical since aldehydes are rapidly oxidized further to the corresponding acids. Thus it is not possible to convert I-hexanol into hexanal, only hexanoic acid being formed even when an excess of the alcohol is present. Lower molecular weight primary alcohols are oxidized to the corresponding acids in quantitative yields in a solution of periodic and sulfuric acids containing ruthenium salts. However, despite the difficulty of preparing aldehydes from alcohols, Berkowitz and Rylander[19] reported the conversion of benzyl alcohol into benzaldehyde in 90% yield. This is especially interesting since benzene is reported to explode on contact with ruthenium tetroxide.[3] Obviously, the hydroxyl group reacts more rapidly than the aromatic system.

Although there are many oxidants capable of oxidizing secondary alcohols to ketones, ruthenium tetroxide has been found to be more effective in cases where the substrate is fairly labile. Thus the oxidation of cyclobutanols to cyclobutanones is much more efficiently carried out by ruthenium tetroxide than by other oxidizing agents. Caputo and Fuchs[20] used the catalytic two-phase method and oxidized ethyl 3-hydroxycyclobutane carboxylate to ethyl 3-ketocyclobutane carboxylate in 78% yield.

Berkowitz and Rylander[19] found that ruthenium tetroxide converts 1,2-cyclohexanediol into 1,2-cyclohexanedione or 2-hydroxycyclohexanone and menthol is smoothly oxidized to menthone. Deuterated norborneol was oxidized to deuterated norcamphor using fluorotrichloromethane as the solvent.[21]

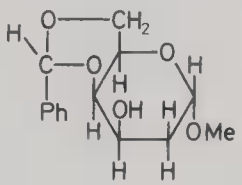
Steroidal alcohols on reaction with ruthenium tetroxide readily give the corresponding ketones. In the preliminary work with this reagent 3β-cholestanol was oxidized to 3-cholestanone. Nakata[22] specifically studied the oxidation of steroidal alcohols by ruthenium tetroxide. Using both the noncatalytic and catalytic methods the alcohols give the corresponding ketones in almost quantitative yields. Thus 5α-androstan-3α-ol-17-one is oxidized to 5α-androstan-3,17-dione; 5α-pregnane-3β,20β-diol is converted into 5α-pregnane-3,20-dione, and cholestan-3β-acetoxy-6β-ol gives cholestan-3β-acetoxy-6-one. 5α-Androstan-3-ol-17-one is oxidized to the corresponding 3,17-dione by a slight excess of sodium metaperiodate in the presence of small amounts of ruthenium dioxide. The catalytic method effects the conversion of cholestan-3β-acetoxy-5α,6β-diol into cholestan-3β-acetoxy-5α-ol-6-one.

Replacement of the sodium metaperiodate with lead tetraacetate and the carbon tetrachloride with glacial acetic acid allows the ruthenium tetroxide oxidation to be carried out in homogeneous conditions. Cholestanol is slowly oxidized to cholestanone in relatively low yield under these conditions. If more vigorous conditions are employed, such as higher temperatures, undesired by-products are formed.[22]

A long-standing need in carbohydrate chemistry has been for an oxidant which will convert glycoside derivatives into glycopyranosiduloses in high yield under mild conditions. Beynon and co-workers[23,24] found ruthenium tetroxide has several advantages over CrO_3–pyridine as an oxidant for secondary hydroxyl groups in monosaccharide derivatives. Difficulty is often encountered in the conversion of the hindered free 3-hydroxyl group of various sugar derivatives into a keto function. Whereas many of the more common oxidizing

agents often fail to react, ruthenium tetroxide generally gives good yields of the desired product.[23,25]

Partially benzoylated, benzylidenated, or isopropylidenated methyl glycosides are converted into methyl glycopyranosiduloses, and furanoid derivatives are also oxidized by ruthenium tetroxide. The glycosidic linkage is untouched by the reagent and axial or equatorial hydroxyl groups are oxidized with equal ease. Among the many examples of carbohydrate oxidations is the conversion of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-lyxo-hexopyranoside (**5**) into methyl 4,6-*O*-benzylidene-2-deoxy-α-D-threo-3-hexulopyranoside (**6**).[24] When CrO_3–pyridine is used as the oxidizing agent methanol is also eliminated to give the pyranodioxin (**7**) as the major product. Generally yields of **6** are better when ruthenium



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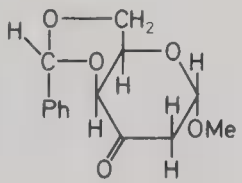

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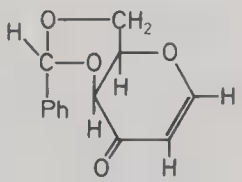

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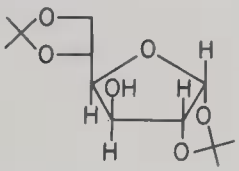
tetroxide is employed. The usefulness of ruthenium tetroxide for the oxidation of hydroxyl groups on furanoid rings is well illustrated by the preparation of 1,2:5,6-di-*O*-isopropylidene-α-D-ribohexofuranos-3-ulose (**9**) in 80% yield from the corresponding di-*O*-isopropylidene-D-glucofuranose (**8**).[24]



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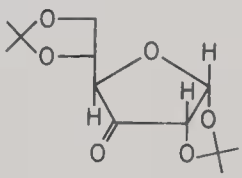


9

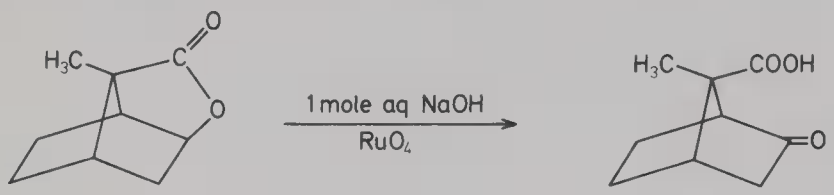
However, the course of ruthenium tetroxide oxidations of carbohydrate derivatives should be carefully monitored since excessive reagent and prolonged reaction times have led to the production of lactones (see oxygen insertion reactions). Ruthenium tetroxide has proved to be successful in some cases where all the standard methods of oxidation have failed. Thus, in the oxidation of the hydroxy-lactone **10** standard oxidizing procedures were unsuccessful, whereas ruthenium tetroxide readily effected the transformation.[26]

The oxidation of tertiary alcohols can proceed only via carbon–carbon bond cleavage or via dehydration. Unlike chromic acid, ruthenium tetroxide is unable to dehydrate tertiary

10 **10a**

alcohols with an adjacent methine group. Thus the tertiary 5α-hydroxyl group in cholestan-3β-acetoxy-5α, 6β-diol is unaffected by ruthenium tetroxide.[22]

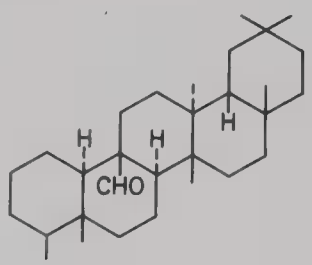
The conversion of γ- and δ-lactones to the corresponding keto-acids via the hydroxy acids has been investigated by Gopal and his collaborators.[27] Hydrolysis of γ- and δ-lactones followed by oxidation with $KMnO_4$ or chromic acid usually results in low yields of the keto-acid. However, ruthenium tetroxide readily converts aqueous alkaline solutions of the corresponding hydroxy acids into the keto-acids in high yields. Thus the lactone **11** was converted into the keto-acid **12** in 97% yield.



11 **12**

3.2. Oxidation of Aldehydes

Aldehydes are rapidly oxidized to acids by ruthenium tetroxide.[19] Thus heptaldehyde gives heptanoic acid and benzaldehyde gives benzoic acid without any difficulty. On very rare occasions, particularly in triterpenes, cases of "nonoxidizable" aldehydes are encountered. Thus the aldehyde **13** could not be oxidized by any of the standard procedures, but it was slowly converted into the acid by ruthenium tetroxide.[28]



13

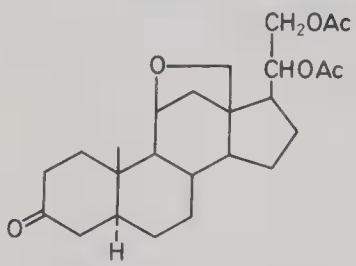
3.3. Oxidation of Ethers

A novel reaction of ruthenium tetroxide is its ability to oxidize ethers to esters. Djerassi and Engle,[3] while searching for a suitable solvent for the reagent, found that it reacted violently with diethyl ether. Berkowitz and Rylander[19] achieved a quantitative conversion of tetrahydrofuran into butyrolactone and *n*-butyl ether into butyl butyrate. Attempts to carry the oxidation of esters further to give anhydrides were unsuccessful. Unlike the α-methylene group of ethers, the methylene adjacent to the alkyl oxygen in esters is unreactive toward ruthenium tetroxide. For the oxidation of ethers to occur there must be at least one methyl or a methylene group adjacent to the oxygen. Even if the adjacent methylene is sterically hindered oxidation can still occur. Thus ruthenium tetroxide is able to oxidize sterically hindered groups that are unreactive toward other oxidizing agents. A synthesis of aldosterone from an alkaloid precursor by Wolff and co-workers[29] requires the oxidation of the ether 20,21-dihdyroxy-11β,18-epoxy-5α-pregnan-3-one diacetate (**14**) to form 3-oxo-11β,20,21-trihydroxy-5α-pregnan-18-oic acid 11-18-lactone 20,21-diacetate (**15**). While chromic acid oxidation of the ether **14** gave only trace amounts of the lactone, ruthenium tetroxide reacted slowly but furnished the desired intermediate in higher yields.

Another example of the potency of ruthenium tetroxide is that it will convert the ether **16** into the lactone **17**, whereas chromic acid oxidation is ineffective.[28] In a study of the oxidation of simple ethers by ruthenium tetroxide, Smith and Scarborough[28a] prepared not only ethers or lactones but also substantial amounts of the carboxylic acids resulting from the hydrolysis of intermediates. Such hydrolysis products are barely detectable when the new acetonitrile modification method[57] is employed.

The ruthenium tetroxide oxidation of 3α-5α-cyclocholestan-6β-yl methyl and ethyl ethers[28b] afforded the formate and acetate esters respectively plus some of the 6-oxo-compound.

It is interesting to note that although methylenes adjacent to an ether oxygen are oxidized by ruthenium tetroxide, methylene groups adjacent to the oxygen atoms of isopropylidine or benzylidine protecting groups [see **5** and **8**] are unaffected by this reagent. However, cyclic acetals have been converted by ruthenium tetroxide into keto-acids.[28c]



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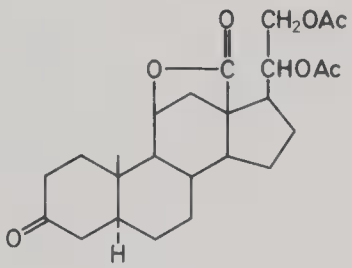

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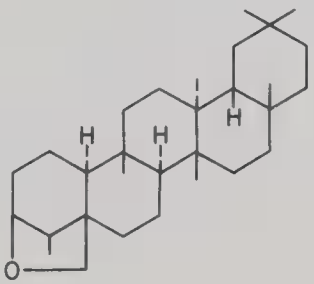

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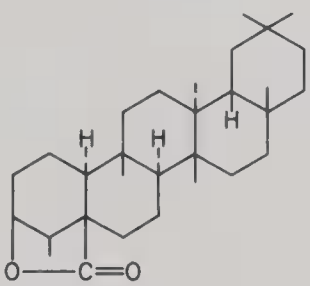


17

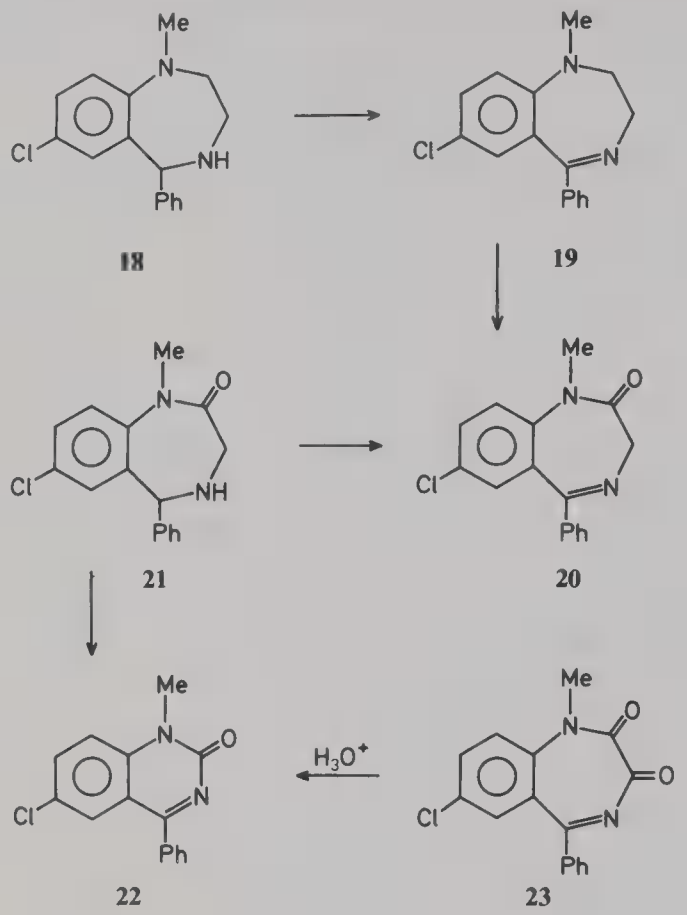
3.4. Oxidation of Amines, Amides, and Nitrogen Heterocyclic Compounds

By analogy with the oxidation of ethers, secondary amines might be expected to react with ruthenium tetroxide to give substituted amides. On treating triamylamine, diethylamine, and piperidine with ruthenium tetroxide, Berkowitz and Rylander[19] obtained intractable products. In each case the reaction mixture had an infrared spectrum indicating the presence of an amide, but no pure oxidation products could be obtained.

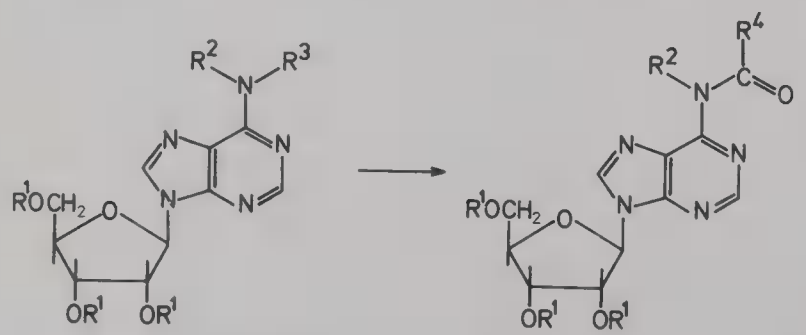
In contrast to esters which are unreactive to ruthenium tetroxide, substituted amides are oxidized to imides by this reagent.[19] Thus, butyrolactam is converted in good yield into succinimide, and *N*-hexylheptamide is oxidized to the corresponding imide. This oxidation of amides provides a new degradative tool in the chemistry of nitrogenous organic compounds.

Although Djerassi and Engle's[3] investigations revealed that ruthenium tetroxide reacted violently with pyridine, the oxidation of some nitrogen heterocyclic compounds has proved successful. Thus the tetrahydro-1,4-benzodiazepine (**18**) is converted into the corresponding dihydro derivative **19** in 43% yield by a solution of ruthenium tetroxide in chloroform. The dihydro derivative is oxidized further by ruthenium tetroxide to the derivative **20**. The dehydrogenation of **18** to form **19** constitutes another variation in ruthenium tetroxide oxidations. Thus instead of converting a methylene group adjacent to the NH function into a

carbonyl group as happens when **19** is oxidized to **20**, a cyclic imine is formed. Conceivably, the doubly benzylic methine adjacent to the NH function is first oxidized and the product is converted into compound **19**. Oxidation of the compound **21** also affords **20** plus a quinazoline **22**. The formation of the quinazoline proceeds via the oxidation of **20** or **21** to the dione **23**, which loses a carbon atom and undergoes a ring contraction to give the quinazoline **22**.[30]



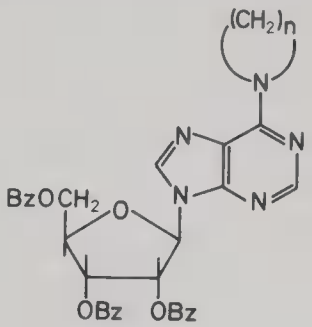
Endo and Žemlička[14] have shown that ruthenium tetroxide is a remarkably selective oxidizing agent toward N^6,N^6-dialkyl-2′,3′,5′-tri-*O*-acyladenosines (**24a–24d**). Thus only the monoamido compounds (**25a–25d**) were formed and no diamido (imido) compounds were detected in the reaction. This is an important reaction because hydrolysis of the amido compound results in an overall *N*-monodealkylation. The yields of the oxidation products (amido compounds) varied depending on the nature of the groups attached to the N^6



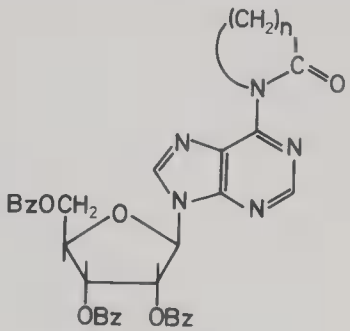
24a: R′ = Ac, $R^2 = R^3 = CH_3$
24b: R′ = Bz, $R^2 = R^3 = CH_3$
24c: R′ = Ac, $R^2 = R^3$ = Et
24d: R′ = Bz, $R^2 = R^3$ = Et

25a: R′ = Ac, $R^2 = CH_3$ R^4 = H
25b: R′ = Bz, $R^2 = CH_3$ R^4 = H
25c: R′ = Ac, R^2 = Et = $R^4 = CH_3$
25d: R′ = Bz, R^2 = Et $R^4 = CH_3$

position. Thus N^6,N^6-dibenzyl derivatives gave only 2% of the desired oxidation product, presumably because the phenyl groups were rapidly oxidized by ruthenium tetroxide. The oxidation of aromatic rings is noted elsewhere in this chapter. However, N^6,N^6-dimethyl-2′,3′,5′-tri-*O*-acetyladenosine gave the N^6-formyl-N^6-methyl derivative in 72% yield. The lack of reactivity of the pyrimidine portion of the purine system to ruthenium tetroxide is ascribed to the strongly electronegative characteristics of the pyrimidine ring. The pyrrolidino and piperidino derivatives (**26a**, **26b**) gave, on oxidation with ruthenium tetroxide, the corresponding lactams (**27a** and **27b**) in 26% and 15% yield, respectively. The oxidation of



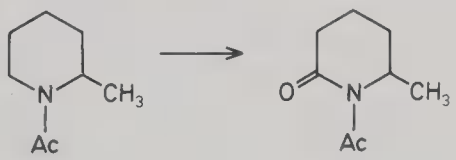
26a: n = 4
26b: n = 5



27a: n = 3
27b: n = 4

N-acyl cyclic amines with varying ring sizes and acyl groups has been shown to produce either lactams or imides.[31] The formation of imides occurred when a two-phase system ("catalytic") was employed with methyloxalyl and trifluoroacetyl derivatives. When the methyloxalyl derivatives were oxidized in a one-phase system the lactams were formed. The use of methyloxalyl derivatives was found to be very practical since the methyloxalyl group can be readily removed from the lactams by sodium methoxide in methanol. See Scheme 6.

Ruthenium tetroxide converts 2-substituted-*N*-acetyl pyrrolidines and 2-substituted-*N*-acetyl piperidines to the corresponding lactams with retention of the absolute configuration.[32] Thus, *N*-acetyl-2-methylpiperidine (**28**) is converted into the piperidone (**29**)

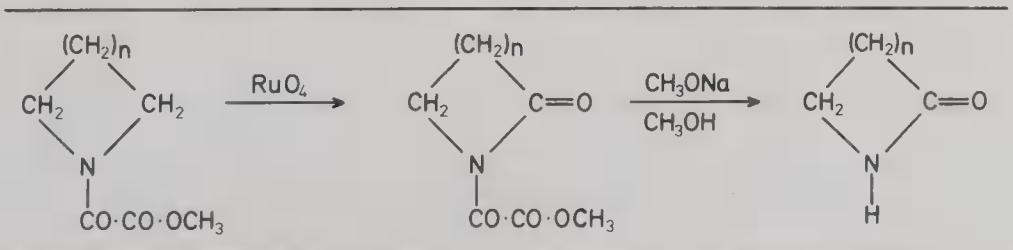


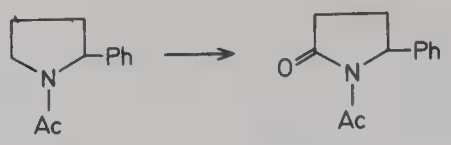
28 **29**

and R-(+)-*N*-acetyl-2-phenyl pyrrolidine (**30**) gave R-(+)-*N*-acetyl-5-phenyl-2-pyrrolidone (**31**). This latter result is interesting and somewhat unexpected since phenyl rings are known to be readily oxidized by ruthenium tetroxide.

The absolute configuration of (−)-3-ethylpiperidine was correlated with that of (R)-(−)-α-ethylglutaric acid.[33] This was accomplished by oxidizing *N*-ethyl- and *N*-benzyl-3-

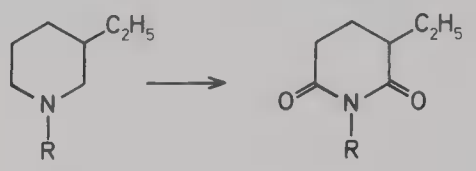
SCHEME 6





30 **31**

ethylpiperidine **32** and **33** with ruthenium tetroxide to yield the corresponding imides **34** and **35** in 60% yield. Hydrolysis of the imides afforded optically active 2-ethylglutaric acid of

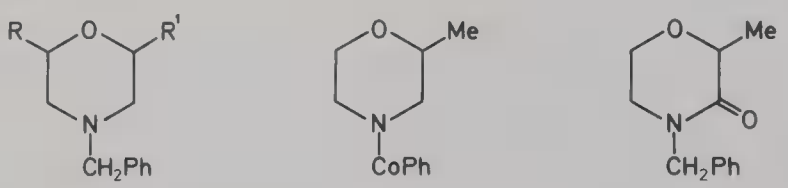


32: R = C_2H_5
33: R = $PhCH_2$

34: R = C_2H_5
35: R = $PhCH_2$

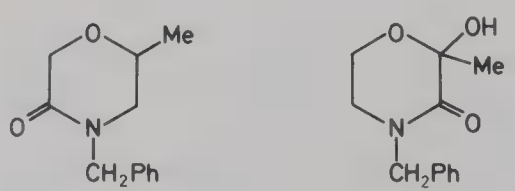
known absolute configuration. The authors commented on the unreactivity of the *N*-benzyl and the *N*-ethyl groups and suggested that the selective oxidation of endocyclic methylenes is due to differences in conformational freedom of endo- and exo-cyclic methylene groups. In another study of the oxidation of *N*-alkyl nitrogen heterocyclic compounds, Bettoni, Tortorella, and co-workers[33a] again observed that endocyclic methylene groups adjacent to the ring nitrogen were more reactive than exocyclic methylenes.

The oxidation of morpholine derivatives[34] by ruthenium tetroxide is interesting because of the possibility of selective reaction adjacent to either the ring oxygen or the ring nitrogen. In the cases studied oxidation takes place preferentially on the carbon α- to the nitrogen atom. Thus when the *N*-benzylmorpholines (**36**) were oxidized with ruthenium tetroxide compounds, **37**, **38**, **39**, and **40** were obtained. Once again, we see an example in which the benzene ring is left intact during the reaction.



36
R, R′ = H, Me

37 **38**

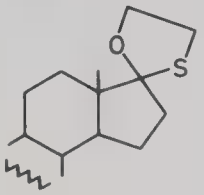


39 **40**

The cleavage of enamines by ruthenium tetroxide is claimed to be a convenient general process. Thus, Desai, Chawla, and Dev[34a] removed an aldehyde group from a compound by converting it into an enamine, which was then oxidized by ruthenium tetroxide to a *nor* ketone.

3.5. Oxidation of Organic Sulfides

Unlike ethers, amines, or amides, where the methylene adjacent to the heteroatom is oxidized, organic sulfides are oxidized by ruthenium tetroxide at the heteroatom itself. The sulfoxide is usually an intermediate of the reaction and this is oxidized further to the sulfone. Both aliphatic and aromatic sulfides react with ruthenium tetroxide. Sulfones are formed from diphenyl, methyltolyl, and methylbenzyl sulfides. In androstan-17-one ethylene hemithioketal (**41**), the sulfur atom is oxidized and the corresponding sulfone **42** is formed.[3]



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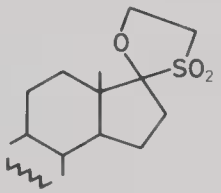
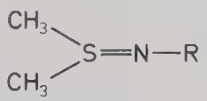


42

Ruthenium tetroxide converts sulfenylimines (**43**) into sulfoximines (**44**) in high yields.[35] However, when R contains a nondeactivated aromatic ring yields are very low owing to the degradation of the ring by the reagent.



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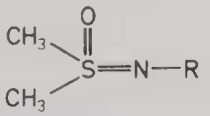
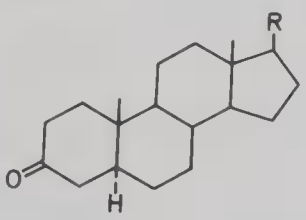


44

3.6. Oxygen Insertion Reactions of Ruthenium Tetroxide

The first observation of an oxygen insertion reaction effected by ruthenium tetroxide was made by Nakata.[22] In order to have homogeneous conditions for the oxidation he replaced sodium metaperiodate by lead tetraacetate and carried out the reaction in glacial acetic acid at room temperature. Oxidation of cholestanol under these conditions is slow and relatively low yields of cholestanone (**45**) were obtained. When the oxidation was carried out at 40°C, 4oxo-A-homo-5α-cholestan-3-one (**46**) was obtained as the major product. One possible rationalization of this result is that the reaction of ruthenium tetroxide and acetic acid gives rise to peracetic acid which oxidizes the cholestanone (**45**), the primary oxidation product, to the lactone by a Baeyer–Villiger oxygen insertion reaction.



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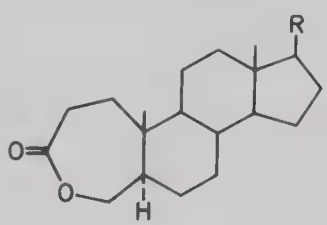
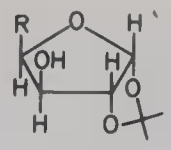
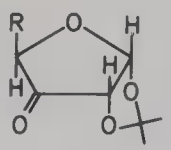


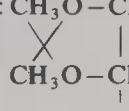
46

The presence of peroxy acids is apparently not essential for this oxygen insertion reaction to occur. Furthermore, the lactones are probably formed by oxidation of the ketones which are initially produced. Thus when the carbohydrate derivatives **47a** and **47b** were reacted with a solution of ruthenium tetroxide in carbon tetrachloride, the free hydroxyl groups were oxidized and the products isolated after a few hours were the ketones **48a** and **48b**. However, when the reaction was worked up after 48 h the lactones **49a** and **49b** were

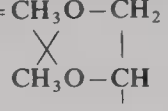




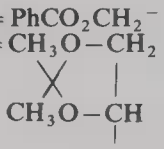
47a: R = $PhCO_2CH_2$
47b: CH_3O-CH_2

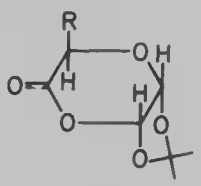


48a: R = $PHCO_2CH_2^-$
48b: R = CH_3O-CH_2



49a: R = $PhCO_2CH_2^-$
49b: R = CH_3O-CH_2

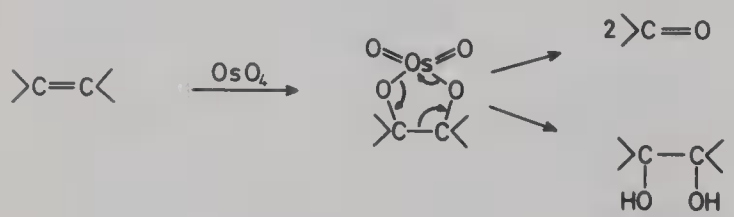




obtained.[36] These lactones represent a new class of carbohydrate derivatives and the oxygen insertion reaction is reported to be a new reaction of ruthenium tetroxide.

3.7. Oxidation of Carbon–Carbon Double Bonds

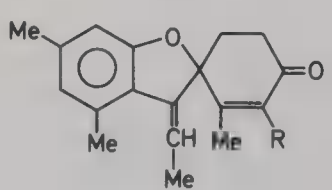
The cleavage of olefinic bonds is an important preparative and degradative process. One of the best known procedures (apart from ozonolysis) involves the oxidation of the olefin by osmium tetroxide to a *vic* diol via an isolable intermediate osmate ester **50**.[6] The glycol is subsequently cleaved by either lead tetraacetate or periodic acid to give carbonyl compounds. In some instances osmium tetroxide cleaves the olefin directly to give the carbonyl compounds. Presumably, the osmate ester **50** is first formed and this breaks down as shown.



50

Ruthenium tetroxide almost invariably cleaves carbon–carbon double bonds to give carbonyl compounds directly. Thus cyclohexene and 1-octene were converted by ruthenium tetroxide into adipaldehyde and heptaldehyde, respectively.[19]

Grisen-3-ones (**52**) are formed from 3-alkylidene grisens (**51**) by ruthenium tetroxide cleavage of the hindered double bond at C3.[37] The reaction seems general though its efficiency is markedly affected by the nature of the substitution pattern. Thus the yields vary up to 30% depending on small differences in the substitution pattern of the parent ring system. Chromium trioxide oxidation and ozonolysis of **51** were unsuccessful.



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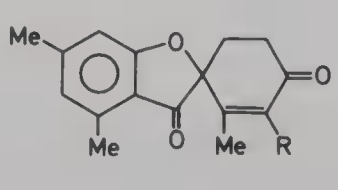
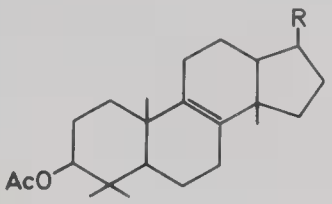


52

Ruthenium tetroxide has also been utilized in the oxidation of unsaturated steroids. The double bond in **53** is unreactive to osmium tetroxide but is readily converted into a diketone (**54**) by ruthenium tetroxide.[38]



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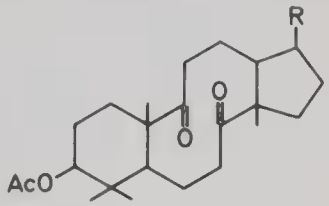
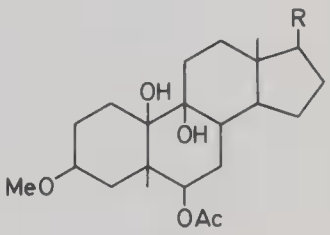


54

When unsaturated steroid **55** was treated with ruthenium tetroxide a small amount of the diol **56** was obtained as well as the diketone **57**.[38] Another useful reaction which has been reported is the degradation of an unsaturated steroidal side-chain into an aldehyde group in



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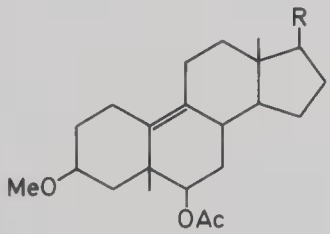
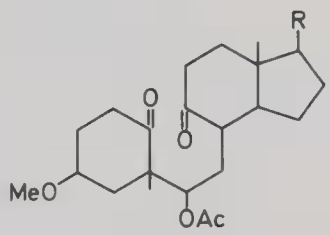


55



57

high yield. An interesting feature of this work is that either an aldehyde or an acid may be prepared depending on the acidity and solvent system being used.[39] When a solution of ruthenium tetroxide in carbon tetrachloride was titrated into a neutral solution of the alkene, high yields of aldehyde were obtained. Treatment of an acidic solution of the alkene afforded a high yield of the carboxylic acid. (See Scheme 7.)

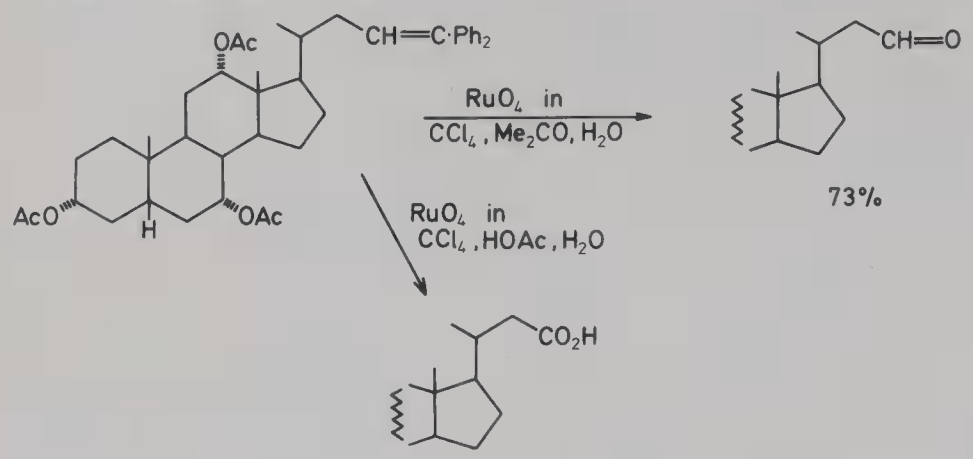
Unsaturated fatty acids[40] and long-chain alkenes[41] have been converted into smaller carboxylic and dicarboxylic acids by ruthenium tetroxide in high yields. It has been reported that increased yields and the *in situ* regeneration of ruthenium tetroxide is facilitated by the use of phase transfer catalysis in these systems.[41]

The oxidative cleavage of fluorinated olefins[42] and an unsaturated side-chain on barbituric acid[43] have been reported to proceed in high yield. Unsaturated polymers have been converted into lower molecular weight polyfunctional or bifunctional α-ω macromolecules by ruthenium tetroxide.[44]

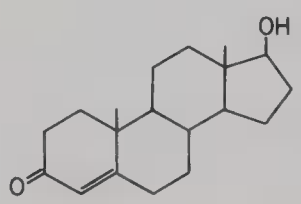
Oxidation of cyclic α,β-unsaturated ketones by ruthenium tetroxide results in the loss of one carbon atom. Thus the oxidation of testosterone (**58**) affords **59** and the α,β-unsaturated ketone **60** is converted into the keto-acid **61**, each with the loss of a carbon atom.[45]

The oxidation of steroidal conjugated homoannular dienes by ruthenium tetroxide has been studied by Rodewald and Bonczatomaszewski.[45a] They found that cholesta-2,4-diene underwent the expected ring cleavage with the loss of two carbons. The product obtained (70% yield) was the hydroxylactone resulting from the cyclization of the hydrate of the keto-

SCHEME 7



acid. However, the oxidation of the 5,7-cholestadiene system did not result in ring cleavage. Instead it was converted into a 5-hydroxy-6-oxo-7,8-epoxycholestane derivative. The difference in behavior of the two structures was attributed to differences in the degree of their steric hindrance.



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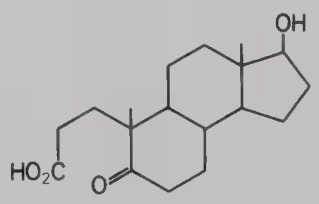

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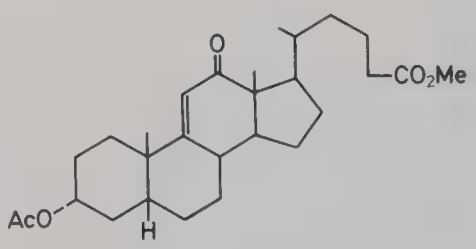

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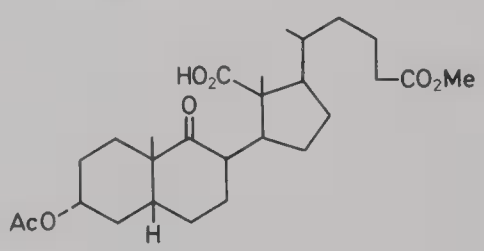


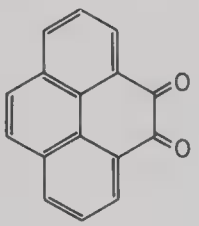
61

3.8. Oxidation of Alkynes

Alkynes may be conveniently converted into α-diketones or carboxylic acids by ruthenium tetroxide.[46] Thus diphenylacetylene was oxidized to benzil in 83% yield using the ruthenium dioxide–hypochlorite reoxidation procedure. This is an interesting result when one remembers that aromatic rings are degraded by ruthenium tetroxide. Terminal acetylenes are converted into carboxylic acids; no α-keto-acids or aldehydes have been isolated from these reactions.

3.9. Oxidation of Aromatic Systems

(a) Polycyclic Aromatic Hydrocarbons. One might expect that those bonds of polynuclear hydrocarbons which exhibit considerable double-bond character would be cleaved by ruthenium tetroxide. However, this is not the case. Thus, while phenanthrene is converted into 9,10-dihydrophenanthrene-9,10-diol by osmium tetroxide, oxidation with ruthenium tetroxide affords 9,10-phenanthraquinone.[3] Pyrene is oxidized in small yields to pyrene 4,5-quinone (**62**) and in lesser amounts to pyrene 1,6-quinone (**63**) and the lactol of 4-formylphenanthrene-5-carboxylic acid **64**.[47]



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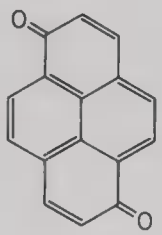

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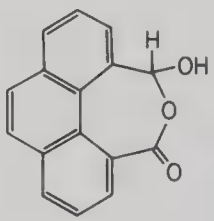


64

Djerassi and Engle[3] doubted that a ruthenate ester was formed as an intermediate in this type of reaction. Whether the formation of phenanthrene quinone is due to direct oxidation at the 9,10-position of phenanthrene or involves further oxidation of an intermediate ruthenate ester is not certain.

The formation of pyrene 4,5-quinone (**62**) and the lactol **64** by the ruthenium tetroxide oxidation of pyrene is indicative that a cyclic ruthenate ester is initially formed at C_4–C_5. Transformation of this ester in the usual way to give the dialdehyde, followed by oxidation, would explain the formation of the lactol **64**. The 4,5-quinone **62** could conceivably be the product of further oxidation of the ruthenate ester or of the corresponding *vic* diol. The formation of the 1,6-quinone must proceed via an entirely different mechanism.

When naphthalene and its derivatives are oxidized by ruthenium tetroxide it is found that electron-donating substituents increase the rate of oxidation and the main product is phthalic acid. On the other hand, electron-withdrawing substituents deactivate the molecule and hence protect the substituted ring and the resulting products are substituted phthalic acids.[48–50]

(b) Destruction of Aromatic Nuclei. Aromatic nuclei possess varying degrees of reactivity toward ruthenium tetroxide. The nature of the substituents determines whether fission of the aromatic ring occurs or not. It is surprising to note that aromatic nuclei can react with ruthenium tetroxide as rapidly as olefinic substances.

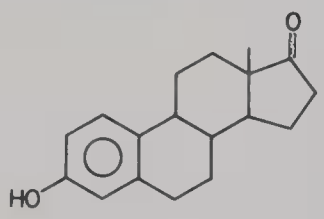
Violent and immediate reaction occurs between ruthenium tetroxide and benzene.[3] Even dilute carbon tetrachloride solutions of benzene react with ruthenium tetroxide, and black ruthenium dioxide is instantaneously precipitated.

The oxidative destruction of aromatic rings can be an extremely convenient and versatile tool in structural and stereochemical studies. Thus the lability of the aromatic nucleus to ruthenium tetroxide enables the alkyl benzenes to be oxidized to form aliphatic carboxylic acids. Caputo and Fuchs[20] used the reagent to establish the stereochemistry of *cis*-3-phenylcyclobutane carboxylic acid. This acid on treatment with ruthenium tetroxide afforded *cis*-1,3-cyclobutanedicarboxylic acid.

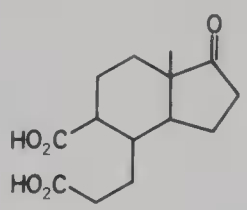
Preparative scale oxidations of *p-tert*-butylphenol and phenylcyclohexane give low yields of pivalic and cyclohexane carboxylic acids, respectively.[20] The direct degradation of an aromatic ring system into a carboxylic acid was the key to the determination of the absolute configurations of dimethyl *tert*-butylsuccinate and *tert*-butyl-α-naphthylacetic acid.[51] Hitherto the chemical correlation of compounds having *tert*-butyl groups at the asymmetric center has been most difficult and the degradation of the naphthalene ring system into

carboxylic acid group by ozonolysis has been very inefficient. It was found that the complete oxidation of the naphthalene ring systems was best achieved by converting them to the tetralin compounds prior to the ruthenium tetroxide oxidation. These correlations are summarized in Scheme 8.

The effect of ruthenium tetroxide on aromatic ring A steroids has been studied by Piatak and his collaborators.[52] They have shown that the aromatic ring of estrone (**65**) is degraded and dicarboxylic acid (**66**) is formed. The same acid **66** was also formed by the oxidation of compounds **67** and **68**.



65



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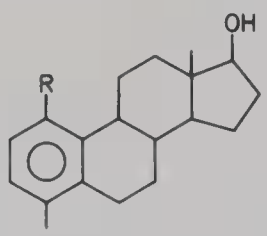
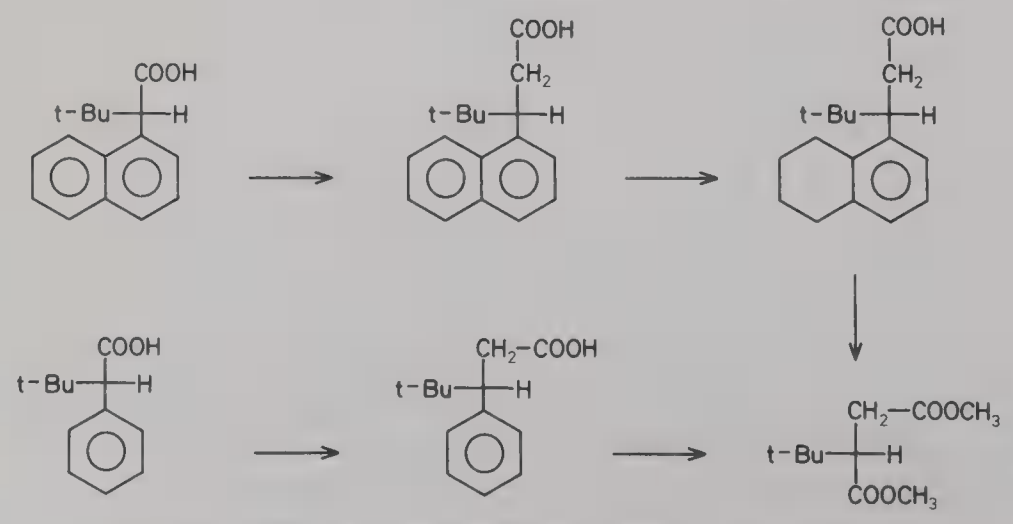
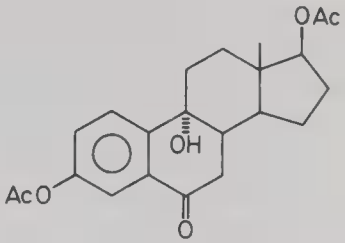


67: R = OH
68: R = H

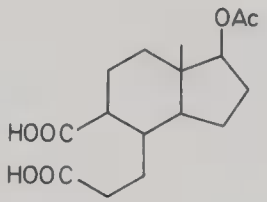
The oxidation of estradiol diacetate with ruthenium tetroxide gave an anomalous result. In this case the main product was an aromatic hydroxy-ketone **69** from a double benzylic oxidation. The expected dicarboxylic acid **70** was obtained also but in lower yield. Piatak and Ekundayo[53] have investigated the structural requirements necessary to give rise to this type of double benzylic oxidation. The sole essential structural feature is that the aromatic ring A should have only a 3-acyloxy group. If aromatic ring A possesses any other group either alone or with a 3-acyloxy group then it is completely degraded by ruthenium tetroxide.

SCHEME 8





69



70

Many other aromatic compounds have been reacted with ruthenium tetroxide, but a thorough examination of the products has not been carried out. No oxidation products were isolated from reaction of the reagent with dibenzyl, triphenylmethane, tetralin, nitronaphthalene, azobenzene, pyridine, phenylacetylene, or tolan.[19]

Despite the lability of aromatic systems to ruthenium tetroxide, it is possible to preferentially oxidize other functional groups in the presence of aromatic systems. Thus the benzene ring in aromatic sulfides and alcohols is relatively inert toward ruthenium tetroxide.[3,19] More complex molecules such as 3-alkylidene grisens[38] (see **51**) and benzoylated or benzylidenated methyl glycosides[20–25] (see **5**) can be specifically oxidized at the nonaromatic portion. However, the reaction of ruthenium tetroxide with the aromatic center in 3-alkylidene grisens may account for the low yields of oxidation products obtained. Other examples of the relative stability of aromatic ring systems have been noted elsewhere in this chapter. Thus the benzene ring of *N*-benzyl derivatives of pyrrolidines and piperidines (**33**) is relatively inert compared with other portions of these molecules.

3.10. Oxidation of Cycloalkanes

Cycloalkanes are relatively inert compounds whose oxidation by the usual reagents requires vigorous conditions. However, Lee and Spitzer[18] have shown that ruthenium tetroxide is capable of oxidizing cycloalkanes into the corresponding cycloalkanones plus the derived dicarboxylic acids under mild conditions. Thus using the two-phase ("catalytic") system at room temperature, with vigorous agitation for periods of from one to eight days, they converted cyclopentane, cyclohexane, cycloheptane, and cyclooctane into the cyclic ketones plus the derived dicarboxylic acids in total yields of 78%–88%. The oxidation products of cyclopentane and cyclohexane contained two to two and a half times as much of the dicarboxylic acids as the cyclic ketones. In contrast, oxidation of cycloheptane and cyclooctane gave much greater proportions of the cyclic ketones.

Ruthenium tetroxide converted *trans*-decahydronaphthalene into *trans*-9-decahydronaphthol in 55% yield along with 7% of decalones.[18] This interesting result illustrates the preferential susceptibility of tertiary carbon–hydrogen bonds to oxidation.

4. EXPERIMENTAL CONSIDERATIONS AND PROCEDURES

Ruthenium tetroxide, like osmium tetroxide, is a poisonous volatile solid. It is a yellow crystalline substance, melting point 25°C, boiling point 100°C. Both ruthenium tetroxide and osmium tetroxide have tetrahedral structures and are extremely soluble in carbon tetrachloride. However, ruthenium tetroxide is a much more vigorous oxidant, and therefore the number of solvents that can be employed is limited. Thus it reacts violently with aromatic hydrocarbons, ethers, and pyridine,[3] and the most suitable solvents are carbon tetrachloride, chloroform, acetone, ethylacetate, butyrolactone, and water. Perhaps the most commonly used solvent is carbon tetrachloride. In one isolated case fluorotrichloromethane has been used.[21]

4.1. Preparation of Ruthenium Tetroxide

Ruthenium tetroxide is obtained when acidic solutions of ruthenium salts are heated with powerful oxidizing agents such as HIO_4, MnO_4^-, Ce^{4+}, BrO_3^-, or Cl_2; ruthenium tetroxide can be distilled from the solutions or swept out by a gas stream. It may also be obtained by distillation from concentrated perchloric acid solutions or by acidification and oxidation of ruthenate solutions.[5] The method developed by Martin[54] involves heating aqueous solutions of ruthenium salts with a suitable oxidizing agent and distilling the volatile ruthenium tetroxide into ice-cold carbon tetrachloride. The yellow solution of ruthenium tetroxide may then be used directly as an oxidant. A simpler procedure is to shake ruthenium dioxide with an aqueous solution of sodium metaperiodate and extract the ruthenium tetroxide as it is formed into carbon tetrachloride.[22]

It is most important to use ruthenium dioxide which has been prepared by a precipitation process.[55] This material is a hydrated form having the probable composition RuO_2–$2H_2O$, and this is the only form of ruthenium dioxide which is oxidizable under the mild conditions previously described. Ruthenium dioxide is also available in an anhydrous form, and since the chemical catalogs list both forms under one heading, it is essential to specify the hydrated form when purchasing. However, Stevens and Bryant[56] have devised a method for converting "inactive" ruthenium dioxide into a form which can be oxidized to ruthenium tetroxide by sodium hypochlorite.

4.2. General Methods of Oxidation with Ruthenium Tetroxide

Two different procedures have been used in ruthenium tetroxide oxidations. In the first method ruthenium tetroxide is prepared and isolated and the appropriate quantity is added to the substrate. The main disadvantage of this method is that the oxidation products are often adsorbed or occluded by the ruthenium dioxide that is precipitated during the reaction, and this results in lower yields. However, Sheehan and Tulis[31] preferred this method when they oxidized cyclic amines because it required a shorter reaction time and the products were therefore not as likely to be hydrolyzed. A typical example of a "single-phase" oxidation follows.

Ruthenium dioxide dihydrate (0.5 g) is shaken with a solution of sodium metaperiodate (2 g in 20 ml water) until the black insoluble ruthenium dioxide disappears. The bright yellow ruthenium tetroxide is then extracted into carbon tetrachloride and may be stored over sodium metaperiodate if necessary. The oxidant solution is added to a solution of the substance to be oxidized and allowed to stand at room temperature. When the reaction is complete excess oxidant is destroyed by the addition of methanol or 2-propanol and the precipitated ruthenium dioxide is removed by filtration. Evaporation of the solvent affords the oxidation product.

The second procedure is sometimes called the "two-phase" or "catalytic" method. In this method small (catalytic) amounts of ruthenium tetroxide are employed. During the reaction the ruthenium tetroxide is converted into ruthenium dioxide, which is reoxidized to the tetroxide by an appropriate oxygen donor such as sodium metaperiodate or sodium hypochlorite. This technique has distinct advantages over the "single-phase" procedure. Thus trace quantities of costly ruthenium dioxide are required and one does not have to isolate the ruthenium tetroxide to carry out the oxidation. Higher yields of oxidation product are often obtained by this method because losses of product due to adsorption and occlusion on the precipitated ruthenium dioxide are reduced. A general outline of the method follows.

The compound to be oxidized is dissolved in carbon tetrachloride or acetone and shaken with ruthenium dioxide dihydrate (20 mg per gram of compound). An aqueous solution of sodium metaperiodate or sodium hypochlorite is added in small portions at intervals so that the reaction mixture remains yellow. When the reaction is finished any excess of

TABLE I. Representative Examples of Ruthenium Tetroxide Oxidations

Substrate	Product	Method[a] and yield (%)	Reference
Hydroxy compounds			
Ethyl-3-hydroxycyclobutane carboxylate	Ethyl-3-ketocyclobutane carboxylate	S, 78	20
Cyclohexanol	Cyclohexanone	S, 79	19
Benzyl alcohol	Benzaldehyde	S, 72	19
1,2:5,6-Di-*O*-isopropylidene α-D-glucofuranose	1,2:5,6-Di-*O*-isopropylidene α-D-ribo-hexofuranosulose	S, 84	23
Methyl-3,4,6-tri-*O*-benzoyl α-D-glucopyranoside	Methyl-3,4,6-tri-*O*-benzoyl α-D-arabino-hexapyranosidulose	S, 50	23
Aromatic compounds			
3-*Tert*-butyl-3-(1′,2′,3′,4′-tetrahydro-5′-naphthyl) propionic acid	Dimethyl-*tert*-butyl-succinate	S, 31	51
3-*Tert*-butyl-3-phenylpropionic acid	Dimethyl-*tert*-butyl-succinate	S, 63	51
Estrone	3-(1-Oxo-8β-methyl-5β-carboxy-*trans*-perhydroindanyl-4α-) propanoic acid	S, 65	52
Phenylcyclohexane	Cyclohexane carboxylic acid	S, 25	20

[a] S, single-phase oxidation; C, "catalytic" or two-phase oxidation; c.p., "catalytic" or phase transfer catalysis.

Table continued

ruthenium tetroxide is destroyed by the addition of methanol or 2-propanol. The ruthenium dioxide is then filtered off and the product is obtained by evaporation of the solvent.

A typical example of the "catalytic" method is the oxidation of estrone.* Estrone (1.00 g) in acetone (100 ml) was added to a stirred, yellow ruthenium tetroxide mixture obtained by combining ruthenium dioxide (400 mg) in acetone (50 ml) with sodium periodate (3.00 g) in water (15 ml). The reaction was kept yellow by adding portionwise a solution of sodium periodate (11.5 g) in acetone–water (1:1, 115 ml) to the stirring mixture. At the end of 4.5 h a few milliliters of isopropyl alcohol were added to terminate the reaction, and the mixture was diluted with an equal amount of acetone. After collection of the precipitated solids on celite, most of the acetone was removed *in vacuo* and solid sodium chloride added. The steroids were taken up in ethyl acetate–ether (1:1), and the acid fraction was isolated as usual with sodium bicarbonate. An acid fraction (670 mg) crystallized on trituration with ethyl acetate.

A greatly improved method for the ruthenium tetroxide oxidation of alkenes, alcohols, ethers, and aromatic rings has been published.[57] This procedure differs from the traditional method of the catalyzed ruthenium tetroxide system simply by the addition of acetonitrile to the carbon tetrachloride/water. The new method is rapid and mild and results in higher yields of products than were previously obtainable by the traditional method.

* Reprinted in part with permission from Piatak, D. M., Herbst, G., Wicha, J. and Caspi, E., *J. Org. Chem.*, **34**, 116 (1969).

TABLE I. *Continued*

Substrate	Product	Method[a] and yield (%)	Reference
Carbon-carbon double bonds			
1-Pentadecene	Myristic acid	c.p., 100	41
3α,7α,12α-Triacetoxy-24,24-diphenyl-5β-chol-23-ene	3α,7α,12α-Triacetoxy-24-nor-5β-cholan-23-al	S, 73	39
3α,7α,12α-Triacetoxy-24,24-diphenyl-5β-chol-23-ene	3α,7α,12α-Triacetoxy-24-nor-5β-cholan-23-oic acid	S, 76	39
5-Ethyl-5-(1-methyl-4-pentenyl) barbituric acid	5-Ethyl-5-(1-Methyl-3-Carboxy-propyl) barbituric acid	C, 81	43
α,β-Unsaturated ketones			
17β-Acetoxy-3-oxo-5α-androst-1-ene	17β-Hydroxy-1,3-seco-2-nor-5α-androstane-1,3-dioic acid	C, 85	45
Cycloalkanes			
Cyclohexane	Cyclohexanone + adipic acid	C, 26 C, 58	18
Cycloheptane	Cycloheptanone + pimelic acid	C, 68 C, 20	18
Nitrogen heterocycles			
N-Methyloxalylpiperidine	*N*-Methyloxalyl-2-piperidone	S, 59	31
N-Acetyl-2-phenylpyrrolidine	*N*-Acetyl-5-phenyl-2-pyrrolidinone	C, 60	32
Sulfur compounds			
S,S-Dimethyl-*N*-(*p*-toluenesulfonyl) sulfenylimine	*S,S*-Dimethyl-*N*-(*p*-toluenesulfonyl) sulphoximine	C, 94	35
Diphenyl sulfide	Diphenyl sulfone	S, 42	3
Diphenyl sulfoxide	Diphenyl sulfone	S, 93	3

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9

Oxidations Using Palladium Compounds

Suzanne F. Davison and Peter M. Maitlis

1. INTRODUCTION

The advent of the Wacker process in the 1950s for the preparation of acetaldehyde from ethylene on an industrial scale using palladium chloride focused attention on the potential of compounds of this metal as oxidants for organic reactions.* The field has expanded greatly since then and Pd(II) is now used for the formation of ketones, esters, ethers, acetals from olefins as well as in olefin coupling reactions. Pd(II) is also active in promoting the coupling of arenes, benzylic oxidation, the oxidation of alcohols, and of oxidative carbonylation. In each case there are many variations which have been explored in order to make the reactions more specific. In addition a wide variety of co-oxidants have been explored; these are used in order to make the reactions catalytic in palladium.

In this chapter we have drawn attention to those features of the oxidation reactions which are likely to be of most interest to the synthetic chemist. The most usual palladium complexes are the chloride, $(PdCl_2)_n$, which is a polymer that only dissolves in the presence of a ligand (or a liganding solvent), and the trimeric acetate $[Pd_3(OAc)_6]$. Both of these are available from Johnson Matthey, Engelhard Industries, and other laboratory supply houses, or can be made from palladium metal.

The reader should also bear in mind, when reading this chapter, that palladium also has a very rich chemistry, especially with unsaturated organic compounds, which is *not* oxidative in nature. For example, both acetylenes and 1,3-dienes are readily oligomerized under mild conditions. Such reactions may therefore limit the utility of Pd(II) in certain types of oxidations.

Platinum(II) will usually effect reactions similar to those induced by Pd(II), but they are

* The early work and the background to all these reactions have been discussed in detail by P. M. Maitlis, in *The Organic Chemistry of Palladium*, Vols. I and II, Academic, New York, 1971, and by P. M. Henry, *Palladium Catalysed Oxidations of Hydrocarbons*, Reidel, Dordrecht, 1980, and the reader is invited to refer to them for further information.

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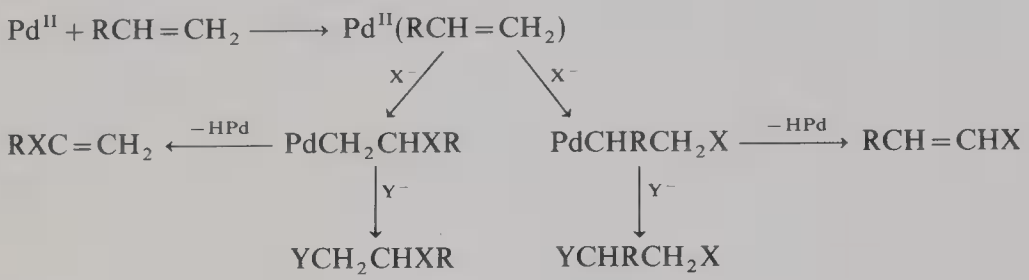
generally substantially slower. Since platinum is also (on a g atom basis) a factor of 5.4 more expensive, it is clearly not the metal of first choice for such oxidations. Attention has therefore been focused on palladium.

Included among the reactions discussed in this chapter is the oxidation of olefins under a variety of conditions. The mechanism of the $PdCl_2$-promoted oxidation of ethylene in water to give acetaldehyde is reasonably well understood in general terms (Section 2.1) and basically consists of the attack of a nucleophile (H_2O or OH^-) on the coordinated ethylene. This nucleophile may attack externally giving a *transoid-β*-hydroxyethylpalladium intermediate. Alternatively there may be a migration of coordinated OH onto the π-complexed ethylene, giving the *cisoid-β*-hydroxyethylpalladium intermediate. These intermediates can then fall apart rapidly, via a series of hydrogen shifts, to give the products. Related schemes can be drawn up for the oxidation of other olefins. Further, analogous reactions by other nucleophiles on coordinated olefins are also possible, and these lead to a wide variety of products. They can be exemplified diagrammatically as



It should be emphasized that this scheme is only for illustration; the actual mechanisms involved are very complex and at present rather poorly understood, and they are even further complicated by subsequent processes.

A further group of reactions may be classified in terms of the formation of σ-arylpalladium intermediates. Formally these intermediates can then react with olefins, by taking the place of X^- in the above diagram, to give aryl substituted compounds. Alternatively such arylpalladium intermediates may couple to give biaryls (Section 4.1), the metal may be displaced by the action of an oxidant (for example, in the presence of acetate to give phenyl acetate, Section 4.2), or they may be carbonylated (Section 5.2). The carbonylation of intermediates such as $PdCHRCH_2X$ or $PdCH_2CHRX$ under oxidizing conditions may also explain the oxidative carbonylation reactions of olefins (Section 5.1). The last section (Section 6) includes a variety of reactions of alcohols; little mechanistic information relating to these reactions has appeared.

The utility of these palladium-promoted oxidations lies in the fact that they can usually be made catalytic in Pd(II) by the addition of Cu(II) and halide; in turn these reactions can sometimes be driven by the oxidizing power of air or oxygen. The basic reactions for a two-electron oxidation of a suitable substrate, X, are

$$\text{Pd(II)} + \text{X} \longrightarrow \text{oxidation product of X} + \text{Pd(O)}$$

$$\text{Pd(O)} + 2\text{Cu(II)} \longrightarrow \text{Pd(II)} + 2\text{Cu(I)}$$

$$2\text{Cu(I)} + \tfrac{1}{2}\text{O}_2 + 2\text{H}^+ \longrightarrow 2\text{Cu(II)} + \text{H}_2\text{O}$$

The chapter concludes with examples taken from the literature which illustrate some of the more useful reactions.

2. OXIDATION OF OLEFINS

2.1. Oxidation of Ethylene in Water

One of the most studied reactions using palladium is the so-called Wacker process,* in which ethylene is oxidized to acetaldehyde in aqueous solution. The stoichiometry is as follows:

$$C_2H_4 + PdCl_2 + H_2O \longrightarrow CH_3CHO + Pd^0 + 2HCl \quad (1)$$

$$Pd^0 + 2CuCl_2 \longrightarrow PdCl_2 + 2CuCl \quad (2)$$

$$2CuCl + 2HCl + \tfrac{1}{2}O_2 \longrightarrow 2CuCl_2 + 2H_2O \quad (3)$$

$$C_2H_4 + \tfrac{1}{2}O_2 \longrightarrow CH_3CHO$$

The reaction in Eq. (1) has been known since 1894,[1] but it was not until 1959 that it was combined with reactions (2) and (3) by Smidt and co-workers[2,3] to give the catalytic cycle indicated above. This is now the basis of an important industrial process replacing the older production of acetaldehyde from acetylene.

There are two industrial versions of the homogeneous Wacker reaction: a one-stage process in which ethylene oxidation and reoxidation of the catalyst occur in the same reactor, and a two-step process in which the reduced catalyst solution is reoxidized in a separate reactor after the acetaldehyde has been removed. In both processes the crude acetaldehyde contains some lower boiling (MeCl, EtCl, CO_2) and some higher boiling ($ClCH_2CHO$, MeCOOH, H_2O) products, which must be removed by distillation.

Chlorinated products are usually formed when copper(II) chloride is used as a reoxidant. With acetaldehyde mono-, di-, and tri-chlorinated products are formed, as well as acetic acid and $ClCH_2CH=CHCHO$ which result from further oxidation or condensation reactions.

Recently, chloride-free Wacker-type systems have been proposed[4] which use palladium salts together with mixed heteropoly acids, such as phosphomolybdovanadates, as reoxidants. These have the potential advantages of eliminating chlorinated side products and of reducing corrosion effects on the plant.

The Wacker reaction is not a particularly useful method for making acetaldehyde on a laboratory scale. However, it has been extensively studied in small-scale experiments by Henry and others. Such studies have led to the present understanding of the mechanism, the essence of which is shown in Scheme 1.

Steps **1**–**4** are generally agreed and are consistent with the accepted kinetics and the rate expression[5]

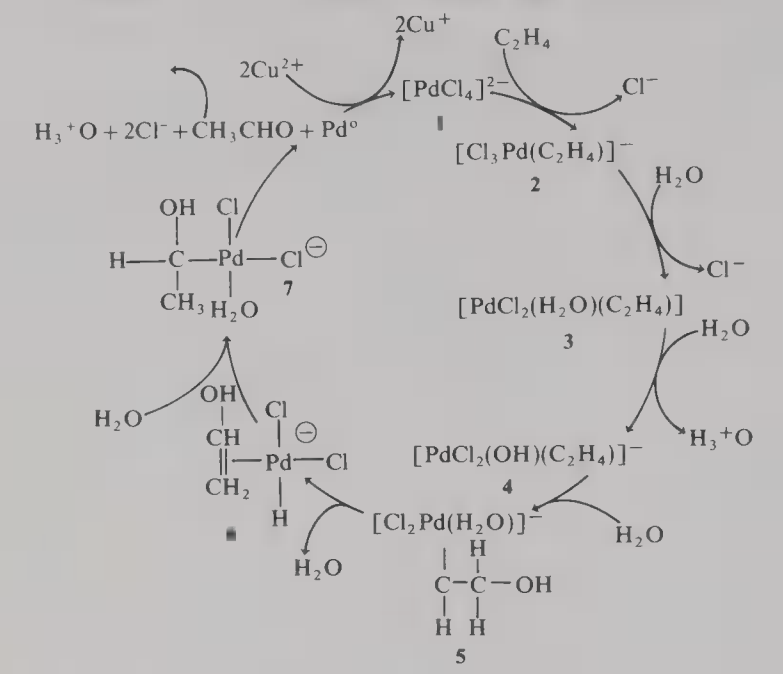
$$-\frac{d[C_2H_4]}{dt} = \frac{k^1K_1[PdCl_4^{2-}][C_2H_4]}{[H^+][Cl^-]^2} \quad (4)$$

Formation of **5**, the hydroxyethyl palladium intermediate, may occur by a *cis*-addition of OH^- from within the palladium coordination sphere, again in agreement with the kinetics, as shown in Eq. (5):

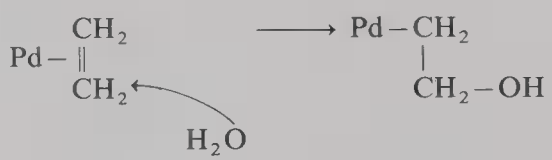
$$\begin{array}{l} Pd-CH_2 \\ | \quad \| \\ OH \quad CH_2 \end{array} \longrightarrow \begin{array}{l} Pd-CH_2 \\ \quad | \\ HO-CH_2 \end{array} \quad (5)$$

* Named after the firm (Wacker Chemie GmbH) where it was first developed.

SCHEME 1

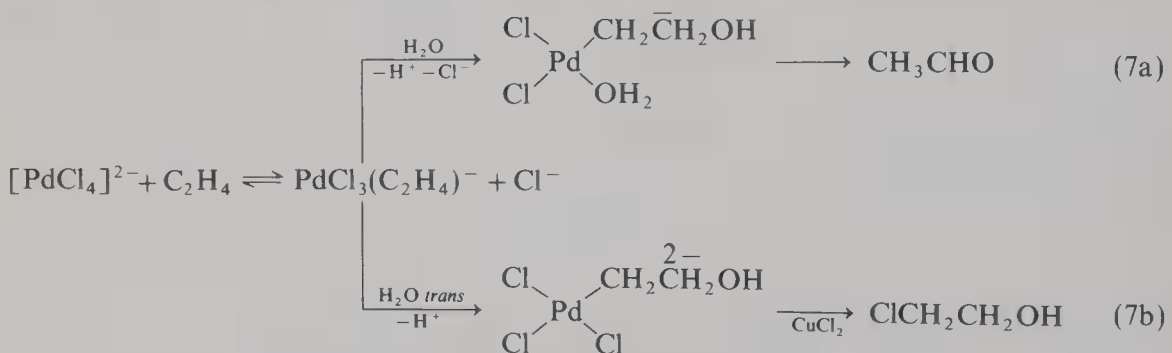


However, studies of the stereochemistry[6,7] using *cis*- and *trans*-CHD=CHD indicate that *trans*-addition by an external nucleophile, as shown in Eq. (6), is also possible:



(6)

More recent studies by Henry and Gragor[8] show that the conditions used in these stereochemical studies, that is high chloride ion concentrations, may lead to an alternative reaction path. They suggest two paths, one of which leads to aldehyde, the other leading to chlorohydrins, thus giving some explanation of the formation of chlorinated side products at high Cl^- concentrations:



(7a)

(7b)

Steps **5**–**7** agree with the observation that when the reaction is carried out in D_2O no deuterium appears in the product. This shows that all the hydrogen in the product must come from ethylene.

The vinyl alcohol π-complex, intermediate **6**, seems a reasonable intermediate since vinyl alcohol complexes of platinum are well known.[9]

Palladium(II) salts, although preferred, are not the only catalysts for oxidizing ethylene in water; other noble metal compounds such as the hydrates of $RhCl_3$, $IrCl_3$, or $RuCl_3$ and Pt^{II} salts have also been reported to be active. Of those platinum(II) salts are the best.

2.2. Oxidation of Ethylene in Acetic Acid

A wide variety of products can be obtained from the oxidation of alkenes in acetic acid. For example, the following products [Eqs. (8)–(11)] are all formed when ethylene is oxidized; small changes in reaction conditions can cause any one of them to predominate.

The list shows the major reaction products only.

$$C_2H_4 + PdCl_2 \xrightarrow{AcOH} CH_2{=}CHOAc \quad (8)$$

$$C_2H_4 + PdCl_2 \xrightarrow[CuCl_2]{AcOH,\ LiOAc} ClCH_2CH_2OAc \quad (9)$$

$$C_2H_4 + PdCl_2 \xrightarrow[CuCl_2]{AcOH,\ NaOAc} AcOCH_2CH_2OAc \quad (10)$$

$$C_2H_4 + PdCl_2 \xrightarrow[LiNO_3]{AcOH} HOCH_2CH_2OAc \quad (11)$$

Where no added reoxidant is used, as in (8), Moiseev and co-workers[10] found that the oxidation of ethylene with palladium chloride in acetic acid containing some sodium acetate gave vinyl acetate as the main product together with some ethylidene diacetate:

$$PdCl_2 + C_2H_4 + NaOAc \longrightarrow CH_2{=}CHOAc + CH_3CH(OAc)_2 \quad (12)$$

Experiments with deuterium labeling[11] have shown that ethylidene diacetate is a primary product; under some conditions it can be up to 50% of the total.

Secondary products are acetaldehyde and acetic anhydride, which can result from the palladium(II) catalyzed decomposition of vinyl acetate:

$$CH_2{=}CHOAc + AcOH \xrightarrow{Pd^{2+}} CH_3CHO + Ac_2O$$

It is generally agreed that the oxidation of ethylene to vinyl acetate occurs via an oxypalladation intermediate, represented as **8** similar to that found in aqueous media:

$$C_2H_4 + Pd(II) + AcO^- \longrightarrow \underset{\mathbf{8}}{L_2XPd^{II}CH_2CH_2OAc} \xrightarrow{-HPd^{II}} CH_2{=}CHOAc$$

Vinyl acetate is then formed when the oxypalladation adduct **8** decomposes to eliminate Pd(II)-hydride which, being unstable, gives Pd^0 and H^+.

Ethylidene diacetate can also result from the oxypalladation intermediate **8**:

$$\mathbf{8} \longrightarrow Me{-}\underset{\displaystyle Pd}{\underset{|}{CH}}{-}OAc \xrightarrow{OAc^-} CH_3CH(OAc)_2 \quad (13)$$

This reaction is faster with added reoxidant.

Initially it was hoped to make the homogeneous production of vinyl acetate a commer-

cial process by the addition of reoxidants such as $CuCl_2$. In addition to the serious corrosion problems resulting from the use of chloride, it was found that 1,2-disubstituted esters were substantial products of this reaction[12]:

$$C_2H_4 + PdCl_2 + CuCl_2 \xrightarrow{AcOH} \begin{matrix} CH_2{=}CHOAc,\ MeCH(OAc)_2 \\ ClCH_2CH_2OAc,\ AcOCH_2CH_2OAc \\ HOCH_2CH_2OAc \end{matrix}$$

Although all the variables affecting the product ratios have not been determined, it is known that chloride ion concentration is very important.[12,13] Chloride is probably needed to keep the oxidation potentials down and also to solublize Cu(II). As the chloride concentration is increased the relative amount of saturated esters increases and the yield of vinyl acetate can even be negligible at high chloride concentration.

The yield of vinyl acetate can be increased by increasing the temperature or by using mixed solvents, acetic acid–*N*,*N*-dimethylacetamide, for example.[13] Addition of complexing agents such as dimethyl formamide, dimethyl sulfoxide alkyl and aryl nitriles, trialkylamines, or esters reduces the rate of decomposition of vinyl acetate to acetaldehyde and acetic anhydride.

The added reoxidant must act by causing the oxypalladium adduct **8** to decompose in a different manner [Eq. (14)].

$$L_2XPd^{II}CH_2CH_2OAc \quad (\mathbf{8}) \quad \begin{matrix} \xrightarrow{-HPd^{II}} CH_2{=}CHOAc \\ \xrightarrow{\text{reoxidant}} \begin{matrix} AcOCH_2CH_2OAc \\ ClCH_2CH_2OAc \\ HOCH_2CH_2OAc \end{matrix} \end{matrix} \qquad \text{Competing reactions} \qquad (14)$$

It is suggested[14] that the reoxidant (e.g., $CuCl_2$) interacts with palladium(II) by removing electrons as the Pd^{II}–carbon bond is breaking, creating a carbonium ion center [Eq. (15)] and aiding the attack of a nucleophile:

$$\text{Oxidant}\text{----}Cl\text{–}Pd(II)\text{----}\overset{+}{C}H_2CH_2OAc \qquad (15)$$

$$X^-$$

For longer-chain alkenes the product distributions are much more complex and not so readily explained (see Section 1.5).

Commercially vinyl acetate is an attractive product, but, as can be seen, a simple Wacker-type homogeneous system is not possible owing to the complicated product mixtures that occur. For these reasons vapor phase heterogeneous processes have been developed; a typical example uses Pd^0 or Pd(II) and KOAc on carbon and a gas stream of ethylene, oxygen and acetic acid at 120°C.

2.3. Oxidation of Ethylene in Alcohols

The oxidation of ethylene by palladium(II) in alcohols was also first reported by Moiseev[10]:

$$C_2H_4 + ROH \xrightarrow{PdCl_2} CH_2{=}CHOR + CH_3CH(OR)_2 \qquad (16)$$

Unlike the oxidation in acetic acid, where vinyl acetate is the major product, the product is almost exclusively $CH_3CH(OMe)_2$ with very small amounts of methyl vinyl ether. The reaction is complicated by the fact that the alcohol solvent can also be oxidized by palladium(II) salts to give carbonyl compounds (see Section 5.1), which can react to give acetals. In the case of ethylene in ethanol 15% of the 1,1-diethoxyethane product was shown by deuterium labeling to come from the ethanol.

Similarly to the previously described reactions in water and acetic acid, the reaction goes via an oxypalladation intermediate. However, as before, it is not clear whether the adduct is formed by *cis*- or *trans*-alkoxypalladation. Two routes of decomposition have been proposed. In one,

$$L_2XPdCH_2CH_2OMe \longrightarrow \underset{\underset{LXPdH}{|}}{CH_2{=}CHOMe} \longrightarrow \underset{\underset{L_2PdX}{|}}{CH_3{-}CH{-}OMe} \xrightarrow{+OMe^-} CH_3{-}CH(OMe)_2 + Pd^0 + X^- + 2L \qquad (17)$$

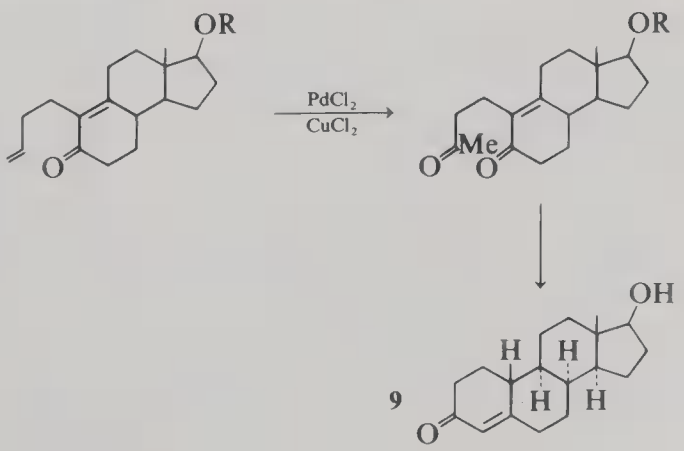
Pd(II) moves to the α-carbon and then leaves as palladium(0); alternatively, the ylidic σ-bonded form of the π-bonded vinyl methyl ether is attacked by methanol:

$$\underset{\underset{LXPdH}{|}}{CH_2{=}CHOMe} \longrightarrow \underset{\underset{H}{|}}{Pd{-}CH_2{-}\overset{\overset{Me}{O^{\oplus}}}{\overset{\|}{C}}H} \xrightarrow{OMe^-} \underset{\underset{H}{|}}{Pd{-}CH_2CH(OMe)_2} \longrightarrow CH_3CH(OMe)_2 + Pd^0 \qquad (18)$$

Unlike the oxidations in water and acetic acid, no commercial process has been developed using the oxidation of olefins in alcohols, although many patents cover the subject.

2.4. Oxidation of Higher Olefins in Water

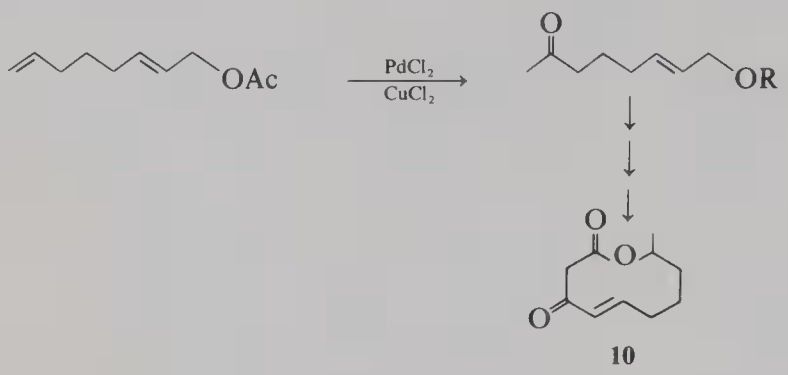
As might be expected, α-olefins react to give methyl ketones and aldehydes, with the methyl ketones usually being the major products. The ratio of aldehyde to ketone can be significantly varied; for example,[15] propylene gives 2% propionaldehyde when PdF_2 is used



9

in 0.9 *M* HF solution and 20% propionaldehyde when K_2PdCl_4 in 1 *M* HCl solution is the oxidant. In each case the remainder is acetone.

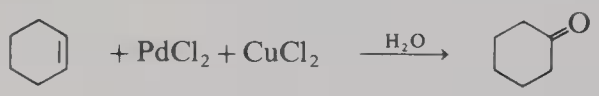
This reaction is relatively general and under suitable conditions has been used as an important step in synthesis of molecules such as (+)-19-nortestosterone[16] (**9**) and diplodialidine B(7)[17] (**10**).



10

Internal olefins give ketones only, while α-olefins with a secondary alkyl substituent give allylic alcohols and allylic aldehydes,[18] the aldehydes resulting from further oxidation of the alcohol.

Cyclic olefins give cyclic ketones:



(19)

α,β-Unsaturated acids, esters, and amides all give the same product by virtue of the rapid hydrolysis of the esters and amides. The products are carbonyl compounds from oxidation followed by decarbonylation:

$$RCH{=}CHCO_2H \xrightarrow[CuCl_2,\,H_2O]{PdCl_2} RCHCCO_2H \xrightarrow{-CO_2} RCH_2CHO \qquad (20)$$

Allylic alcohols give unsaturated aldehydes and ketones, the reaction going via normal oxidation to a β-hydroxy carbonyl followed by dehydration:

$$RCH{=}CHCH_2OH \xrightarrow[CuCl_2,\,H_2O]{PdCl_2} RCCH_2CH_2OH \xrightarrow{-H_2O} RCCH{=}CH_2 \qquad (21)$$

Olefins with electron withdrawing groups (X) give aldehydes:

$$XCH{=}CH_2 \xrightarrow[CuCl_2,\,H_2O]{PdCl_2} XCH_2CHO \qquad (X = CN,\ NO_2) \qquad (22)$$

For practical purposes the main difficulty in oxidizing higher olefins is the lack of solubility in the aqueous phase. Many mixed solvent systems have been tried in an attempt to improve this; the best so far seems to be an aqueous sulfolane system.[19] Yields can also be

increased by carrying out a preliminary oxymetallation reaction between the olefin and a mercury(II) salt,[20] e.g., $Hg(OAc)_2$. The oxymercurial formed then reacts with palladium(II) to give the oxidation product:

$$RCH=CH_2 + Hg(OAc)_2 + H_2O \longrightarrow \underset{\displaystyle \downarrow \; PdCl_2, CuCl_2, H_2O}{\overset{\displaystyle OH}{\overset{|}{RCH}}-CH_2HgOAc} + HOAc \qquad (23)$$

$$\underset{\displaystyle O}{\overset{\displaystyle \|}{RCCH_3}}$$

2.5. Oxidation of Higher Olefins in Acetic Acid

As previously indicated, product distributions for higher olefin oxidation in acetic acid are very complex. As with ethylene, the presence of added reoxidant allows the formation of saturated esters, glycols, and, where $CuCl_2$ is used, chloro-esters. However, isomerization of the oxypalladation intermediate allows for an even wider range of products, if we take but-1-ene as an example[12] (Table I).

Another interesting example is cyclohexene, which in the absence of reoxidant gives only benzene and cyclohexane by disproportionation.[21] Oxidation in the presence of $PdCl_2$ and $CuCl_2$ gave 2-cyclohexen-1-yl acetate and 3-cyclohexen-1-yl acetate as well as possible positional isomers (1,2, 1,3, and 1,4) but no 1-cyclohexen-1-yl acetate.[22,23]

Generally the addition of NaOAc has a marked effect on product distributions. For example for propene:

Propene $\xrightarrow[NaOAc, HOAc]{PdCl_2}$	*iso*-propenyl acetate	44%
	allyl acetate	3%
	trans-propenyl acetate	17%
$\xrightarrow[HOAc]{PdCl_2}$	*iso*-propenyl acetate	98.6%

A similar effect is observed with 1-hexene.[26,27]

2.6. Oxidation of Higher Olefins in Alcohols

As with ethylene, oxidation of higher olefins in alcohols can give complex product distributions; unfortunately, product distributions reported by different workers for the same reaction show wide variations due to small differences in reaction conditions.

In general, if small amounts of water are present, ketones are formed. Carbonyl compounds are also formed when an hydroxy-mercuration/$PdCl_2$ method similar to that discussed above is used.[28] Here it seems that carbonyls are produced from the hydrolysis of acetals during the aqueous work-up.

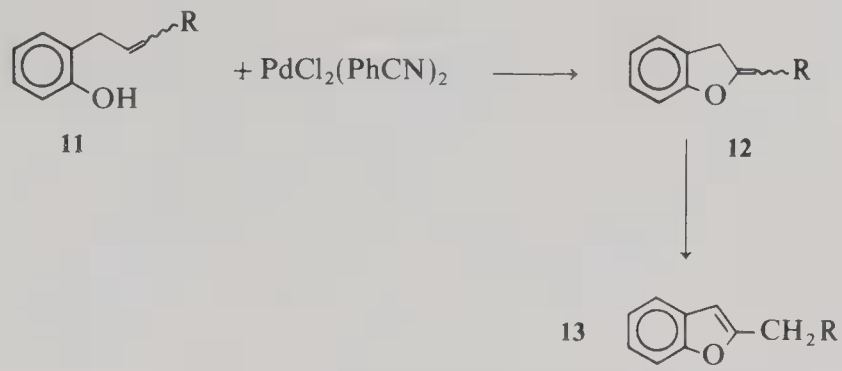
If glycolic solvents are used the products are dioxolanes.[29] Again an oxymercuration procedure can be used.

Interesting reactions involving alcoholic and olefinic groups in the same molecule have been noted, for example, the formation of **12** and **13** from **11**[30]:

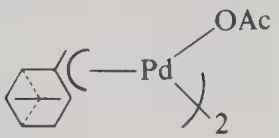
TABLE I. Oxidation of But-1-ene in Acetic Acid—Product Distribution

Starting material	Oxypalladation adduct[a]	Product with reoxidant[a]		Product without reoxidant	
$CH_2=CHCH_2CH_3$	$CH_3CH_2\underset{\displaystyle OAc}{\underset{\vert}{C}}HCH_2PdX$	$CH_3CH_2\underset{\displaystyle OAc}{\underset{\vert}{C}}HCH_2X$	89%	$CH_3CH_2\underset{\displaystyle OAc}{\underset{\vert}{C}}=CH_2$	80%
	$CH_3CH_2\underset{\displaystyle PdX}{\underset{\vert}{C}}HCH_2OAc$	$CH_3CH_2\underset{\displaystyle X}{\underset{\vert}{C}}HCH_2OAc$		$CH_3CH_2=CHOAc$	9%
	$CH_3\underset{\displaystyle PdX}{\underset{\vert}{C}}HCH_2CH_2OAc$	$CH_3\underset{\displaystyle X}{\underset{\vert}{C}}HCH_2CH_2OAc$	9%	$CH_3CH=CHCH_2OAc$	9%
				$CH_3CH=CHCH_2OAc$	
				$CH_2=CHCH_2CH_2OAc$	
	$CH_2CH_2CH_2CH_2OAc$ (PdX)	$CH_2CH_2CH_2CH_2OAc$ (X)	2%	$CH_2=CHCH_2CH_2OAc$	

[a] X^- is a nucleophile, e.g., ^-OH, ^-OAc, Cl^-.

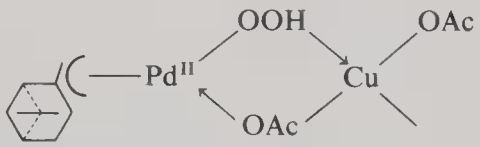


When isomerization cannot occur, only the exo product **12** is formed. A more recent study of oxidative cyclization of 2-allyl phenols[31] shows that asymmetric cyclization of these compounds to give optically active 2,3-dihydrobenzofurans can be achieved using chiral palladium(II) complexes such as (+)-(η^3-pinenyl)palladium(II) acetate (**14**).



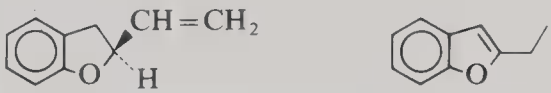
14

The reaction is carried out in the presence of copper(II), preferably $Cu(OAc)_2$, and oxygen. The results suggested a mechanism in which Pd(II) does not change its formal oxidation state and the active catalyst is most likely a hydroperoxopalladium(II)–copper(II) species, e.g., **15**:



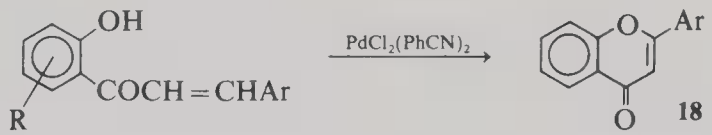
15

The experimental procedure to make (**16**) and (**17**) is described by Hosokawa *et al.* (Section 5.3)[31]:



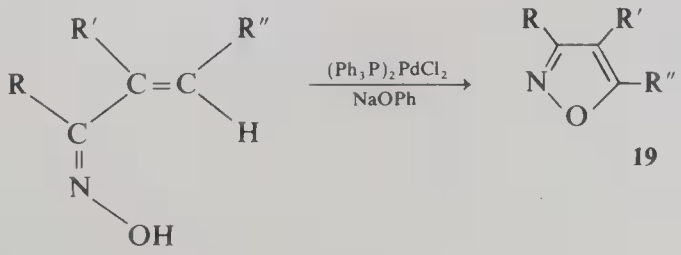
(S)(+) **16** **17**

Another reaction is the formation of flavones[32] (**18**):



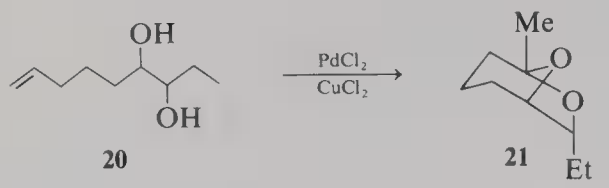
18

Also of interest is the formation of isoxazoles[33] (**19**) from α,β-unsaturated ketoximes:



19

In this reaction the reactants are refluxed in benzene for 8 h and the reduced palladium is removed by filtration. Glycolic groups have also been found to cyclize, for example[34] **20** to **21**:



20 **21**

3. VINYLIC SUBSTITUTION REACTIONS

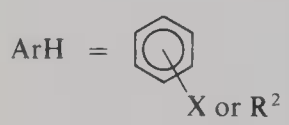
This is a useful reaction as palladium(II) can cause the formation of new C–C bonds by oxidation.

3.1. Olefin Arylation

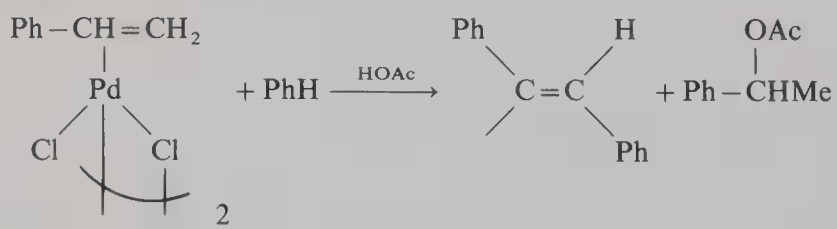
Equation (24) gives the general reaction which is known as olefin arylation:

$$R^1CH=CH_2 + ArH \longrightarrow R^1CH=CHAr \tag{24}$$

where



This was first discovered independently by Heck[35] and Moritani.[36,37] It was found that the $[Pd_2Cl_4(styrene)_2]$ π-complex reacted in a benzene–acetic acid solvent to give *trans*-stilbene and some 1-acetoxyethylbenzene:



(25)

The 1-acetoxyethylbenzene arises from a nonoxidative reaction with acetic acid which can be eliminated by using palladium(II) acetate or adding NaOAc.[38]

This reaction has been found to be effective for many different olefins and aryl groups. For example, benzene and ethylene give styrene and stilbene[39]:

$$C_2H_4 + C_6H_6 \xrightarrow[AcOH]{Pd(OAc)_2} H_2C=CPhH + PhCH=CHPh$$

whereas substituted olefins give only styrene derivatives[40] and some unsaturated esters and no stilbene derivatives. Olefins with electron with drawing groups (X) undergo arylation at the unsubstituted carbon[41]:

$$XHC=CH_2 \xrightarrow[AcOH]{Pd(OAc)_2} CH_2=CHPh$$

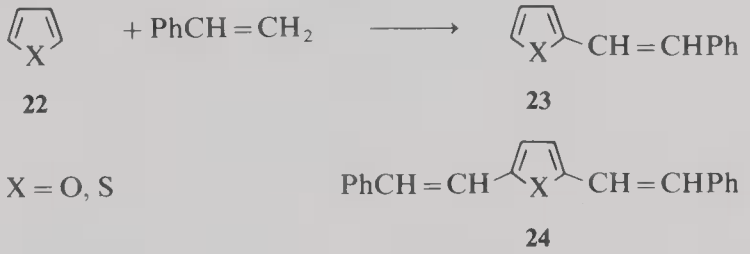
TABLE II. Olefin Arylation—Variation of Product Distribution with Aromatic Substituent

	Products *trans*-$XC_6H_4CH=CHPh$		
Substrates XPh	*o*-	*m*-	*p*-
C_6H_5OMe	30%	5%	48%
$C_6H_5NO_2$	4%	29%	4%

Substituted benzenes give stilbenes of *ortho*-, *meta*-, and *para*-orientation depending on the substituent (Table II):

$$CH_2=CHPh + X-Ph \longrightarrow \text{trans-}XC_6H_4CH=CHPh$$

Heterocyclic five-membered ring compounds react to give both mono- and di-olefin products[42]; for example, **22** gives **23** and **24**:



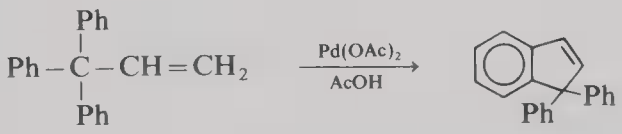
22 **23** **24**

Cyclic olefins lead to a mixture of positional isomers in the product.[43] For example, cyclooctene gave **25–28** with benzene:

6% 8% 12% 2%

25 **26** **27** **28**

Olefin arylation can also occur internally[44] and **30** can be made from **29**:



29 **30**

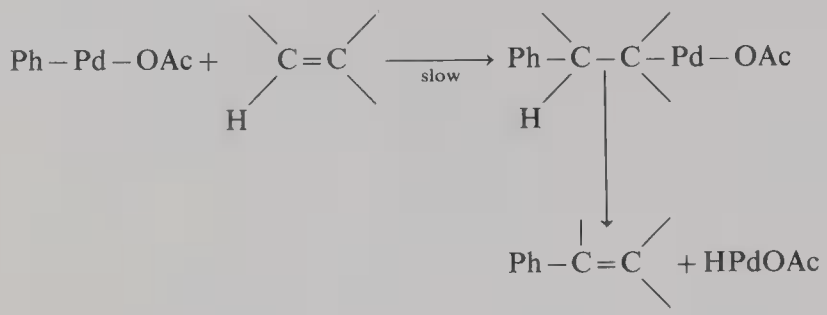
Olefin arylations can be performed catalytically using $Pd(OAc)_2$ under an oxygen atmosphere in the presence of $Cu(OAc)_2$ or Ag(OAc).

3.1.1. Mechanisms

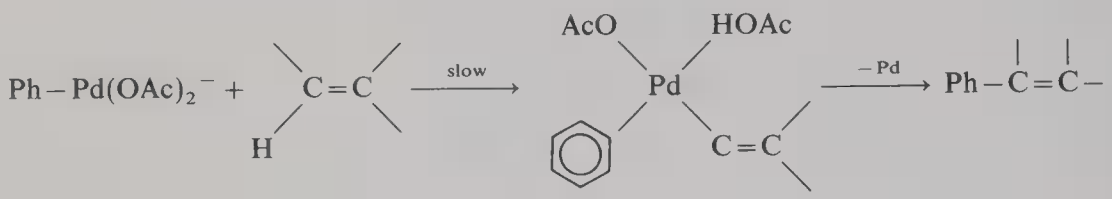
Two mechanisms have been proposed for olefin arylation, the aryl palladation and the vinylic mechanism.

(i) Aryl palladation[39]:

$$PhH + Pd(OAc)_2 \rightleftharpoons Ph-Pd-OAc + HOAc$$



(ii) Vinylic mechanism:



Evidence has been produced for both mechanisms, but on balance the aryl palladation pathway seems to be the most likely.[45]

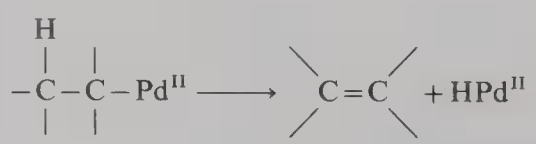
3.2. The Heck Reaction

The Heck reaction is a synthetically useful variation on olefin arylation which uses main group organometallics, principally mercurials, to prepare organic complexes of palladium (II) *in situ*, which can then be used to substitute for vinylic hydrogen in olefins. A simple example is the reaction between phenylmercuric chloride and ethylene in the presence of a palladium(II) salt:

$$PhHgCl + C_2H_4 + Li_2PdCl_4 \longrightarrow CH_2=CHPh + Pd^0 + HgCl_2 + 2LiCl + HCl \qquad (26)$$

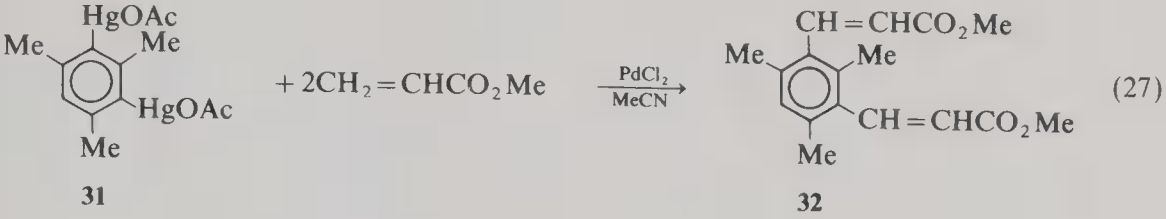
Unlike the palladium-only arylation system, there is little doubt that this reaction goes by the aryl palladation mechanism involving *cis*-addition of R – Pd – X and *cis*-elimination of H – Pd – X.

This reaction extends to substitution by any organic group which does not contain a β-hydrogen. Groups with β-hydrogen cannot be used since rapid Pd(II) hydride elimination to give olefin prevents formation of the organopalladium intermediate:



The advantages in synthesis of this method are that the reaction goes more readily, often

specifically. Mercurated compounds can be used to prepare specifically substituted products; dimercurated materials can also be used to prepare disubstituted products, for example,

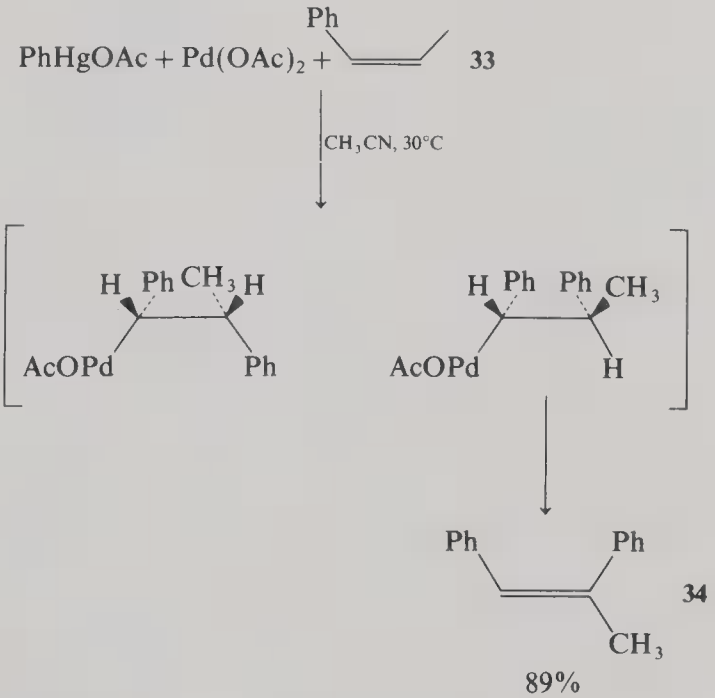


31 **32** (27)

The following solvents have been used in the Heck reaction: methanol, ethanol, acetone, acetonitrile, and acetic acid. The reaction can be made catalytic in palladium by using $Fe(NO_3)_3$, $Hg(NO_3)_2$, $Hg(OAc)_2$, or $CuCl_2$ as reoxidants in the presence of air. If $CuCl_2$ is used, saturated chlorides are formed which can be made the main products by suitable variations in conditions. For example, phenyl mercuric chloride gives β-chloroethylbenzene.[46] This reaction is related to the formation of β-chloroethyl derivatives (see Section 2).

The phenylation of cyclic olefins by this method gives all isomers except the 1-aryl-1-olefin isomer.

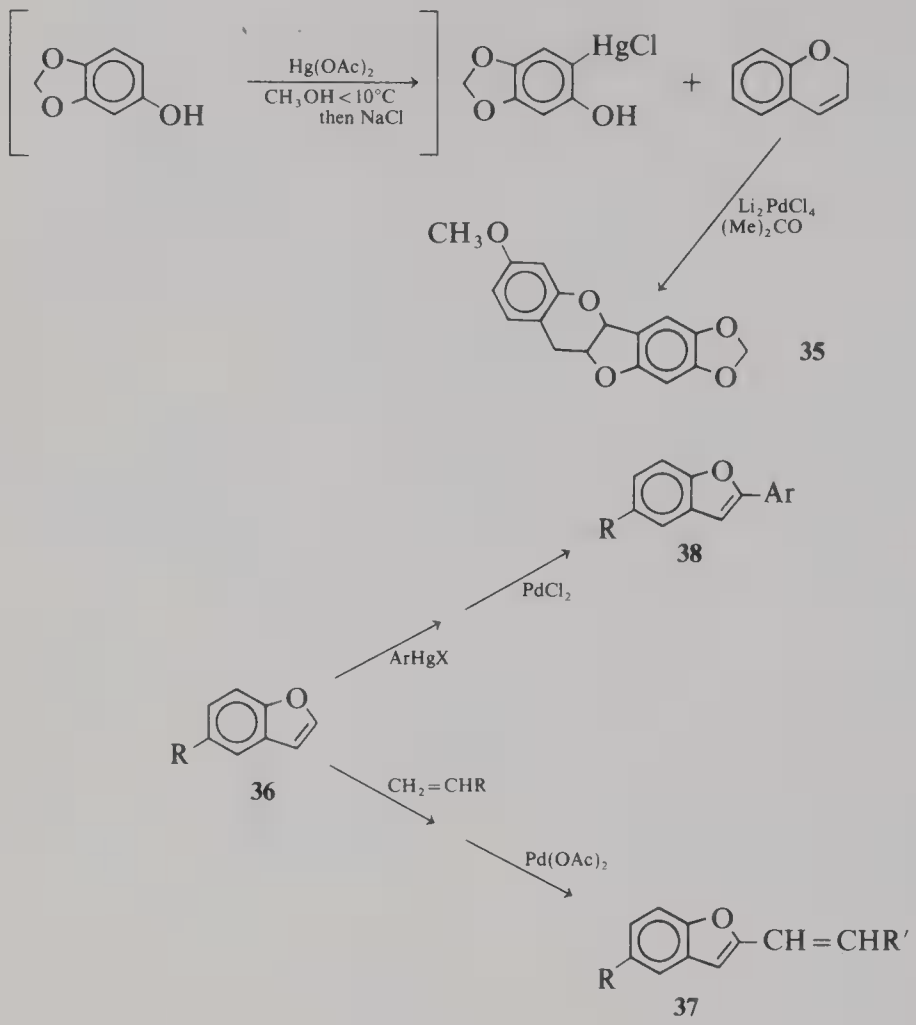
The Heck reaction has been utilized in many useful synthetic reactions. For example, *Z*-1-phenylpropene (**33**) is converted into *Z*-1,2-diphenylprop-1-ene (**34**),[47] showing a formal inversion of stereochemistry:



Likewise *E*-1-phenylpropene goes to *E*-1,2-diphenylprop-1-ene. The stereochemistry is inverted by virtue of the *cis*-addition of Ph – PdOAc and the *cis*-elimination of H – PdOAc.

An efficient synthesis of pterocarpin[48] (**35**) uses this method. This also illustrates an intramolecular trapping of the σ-palladium intermediate resulting in cyclization.

Another interesting example is the reaction of benzo(b)furan (**36**), which can react either as the arene to give **37**[49,50] or as the olefin to give **38**.

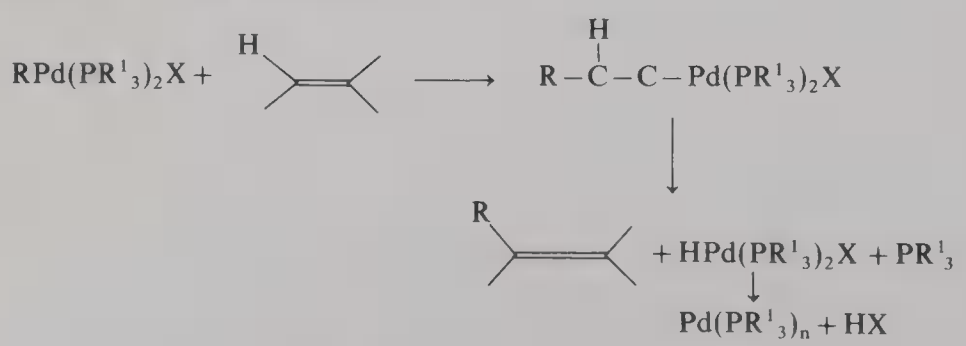


A disadvantage of the Heck reaction is that many of the main group organometallics needed for use as starting materials are inaccessible and even when available must be used in stoichiometric quantities.

Another interesting and useful method has been developed which overcomes these problems but is closely related to the original Heck reaction. This involves the preparation of organopalladium complexes from organic halides[51,52,53] and palladium(O) phosphine complexes instead of from organic mercurials and Pd(II) compounds:

$$RX + Pd(PR^1_3)_n \longrightarrow RPd(PR^1_3)_2X + (n-2)\,PR^1_3$$

The reaction then formally proceeds as shown:



(28)

The system is made catalytic by the addition of base to remove HX from the final equilibrium; usually triethyl- or tri-*n*-butyl-amine is used.

As before the method can only be applied to organic precursors with no β-hydrogen, i.e., aryl, heterocyclic, benzylic, or vinylic halides. The following generalizations can be applied to the reaction:

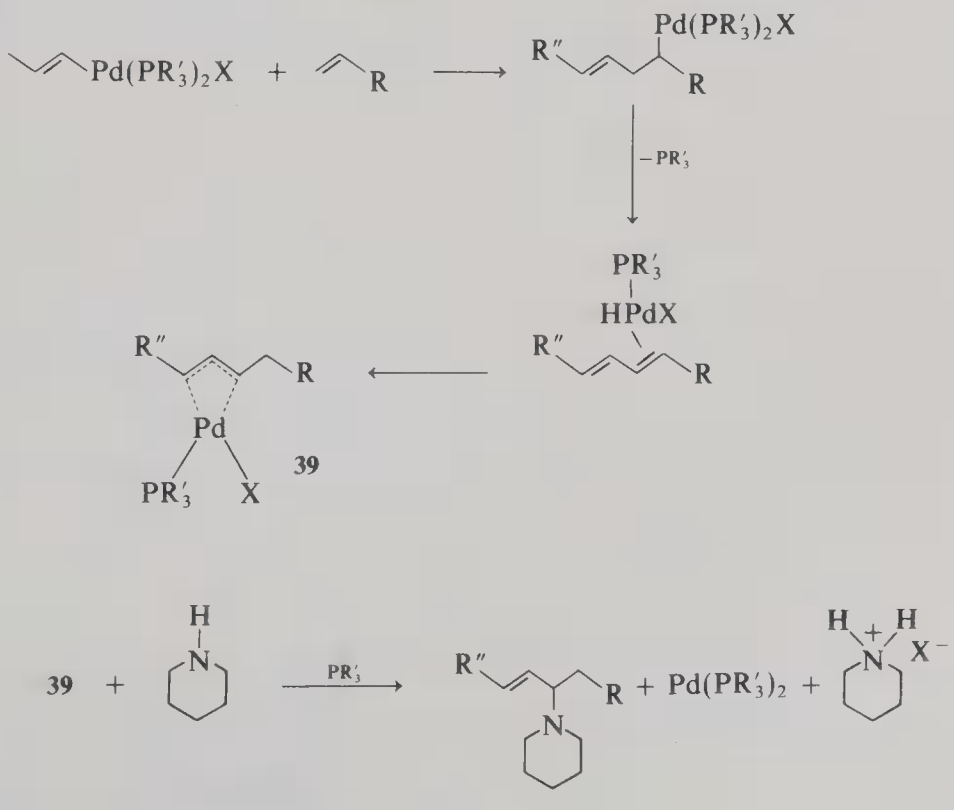
(i) The organic group of RX adds predominantly to the least substituted carbon of the double bond; addition to the other carbon occurs only if steric factors are similar.

(ii) The reaction is stereospecific for 1,2-disubstituted alkenes, proceeding by a *cis*-addition, *cis*-elimination sequence. If there is a choice of hydrogens for elimination, the most stable products are preferred and the most hydridic hydrogen tends to be lost.

(iii) Generally, organic bromides do not undergo the reaction well unless the catalyst is a triarylphosphine or secondary amine complex. Organic iodides do not require the phosphine or secondary amine. Organic chlorides do not undergo the reaction under the usual conditions.

In some cases special variations are needed. For example, the nature of the triarylphosphine in $Pd(PAr_3)_n$ is not usually critical except in reactions of aryl bromides possessing strong electron-donating groups, where tetraarylphosphonium bromides are rapidly formed in a side reaction causing decomposition of the catalyst to inactive Pd^0. This can be overcome by using sterically hindered tri-*o*-tolylphosphine. In most reactions the phosphine required is usually at a level of two equivalents per palladium.

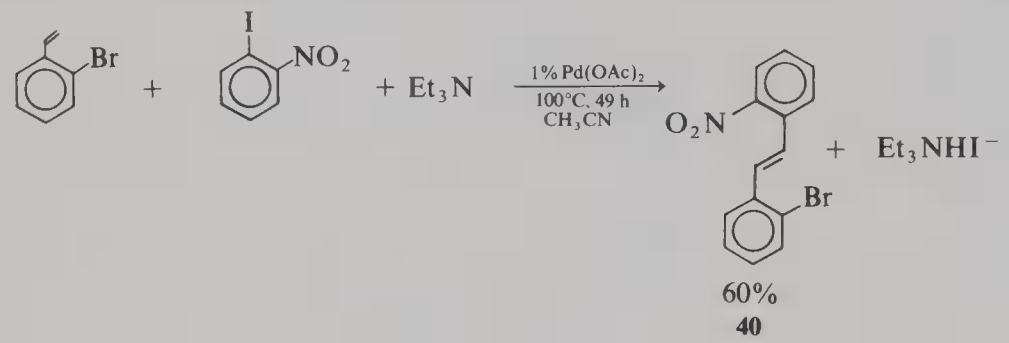
Another variation on the method can be used to extend this type of reaction to olefins without an activating carboxyl. A deviation from the usual conditions is necessary because substitution, by this method, into olefins $CH_2=CHR$, where R is not an activating carboxyl or nitrile, is very slow. This is because the newly formed adduct between the vinylpalladium halide and olefin undergoes β-elimination and the hydride adds back on to the newly formed double bond to give an allyl palladium derivative (**39**), whereas if an activating carbonyl or nitrile is present the α-hydrogen is acidic enough to be removed by a tertiary amine. When no activating group is present a more basic secondary amine is added which displaces the β-hydrogen to form a tertiary allylic amine and the palladium(O) triarylphosphine:



The amine function can then be removed by Hofmann elimination, hydrogenolysis, or a von Braun-type reaction.

These reactions can have very wide applications; the following reactions (which use approximately one mole per cent of catalyst) indicate the range.

(i) To illustrate the selective use of iodo and bromo organics to give highly specific reactions[52]; 2-bromostyrene and 2-iodonitrobenzene react with palladium acetate catalyst to form only *E*-2-bromo-2′-nitrostilbene (**40**).

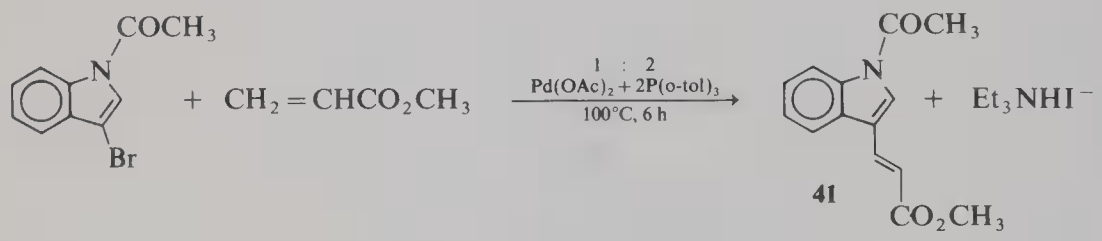


60%

40

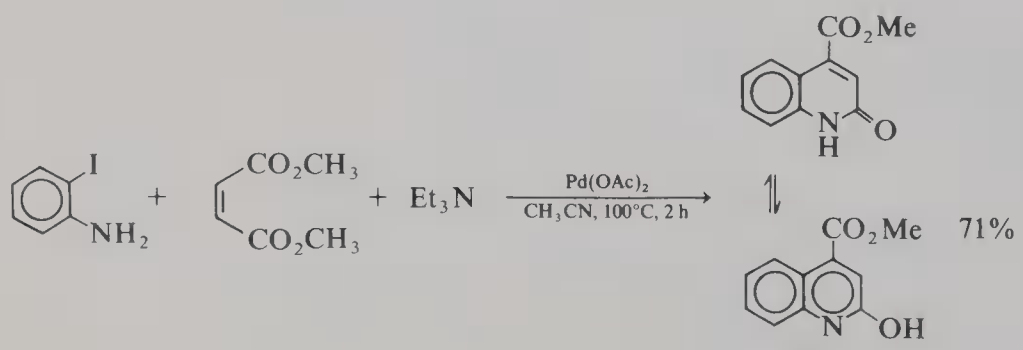
In the absence of triphenylphosphine only the organic iodide is active. Similarly 4-bromoiodobenzene and methyl acrylate in the presence of $Pd(OAc)_2$ form *E*-methyl-*p*-bromocinnamate in 76% yield.

(ii) Heterocyclic halide compounds may also be used[54] for example to form (**41**):



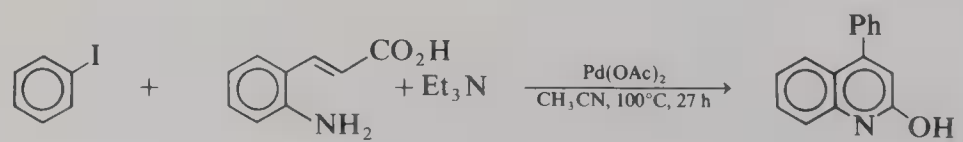
41

(iii) Heterocyclic rings, e.g., **42** or **43**, can be formed from the appropriate 2-substituted vinylic or aryl-halides[155]:



42

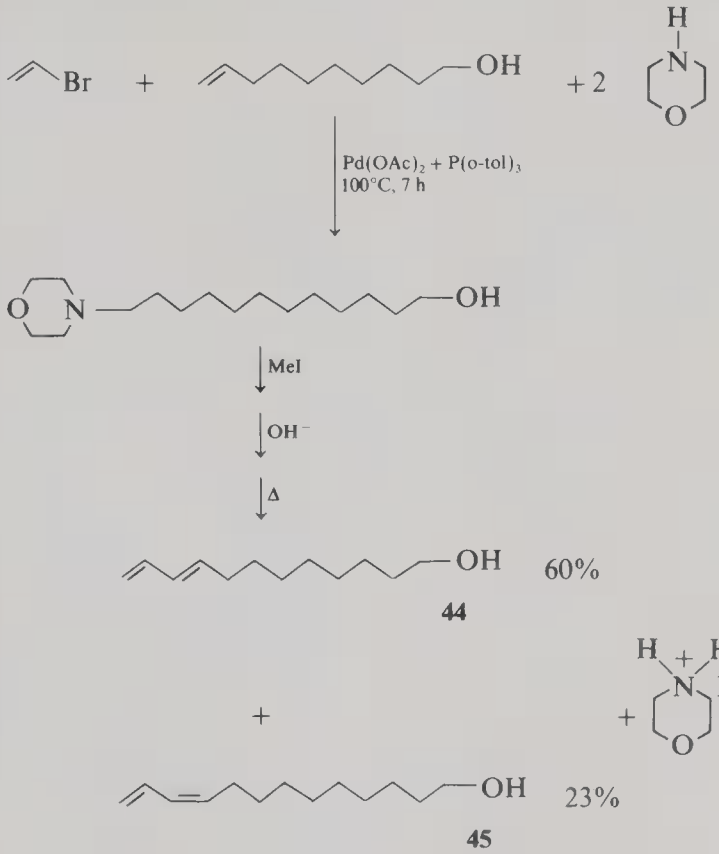
+ MeOH + Et_3NHI



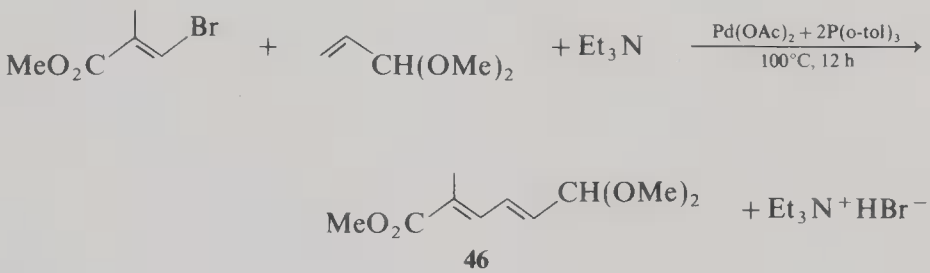
43

+ H_2O + $Et_3NH^+I^-$

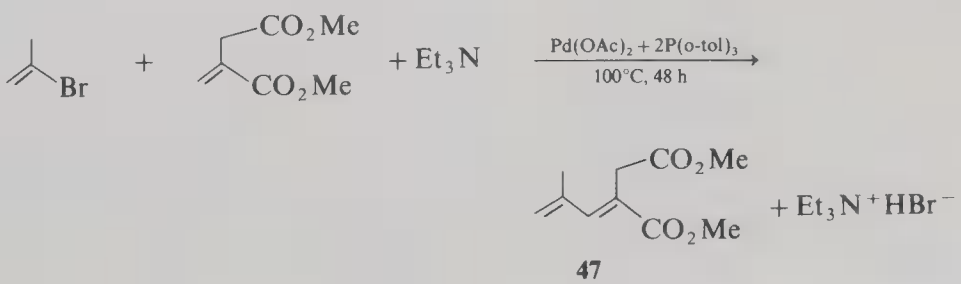
(iv) An example that illustrates the use of a secondary amine to allow the inclusion of olefins with no activating group is[53] the formation of the 12-hydroxydecadienes (**44**) and (**45**):



(v) Recent work by Heck gives a convenient synthesis of conjugated dienals.[56] For example,



(vi) Another extension of this reaction gives 2,4-dienoic acid derivatives,[57] for example **47**:



In summary the advantages of the vinylic substitution reaction using organic halides are

(i) The reaction can usually be achieved in one step.

(ii) The reaction occurs under mild conditions and is not affected by water or air. (Inert atmosphere is preferred where phosphines are used.)
(iii) The reaction is regioselective and stereospecific.
(iv) The reaction is tolerant of almost every function (see Section 5.1).

4. AROMATIC SUBSTITUTION REACTIONS

4.1. Arene Coupling and Related Reactions

The oxidative coupling of aromatic compounds under the influence of Pd^{II} was first reorted by Van Helden and Verberg[58] in 1965 who found that biaryls were formed in acetic acid:

$$2ArH + Pd^{II} \longrightarrow Ar-Ar + Pd^{0} + 2H^{+} \tag{29}$$

In general[59] it has been found that aromatics treated with $PdCl_2$ and NaOAc in acetic acid give biaryls in yields of between 25% and 81% [based on Pd(II)] depending on the starting material. Reaction does not occur in the absence of NaOAc. If palladium acetate is used acetoxylations of the side chains and ring also occur,[60,61,62] but in this reaction the addition of $HClO_4$ increases the yield of coupled products by suppressing acetoxylation.[60,62] The percentage acetoxylation can be increased by the addition of alkali metal acetates.[62]

The overall yield of coupled products also varies with the form of Pd(II) used. $Pd(OAc)_2$ in acetic acid and $PdCl_2$ with NaOAc in acetic acid can lead to some acetoxylation as well as oxidative coupling. Palladium trifluoroacetate in trifluoroacetic acid[63,64] gives mainly coupled products with some phenols which arise from hydrolysis of aryltrifluoroacetates during the work-up procedure. However, in the strongly acidic media of trifluoroacetic acid or acetic acid/$HClO_4$ attack at the side-chain often occurs. For example phenyl(tolyl)methane is found in the reaction of toluene with $Pd(OAc)_2$ in acetic and $HClO_4$.[62] Neither palladium bromide nor iodide in acetic acid gave oxidatively coupled products with aromatics,[58] while palladium nitrate gives mainly acetoxylation and nitration products.[65]

Oxidative coupling is facilitated by the presence of electron-donating substituents and is retarded by electron-withdrawing substituents on the aromatic ring.[58] This is the same trend as that shown for aromatic electrophilic substitution. However, the isomer distribution from substituted aromatics shows an unusually high proportion of *meta*-substitution products even when the groups are *para*-directing. This distribution is unaffected by added metal salts and complexing agents but is strongly temperature dependent.[66] Steric effects are also very important in determining products. With mono-substituted benzenes all six biaryl isomers are produced, but the 2,2′-isomers are usually present in very small quantities, the main products being the 3,4′- and 4,4′-isomers.[59]

Aromatic heterocycles also undergo oxidative aromatic coupling under the influence of Pd(II), provided that they do not form inert complexes with Pd(II) through their heteroatoms. Restrictions on the range of coupling reactions undergone by these compounds result from the properties of individual classes of heterocycles; for example, furan derivatives undergo ring opening in aqueous mineral acids[67]; otherwise, the conditions for coupling heterocycles are similar to those used in other aromatic coupling (see Table III), but heterocyclic aromatics have a higher reactivity. Heterocycles can be coupled in a wide range of solvents such as acetic acid, DMF, and ethanol, as well as in mixed solvents and in basic aqueous media.[68,69]

The reactivity of 2-substituted furans decreases with substituent as follows: H, CH_3, CHO > COOMe, COOEt, $CH(OOCCH_3)_2$ > COOH. Furan and thiophen can be coupled together to give 2-(2′-furyl)-thiophen and a small amount of 3-(2′-furyl)thiophen.

TABLE III. Some Representative Examples of Arene Coupling Reactions

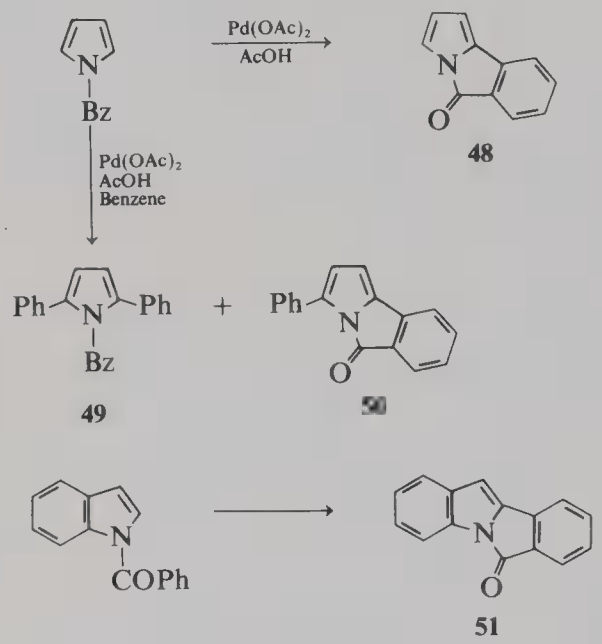
Arene	Solvent	Pd^{II} salt	Conditions	Products	Yield[a]	Selectivity	Reference
Benzene	NaOAc/AcOH	$PdCl_2$	90°C, 5.5 h	Biphenyl	71%	—	58
Toluene	AcOH/$HClO_4$	$Pd(OAc)_2$	50°C, 1.5 h	Bitolyl	37%	3,4′—34% 4,4′—42%	62 62
Toluene	AcOH/$HClO_4$/ $Hg(OAc)_2$	$Pd(OAc)_2$	25°C. 30 h	Bitolyl	95%	3,4′—27% 4,4′—67%	66
Furan	DMF	$Pd(OAc)_2$	96°C, 3 h	Bifuryl	98%	2,2′—90%	68
Thiophen + furan	AcOH	$Pd(OAc)_2$	35°C, 4 h	2-(2 Furyl)thiophen 3-(2 Furyl)thiophen Bithienyl Bifuryl	16% 4% 15% 9%		

Catalytic systems

Arene	Solvent	Oxidant	Conditions	Products	Turnover No.[b]	Selectivity	Reference
Furan	DMF	$Pd(OAc)_2/CuCl_2$	132°C, 6h	Bifuryl	90	2,2′—91%	69
Toluene	Toluene	$Pd(OAc)_2$[c]	150°C, 16 h	Bitolyls	206	3,3′—27% 3,4′—35% 4,4′—13%	81
Toluene	H_2O–HOAc	$Pd(OAc)_2$ $H_5PMo_{10}V_2O_{40}$	70°C, 2 h	Bitolyls	18	2,4′—21% 3,4′—31% 4,4′—22%	75

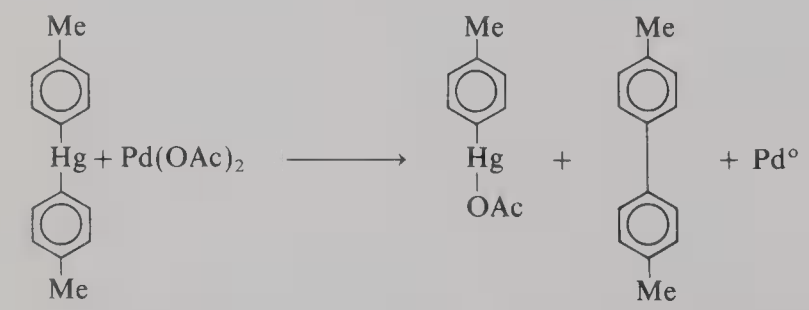
[a] Yield based on palladium.
[b] Palladium(II) turnover numbers.
[c] Reaction in the presence of acetylacetone under 150 atm $O_2:N_2 = 1:1$.

The use of oxidative coupling of pyrroles and indoles is a route to naturally occurring compounds,[70] such as 3,4,5-tribromo-2-(3,5-dibromo-2-hydroxyphenyl)pyrrole, which have previously been prepared by longer synthesis. It was found that 1-benzoylpyrrole in acetic acid with 1 equivalent of palladium acetate gave the ring closed compound **48** after refluxing for 14 h, but in the presence of benzene **49** (25%) and **50** (20%) were obtained. However, 1-benzoylindole gave only **51**:



48 49 50 51

Mercury(II) salts promote the coupling of arenes and of aromatic heterocycles. For example, in the coupling of thiophen, addition of mercury(II) increases the yield of bithienyls, while in the coupling of alkylbenzenes the addition of mercury(II) increases the amount of the 4,4′-isomer produced.[66] Electrophilic mercuration of the aromatic occurs more easily than palladation, and mercury, being larger, has a more marked preference for *para*-substitution. The aryl-mercury complex undergoes exchange with Pd(II) and the reaction then proceeds in the usual way. For instance, in the preparation of 4,4′-bitolyl the ideal Hg^{II}: Pd^{II} ratio is 2:1:



[1 mol] [0.5 mol] [1 mol] [0.5 mol] [0.5 g atom]

The rate of mercuration is increased on addition of a strong, noncomplexing acid; $HClO_4$ is often used. The use of Hg(II) is illustrated by the synthesis in Example 5 of Section 7, described by Unger and Fouty.[66]

In an attempt to achieve better stereochemical control, aryl iodides have been used in coupling reactions in basic media[71]:

$$2ArI \xrightarrow{\text{base/Pd}^{II}} Ar_2 \qquad (30)$$

Only catalytic amounts of $Pd(OAc)_2$ are then required. Coupling always occurs at the iodide position, but some iodine is lost. A typical reaction described by Norman[71] *et al.* is given in Example 6 of Section 7; however, the yields are depressed by the formation of an insoluble high molecular weight material, and, for mixed systems, the selectivity is only modest.

Some useful internal oxidative coupling reactions have also been found to occur, for example, **52** → **53**[72]:

52 **53**

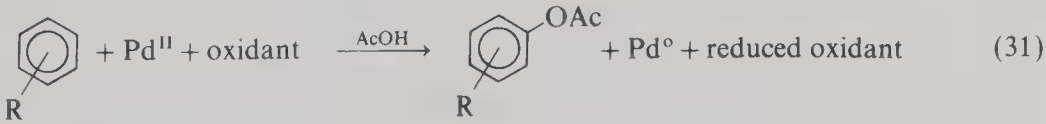
As with many palladium catalyzed oxidations, aromatic coupling reactions can be made catalytic by the use of suitable reoxidizing agents for palladium. Some compounds which have been used include $CuCl_2$, iron(II) salts,[73] and V_2O_5.[74] Copper(II) salts tend only to be useful for the more reactive heterocyclic systems, and require Cl^- concentrations of about 1 *M* in aqueous solution, which, as for other systems, can lead to chlorinated side products. V_2O_5 has been used only for thiophen coupling. The most interesting co-catalysts for aromatic coupling are mixed heteropoly acids of the type $H_{3+n}PMo_{12-n}V_nO_{40}$,[75–77] which appear to have few of the drawbacks of $CuCl_2$.

It has also been found that palladium(II) can be regenerated by oxygen without a co-catalyst during oxidative aromatic coupling.[58] The yield and rates of these reactions depend on the anion; ClO_4^- is twice as active as ^-OAc. **[CAUTION: PERCHLORATES ARE HIGHLY DANGEROUS AND CAN LEAD TO EXPLOSIONS.]** The pressures of O_2 vary between 1 and 50 atm depending on the reaction; the yields of coupled products usually increase with O_2 pressure to 50 atm. The use of O_2 as a reoxidant for palladium is also found to suppress acetoxylation reactions.[78] When O_2 is used as a reoxidant it is found that addition of complexing agents such as acetylacetone and ethylenediaminetetraacetic acid increases the yields.[79] It is also found that the addition of polar solvents, inorganic acids, alkali metal acetates, and some ligands such as halides reduce the yield of coupled products,[80] frequently to zero.

Table III lists a variety of coupling reactions, the conditions needed, and the yields obtained.

4.2. Aromatic Acetoxylation Reactions

Nuclear aromatic acetoxylation reactions were first discovered by Davidson and Triggs in 1968[61]:



(31)

In 1971 Henry[82] showed that acetoxylation only occurred in the presence of a second oxidant such as Cr(VI), $Pb(OAc)_4$, $NaClO_3$, $KMnO_4$, $NaNO_3$, or $NaNO_2$; of these, Cr(VI), in the form of $K_2Cr_2O_7$ was the best. In some cases O_2 at 50 atm could be the second oxidant. In the absence of a second oxidant only coupled products are formed. Henry also reported substitution into the aromatic ring by N_3^-, Cl^-, NO_2^-, Br^-, CN^-, and SCN^-, the nucleophile being introduced as an alkali metal salt.

A detailed study of aromatic acetoxylation was carried out by Eberson and co-workers, who found that the addition of metal acetates favored the formation of side-chain acetoxylation products.[83] For example, *p*-xylene with added sodium acetate gave *p*-methyl benzylacetate in refluxing acetic acid in the presence of oxygen. In the absence of added

acetates 2,5-dimethylphenyl acetate was the main product. It was also shown that with mono-substituted aromatics reversal of the normal isomer pattern for electrophilic substitution occurred.[84] That is, with *meta*-directing substituents mainly *ortho*- and *para*-substitution was observed and with *para*-directing substituents mainly *meta*-products were produced. For example, with anisole (*ortho*-, *para*-directing) 97% of the product was *meta*-, and with methyl benzoate (*meta*-directing) the product distribution was *o*-44%, *m*-35%, *p*-21%.

Yields of aryl acetates can be increased by the addition of a strong acid such as $MeSO_3H$. As with coupling, aryl mercury compounds, preprepared or made *in situ*, can be used as starting materials. This does not increase the yield but does increase the selectivity towards *para*-substitution, particularly where the aryl mercurial is preformed. A remarkably clean acetoxylation reaction has been found[85] using palladium(II) complexes with bipyridine and potassium peroxydisulphate, and in this the preference for *meta*-substitution is retained.

Some examples to illustrate the above points follow.

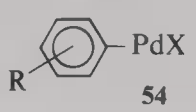
The usefulness of aromatic acetoxylation reactions is limited by slow rates, side reactions, and the need for expensive oxidizing agents. However, it can be a useful method for producing aromatic acetates not available by other means.

From the examples already described it is obvious that coupling and acetoxylation of aromatics are closely related. The interchangeable nature of these reactions is illustrated in Example 11 in Section 7.

4.3. Mechanisms

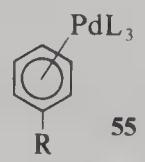
The relationship between coupling and acetoxylation is also reflected in the mechanisms.

It is generally agreed that a common intermediate is responsible for coupling and acetoxylation reactions; this intermediate gives mainly coupled products in the absence of added oxidant and nuclear acetoxylation products in the presence of an oxidant. Most evidence[59,82,86] points to a σ-aryl palladium intermediate (**54**):



54

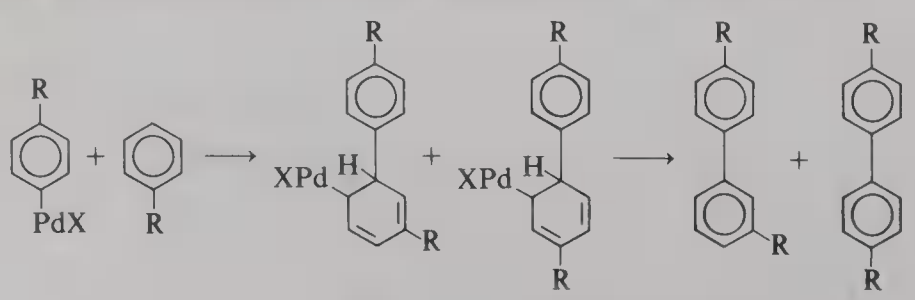
Eberson and Gomez-Gonzalez proposed[87] an initial π-complex (**55**) which gave different intermediates;



55

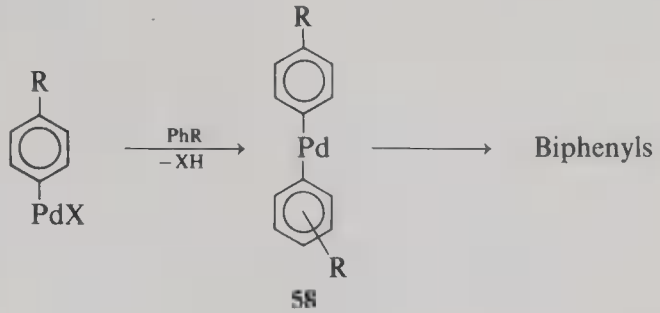
but in the light of recent work[86] this seems unnecessary and palladation to a common intermediate **54** is more probable.

The path from this common intermediate is less well agreed. For coupling it is thought that the σ-aryl palladation intermediate can attack another aromatic which behaves like an olefin, giving, for example, **56** or **57**, which then give the observed products



56 **57**

Alternatively, the second step is a further aromatic palladation of lower selectivity and proceeds via **58**

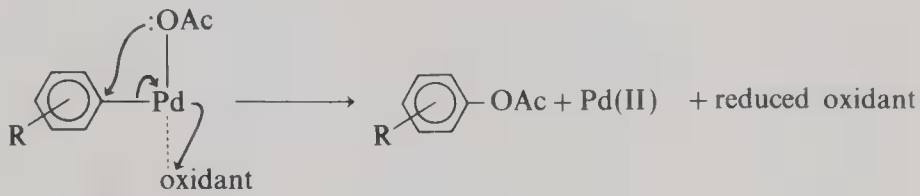


58

Both these routes account for the formation of 2,4′-, 3,4′-, and 4,4′-isomers. Recently it has been proposed, on the basis of kinetic effects,[86] that the second route is the more likely.

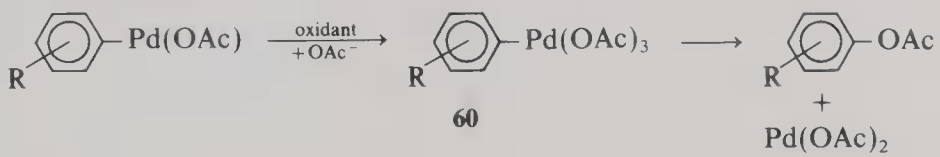
For acetoxylation reactions there are again several proposed pathways. The differences are based on the role that the oxidant is thought to play.

If the oxidant simply acts as an electron sink and aids the removal of palladium from the aromatic ring, an intermediate step involving a species such as **59** is proposed:



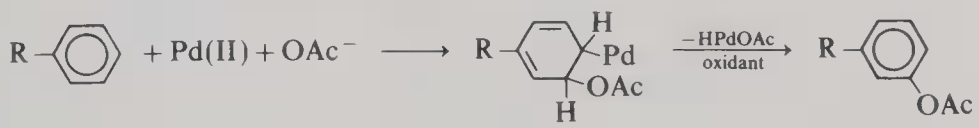
59

The oxidant can also be regarded as oxidizing the σ-aryl intermediate to a palladium (IV) species (**60**)[86] as follows:



60

Eberson and co-workers proposed the formation of the intermediate (**61**),[87]



61

which readily explains the reversal of the expected isomer distributions. Here the oxidant simply aids in the loss of HPdOAc.

5. OXIDATIVE CARBONYLATIONS

5.1. Oxidative Carbonylation of Olefins

Oxidative carbonylation of olefins was first reported by Tsuji, who found that[88,89]

$$RCH{=}CH_2 + PdCl_2 + CO \xrightarrow{C_6H_6} RCHClCH_2COCl$$

Loss of HCl from this product would give acrylic acid or substituted acrylic acids, which are very desirable products.

Fenton found that in acetic acid[90] acrylic acid and β-acetoxyacrylic acid were the products from ethene:

$$C_2H_4 + CO + PdCl_2 \xrightarrow[H_2O]{HOAc} CH_2{=}CHCO_2H + AcOCH_2CH_2CO_2H + Pd^0 + 2HCl \quad (32)$$

This reaction can be made catalytic by the addition of $CuCl_2$ in the presence of air, but this causes the production of CO_2 (see Section 6) with water. Another side product resulting from the presence of water is acetaldehyde, hence dehydrating agents such as triethyl formate are used to reduce the amount of CO_2 and acetaldehyde formed.

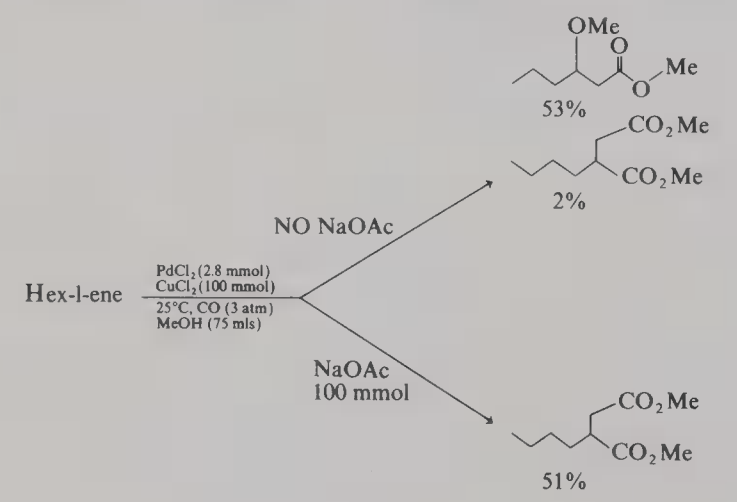
Carbonylation can also be carried out using alcohols as solvents[91]:

$$C_2H_4 + CO + ROH + O_2 \xrightarrow[CuCl_2]{PdCl_2/} CH_2{=}CHCO_2R + ROCH_2CH_2CO_2R + RO_2CCH_2CH_2CO_2R \quad (33)$$

The reaction takes place at a total pressure of about 1000 psig. If the CO: C_2H_4 ratio is 1 then succinate is the main product, but if the ratio is 0.5 acrylate esters are the main products.

The carbonylation in methanol of several olefins has been studied by James and Stille.[92–95] The reaction was found to be stereospecific,[94] *cis*-but-2-ene giving the *threo*-β-methoxy ester and the *meso*-diacid ester, while *trans*-but-2-ene gave the *erythro*- and the *d*-, *l*-isomers, respectively. Under neutral conditions the β-methoxy ester was the predominent product, but with added NaOAc the succinate ester became the main product. Scheme 2 shows the products from hex-1-ene carbonylation[95]:

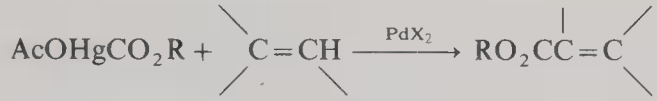
SCHEME 2



Cyclic olefins give *trans*-β-methoxy esters and *cis*-1,2- and -1,3-diacid esters. The ratio of the products depends on the CO pressure and on the presence or absence of base (e.g., NaOAc). An example is reported by James and Stille.[95]

As with other palladium catalyzed oxidation reactions, alkyl mercurials can be used as starting materials to give carboalkylation[96–98]:

$$Hg(OAc)_2 + CO + ROH \longrightarrow AcOHgCO_2R + AcOH \quad (34)$$



$$AcOHgCO_2R + \diagup C{=}CH \diagdown \xrightarrow{PdX_2} RO_2CC{=}C + HgX_2 + HOAc \qquad (35)$$

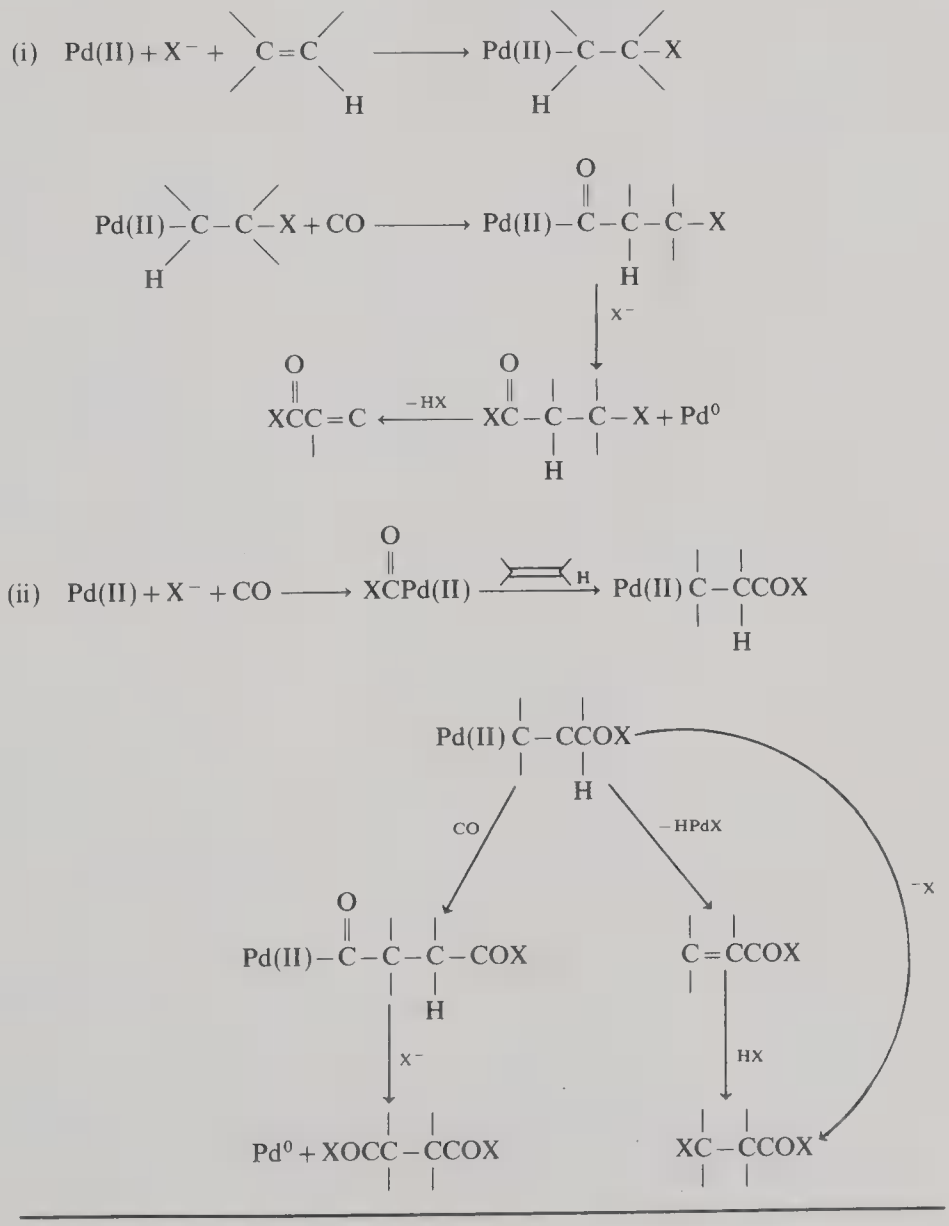
This reaction has the advantage of giving fewer different products. With cyclic olefins 2-, 3-, and 4-carboalkoxyolefins are the products, whereas vinyl-substituted olefins give the carboxy group on the unsubstituted carbon. If the step involving palladium and olefin is carried out under CO pressure the products are succinates.

The carboalkoxymercuric acetate is prepared by the method of Schoeller *et al.*[99] This is used as illustrated in Example 13 in Section 7.

5.1.1. Mechanisms

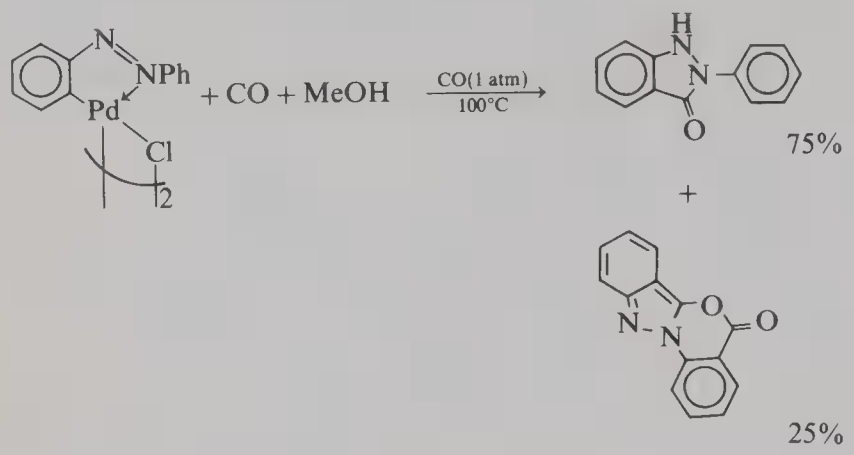
The two proposed mechanisms for oxidative carbonylation of olefins are shown in Scheme 3.

SCHEME 3



5.2. Oxidative Carbonylation of Aromatics

Insertion of CO into arylpalladium(II) bonds to give aromatic acyl compounds has been known for a long time.[100] The products of these reactions vary with solvent and structure. The yields can be increased by running at higher temperatures and pressures; further, acetates react more readily than chlorides. An example is given in Eq. (36)[101]:



(36)

Aryl mercurials can also be used as starting materials[102,103]:

$$RC_6H_4HgCl + CO + R^1OH + PdCl_2 \xrightarrow{1\,atm/25^\circ C} RC_6H_4CO_2R^1 + Pd^0 + HgCl_2 + HCl \qquad (37)$$

Here the CO always enters at the position where the mercury was. At higher CO pressures diaryl ketones become the major products. The aryl mercury compound can be made *in situ* and the reaction can be made catalytic by the use of $CuCl_2$ and air.

Carbonylation does not occur in the absence of aryl-metal intermediates, but aromatic halides can be used in the same way as for olefin arylation (see Section 3.2). Aryl halides (ArBr, ArI) react with CO in the presence of Pd(II) catalysts and a base to give carboxylic acid derivatives. The CO adds to the carbon to which the halide was originally attached.

6. SOME REACTIONS OF ALCOHOLS

6.1. Oxidation

It has already been noted, in the section on olefin oxidation in alcohols, that $PdCl_2$ will oxidize alcohols to aldehydes and to acetals in the presence of excess alcohol[104]:

$$PdCl_2 + EtOH \longrightarrow EtOPdCl \longrightarrow MeCHO \xrightarrow{EtOH} MeCH(OEt)_2 \qquad (38)$$

This reaction is slower than the corresponding ethylene oxidation. The oxidation of ethanol can be made catalytic in aqueous solution by the use of $CuCl_2$ as a co-catalyst in the presence of air.[105] It was found that the oxidation was better in alcoholic solvents[106] with the use of $Cu(NO_3)_2$ as a co-catalyst.

Davidson[107] carried out the oxidation of alcohols with $PdSO_4$ under O_2 pressure and found that primary alcohols gave the acids, whereas secondary alcohols gave ketones:

$$EtOH \xrightarrow[O_2]{PdSO_4} AcOH \tag{39}$$

$$\begin{matrix} EtCHCH_2Et \\ | \\ OH \end{matrix} \longrightarrow \begin{matrix} EtCCH_2Et \\ \| \\ O \end{matrix} \tag{40}$$

6.2. Oxidative Carbonylation

Alcohols can also be oxidized with palladium (II) salts in the presence of CO to give carbonates and chlorocarbonates at lower pressures[108]:

$$CO + ROH \xrightarrow[ROH]{PdCl_2} CO(OR)_2 + CO(OR)Cl \tag{41}$$

and oxalates at higher pressures[109]:

$$PdCl_2 + 2CO + 2ROH \xrightarrow[CH(OEt)_3]{500\text{–}1000\,psig} RO_2CCO_2R \tag{42}$$

These reactions can be made catalytic by the use of a co-catalyst; the best co-catalysts were found to be copper(II) salts, usually $CuCl_2$. The reaction at lower CO pressures can be tuned to give mainly chlorocarbonates by the addition of LiCl or the carbonate if a small amount of Na_2CO_3 is added.

The higher-pressure reactions require the addition of drying agents such as triethyl formate since CO_2 becomes the main product in the presence of water:

$$2CuX_2 + CO + H_2O \xrightarrow{Pd} 2CuX + CO_2 + 2HX^{110} \tag{43}$$

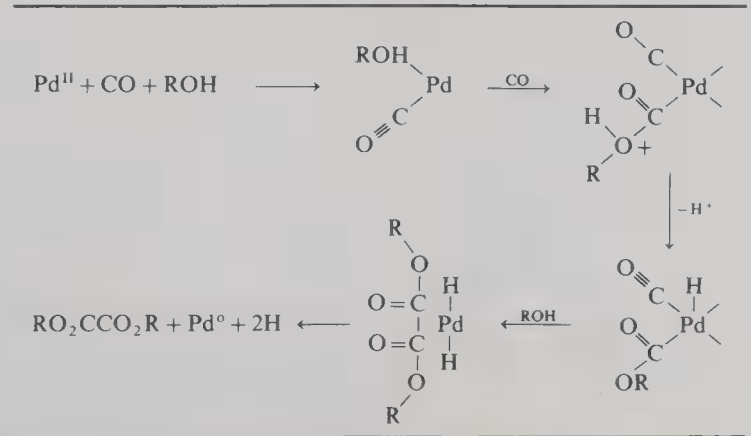
Acetate is another side product in this reaction and arises from the oxidation of the alcohol to acetaldehyde and eventually acetate as previously described.

A typical reaction for the production of oxalate uses $PdCl_2$ and $CuCl_2$ in a ratio of 1:6 in equal volumes of ethanol and triethyl formate and pressure of about 1000 psig CO with O_2 added in small increments. *In view of the potential hazards of this procedure it should only be attempted by highly experienced workers.* For ethanol the percentage yield of carbonate and oxalate is 81% of the total, of which 47% is oxalate and 33% carbonate.

The use of $FeCl_3$ as a co-catalyst increases the proportion of oxalate, but large amounts of acetate are also produced.

The proposed mechanism for oxalate formation is shown in Scheme 4.

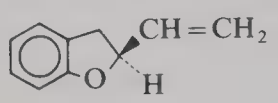
SCHEME 4



7. EXAMPLES*

Example 1: 1-Hexene to 2-Hexanone (Ref. 20). Mercuric acetate (2 mmol) and hex-1-ene (2 mmol) are stirred at 25°C for 15 min in methanol and then added to a stirred methanolic solution of copper(II) chloride (6 mmol) and Li_2PdCl_4 (0.2 mmol). At 65°C a quantitative yield of 2-hexanone is obtained after 30 min. In the absence of $CuCl_2$, equimolar quantities of Li_2PdCl_4 in methanol give a quantitative yield of hexan-2-one after 2 h at room temperature.

Example 2: Oxidation in Glycol to Give 1,3-Dioxolanes (Ref. 45, p. 134). A solution of anhydrous $Hg(OAc)_2$ (1 mmol), olefin (1 mmol), and *p*-toluene sulfonic acid (10 mmol) in equal volumes of anhydrous ethylene glycol and anhydrous THF is stirred. It is allowed to stand at room temperature for 0.5 h and is then poured into an equal volume of anhydrous THF containing $CuCl_2$ (3 mmol), Li_2PdCl_4 (0.1 mmol), and Li_2CO_3 (0.3 mmol). The mixture is then heated (at 64°C/0.5 h), and cooled to room temperature. The ketal product is isolated by pouring the solution into aqueous ammonia (50% v/v), extracting with ether, drying over $MgSO_4$, filtering, and evaporating under reduced pressure. The residue can then be distilled. For example, hex-1-ene gives 2-butyl-2-methyl-1,3-dioxolane in 77% yield.



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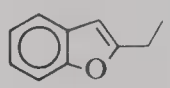

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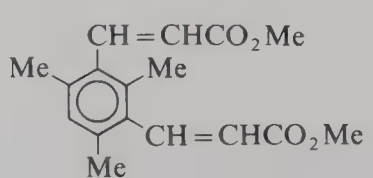
Example 3: (S)(+) 2-Vinyl-2,3-dihydrobenzofuran (**16**) *(Ref. 31).* Complex **14** (0.526 g, 0.87 mmol as dimer) and $Cu(OAc)_2$ (0.317 g, 1.75 mmol) are added to a flask which is connected to an O_2 supply. The flask is flushed with O_2 and then a solution of *trans*-2-(2-butenyl)phenol (2.59 g, 17.5 mmol) in anhydrous methanol (35 ml) is added with stirring. After 4.5 h the reaction mixture is extracted with ether, washed with water and sodium chloride solution, and dried over Na_2SO_4. The solvent is removed under vacuum and the residue chromatographed on a short alumina column with hexane as eluant. A total yield of 2.0 g (77%) of a mixture of **16** and **17** is isolated, of which 83% is **16**.

16 and **17** can be separated by preparative TLC (SiO_2, hexane/toluene = 4/1). **16** is found to be 18% optically pure.

Example 4: 1,3,5-Trimethyl-2,4-bis(1-methoxycarbonyl-2-ethenyl)-benzene (**32**) *(Ref. 35).* The dimercurial (**31**) is prepared by the reaction of mesitylene (20 ml) mercuric acetate (64 g), methanol (100 ml), and 70% perchloric acid (1 ml). The mixture is refluxed for 1 h, cooled, and filtered. The filtrate is cooled in a solid-CO_2/acetone bath, the crystals are collected and dissolved in hot chloroform (300 ml); the solution is then filtered and the product precipitated with pentane giving 19 g of product (**31**) m.p. 224–227.

A mixture of the dimercurial (**31**) (3.26 g), methyl acrylate (5 ml), and an equimolar quantity of Li_2PdCl_4 in acetonitrile (100 ml) is stirred at 20°C overnight. The palladium metal is precipitated and filtered off; the filtrate is concentrated under reduced pressure leaving an oil which is crystallized from aqueous methanol to give 0.2 g (12%) of colorless plates of 1,3,5-trimethyl-2,4-bis(1-methoxycarbonyl-2-ethenyl)benzene (**32**).



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* All examples are quoted with permission of the copyright holders; see appropriate references.

Example 5: *Coupling of Toluene to Bitolyls (Ref. 66).* Mercuric(II) acetate (3.1 g, 0.01 mol) is added at 25°C to a mixture of toluene (9.2 g, 0.1 mol) and acetic acid (6 g, 0.1 mol). On addition of $HClO_4$ (1.25 ml) mercuration occurs rapidly and is complete in 5 min. Then $PdCl_2$ (0.44 g, 0.0025 mol) is added. Palladium is filtered off after 30 min, g.l.c. analysis shows the products to be 3,4′-bitolyl (35%) and 4,4′-bitolyl (60%). If excess $Hg(OAc)_2$ is used, yields of bitolyl of 100% based on palladium can be achieved.

Example 6: *Coupling of Iodobenzene and Iodotoluene (Ref. 71).* A mixture of iodobenzene (20 mmol), 4-iodotoluene (20 mmol), palladium acetate (0.48 mmol), and triethylamine (20 mmol) is stirred for 48 h at 110–120°C. Water is then added and the solution extracted with ether. The ether extract is washed with 2 *M* HCl and water and dried over K_2CO_3. Removal of solvent leaves an orange oil which can be shown by g.l.c. to be 19% biphenyl, 9% 4-methylbiphenyl, and 10% 4,4′-bitolyl (yields based on iodides consumed).

Example 7: *Cyclization of Diphenylether to Dibenzofuran (Ref. 72).* A solution of diphenylether (52; X = O, R = H) (2 mmol) is heated with palladium acetate (4 mmol) in acetic acid (86°C, 24 h) until the starting material is consumed. Yield of dibenzofuran (**53**) is 90%. The reaction also works well where X = O, NH, CO, or CONH and R = Me, MeO, H, Cl, Br, NO_2, or CO_2H.

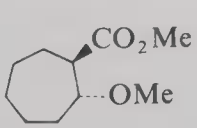
Example 8: *Cresol Acetates from Toluene (Ref. 82).* Palladium acetate (0.5 mmol) and toluene (32 mmol) are heated at 90°C for 16 h in acetic acid (25 ml) containing $K_2Cr_2O_7$ (15 mmol) and CH_3SO_3H (3.1 mmol). 1 mmol of cresol acetate is formed with the isomer distribution, *ortho*-19%, *meta*-62%, *para*-19%.

Example 9: *Cresol Acetates from p-Tolylmercuric Acetate (Ref. 82).* Palladium acetate (1 mmol) and *p*-tolylmercuric acetate (20 mmol) are heated at 90°C for 16 h in acetic acid (25 ml) containing LiOAc (25 mmol) and $K_2Cr_2O_7$ (15 mmol). 0.4 mmol of cresol acetate is formed which is 100% *para*-substituted. Alternatively the aryl mercurial can be generated *in situ*. Palladium acetate (0.5 mmol) and toluene (32 mmol) are heated at 50°C in acetic acid (25 ml) containing $K_2Cr_2O_7$ (15 mmol) and $Hg(OAc)_2$ (3 mmol) for 22 h. The product is cresol acetate (0.16 mmol) with isomer distribution, *ortho*-6%, *meta*-19%, *para*-75%.

Example 10: *Cresol Acetates from Toluene Using Bipyridylpalladium Acetate Catalyst (Ref. 85).* Palladium acetate (1 mmol) and toluene (10 mmol) are heated at 110°C in glacial acetic acid (50 ml) containing 2,2′-bipyridyl (1 mmol) and $K_2S_2O_8$ (10 mmol) for 4 h. The cresol acetate product (1 mmol) has isomer distribution, 3% *ortho*, 60% *meta*-, 37% *para*. Benzylacetate (0.22 mmol) is also produced.

Example 11: *Phenyl Acetate or Biphenyl from Benzene (Ref. 82).* Benzene (56 mmol) and palladium acetate (1 mmol) are refluxed in acetic acid (35 ml) for 16 h. In the absence of added oxidant the product is 22% biphenyl based on palladium acetate, but if $Na_2Cr_2O_7 2H_2O$ (15 mmol) is added the reaction gives 403% phenyl acetate and only trace amounts of biphenyl.

Example 12: *Oxidative Carbonylation of Cycloheptene (Ref. 95).* Cycloheptene (50 mmol), $PdCl_2$ (2.8 mmol), $CuCl_2$ (100 mmol), and methanol (75 ml) are reacted under a CO pressure of 3 atm at 28°C. The products are **62** 2%, **63** 34%, and **64** 63%. The total yield based on cycloheptene is 58%.



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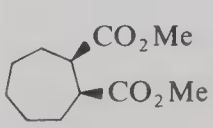
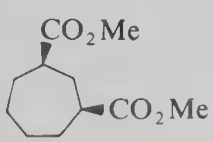


63



64

If NaOAc (100 mmol) is added the total yield is 30% all of which is diacid esters **63** and **64** in the ratio 80:20. Increasing the CO pressure to 15 atm in the absence of NaOAc increases the yield of the **62** at the expense of the **63**. The total yield is decreased to 30% and the ratio of **64**:**63** is 33:67.

Example 13: *Carboalkylation with Carboalkoxy Mercury Compounds (Ref. 98)*. Carboalkoxymercuric acetate 99 (5 mmol) and palladium acetate (5 mmol) are placed in a heavy walled Pyrex bottle fitted with a magnetic stirrer. The bottle is capped with a neoprene rubber lined cap with two small holes to admit syringe needles. The air in the bottle is replaced first by nitrogen and then by olefin (e.g., ethene, propene, or butene). The bottle is thermostatted at 30°C and the olefin pressure raised to 30 psig. A previously prepared saturated solution of olefin in acetonitrile (10 ml) at 30°C is transferred to the bottle by syringe and stirring commenced. The olefin pressure is maintained at 20 psig with stirring for 1 h. The pressure is released and the palladium metal removed. The mixture is analyzed by gas chromatography.

If the olefin is a liquid the reaction can simply by carried out in a conical flask with the olefin in solution.

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10

Silver Carbonate on Celite Oxidations

Marcel Fetizon, Michel Golfier, Philippe Mourgues, and Jean-Marie Louis

1. INTRODUCTION

Reactions that take place under heterogeneous conditions suffer from a major drawback from the point of view of theoreticians, since generally speaking their mechanism is almost totally unknown and very likely difficult to prove beyond reasonable doubt.

However, some of those reactions have long been used on a preparative scale, even to mass produce certain useful chemicals. For instance, although the reaction of methyl bromide on magnesium in diethyl ether still largely remains a riddle, many organic chemists have no qualms in using Grignard reactions. The same applies to catalytic hydrogenation, which, eventually, is a well-established industrial process. The main practical advantage of reactions which take place on the surface of a solid virtually insoluble in organic solvents relies on the ease of separation of the expected compound, as shown for instance by the well documented oxidation of alcohols by manganese dioxide.[1,2] Unfortunately, the scope of the latter reaction is more or less limited to allylic or benzylic alcohols.

A potentially useful oxidizing cation is Ag^+, since the redox potential of the reaction

$$Ag^+ + e^- \longrightarrow Ag^0$$

(0.8 V) is high enough to convert even saturated alcohols into aldehydes or ketones. However, when the oxidation proceeds, the counterion A^- of the original silver salt Ag A picks up a proton from the medium, so that the acidity is changed:

$$Ag^{\oplus}A^{\ominus} + e^- \longrightarrow Ag^0 + A^{\ominus}$$

$$A^{\ominus} + ROH \longrightarrow AH + R-O^{\ominus}$$

Hence, with the exception of very simple substrates, most of these reactions are expected to

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lead to a variety of unwanted by-products. In fact, the use of silver nitrate even in the form of a complex with ammonia (Tollens reagent) has been rather limited.

Obviously, *no such complication is expected when the acid AH decomposes spontaneously*, which logically restricts the field of silver salts as oxidants to silver carbonate.

Some oxidations have been carried out in the past with silver carbonate. In the course of work aiming at the preparation of various glycosides of codeine with the help of the Königs–Knorr synthesis[3–5] consistently poor yields were obtained.

This observation led Rapoport to examine this well established glycosidation reaction in greater detail. He found that codeine could be oxidized into codeinone and methoxymethylmorphine into methoxymethylmorphinone in fair yield.[6–8] However, no reaction took place with dihydrocodeine. Since the cheaper manganese dioxide reagent was also capable of oxidizing many allylic alcohols into unsaturated ketones, no further work was apparently attempted. Besides, in some cases, successful oxidations were observed with manganese dioxide, whereas the same substrates were unaffected by freshly precipitated silver carbonate.[9] Unaware of these findings, we attempted to carry out silver carbonate oxidations, not with the salt itself, but with a reagent consisting of an inert material, such as Celite, coated with precipitated silver carbonate. In sharp contrast with Ag_2CO_3, the new reagent was very easily filtered and dried. On coating Celite with silver carbonate we had no deeper theory than simply increasing the "active" surface of a given amount of oxidizing agent.*

Naturally, we also hoped that some increase of the reaction rate could be noticed, which would have been due to an increase in the entropy of activation, since it is a priori easier to rendezvous on a surface than in the open three-dimensional space. The very first result was indeed rather encouraging, since androstan-17β-ol was converted into androstan-17-one in a virtually quantitative yield in roughly half an hour in boiling benzene (monitored by TLC, product isolated by column chromatography).[10] A thorough investigation of this reaction was therefore decided upon, which eventually led to the following results, to be elaborated in the next sections of this chapter.

(a) *Primary alcohols lead to aldehydes* in generally high yield. *No further oxidation into acids* was ever observed, even when the reaction was conducted under inert atmosphere and in benzene or toluene.

(b) *Secondary alcohols lead to ketones*, also in good yield but tertiary alcohols are unaffected.

(c) Depending upon the distance between the two OH groups, *diols give lactones, hydroxy-ketones, or hydroxy-aldehydes.* Cleavages of α diols are sometimes observed, but this is not a prominent reaction.

(d) *A large number of functional groups may be present without affecting the course of the reaction.*

(e) As expected, since a solid is an extremely bulky reagent for a molecule, *steric hindrance plays a very important role* in the course of the reaction. In particular, oxidations of polyhydroxysteroids are usually regiospecific.

(f) The most interesting point is that silver carbonate on Celite is neutral, and that no acidic products are formed. Thus, *the reaction conditions are extremely mild*, and many sensitive compounds may be successfully oxidized.

Some reviews on Ag oxidations have already been published.[11,12]

(g) Recovery of silver is very easy. It decreases sharply the cost of an oxidation on a large scale (see Section 4.2).

* Dr. Golfier selected Celite among other candidates simply because a large sample of this filter aid was on the shelf right in front of him.

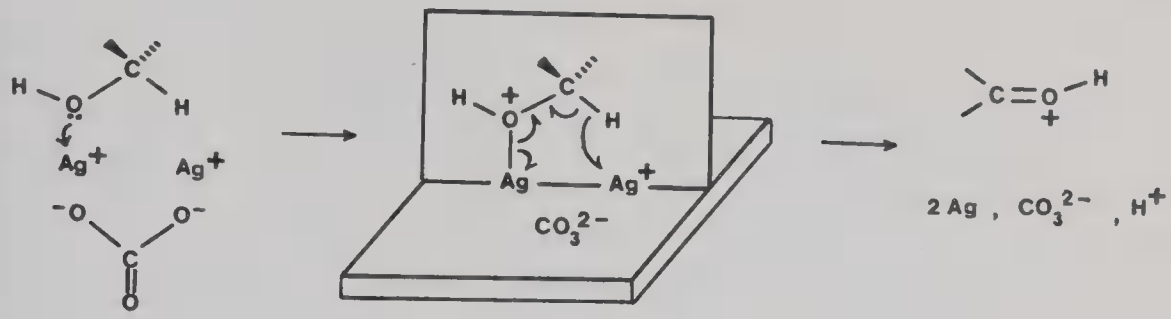


FIGURE 1

2. MECHANISM

Although a detailed discussion of the mechanism of oxidation is beyond the scope of this book, a brief comment upon the rather reasonable hypothesis which explains most of the observed results seems to be necessary, since it can rationalize the course of many silver carbonate/Celite oxidations.

The stoichiometry of the reaction is as follows:

$$Ag_2CO_3 + \underset{R}{\overset{R}{\diagdown\!\!\diagup}}CHOH \longrightarrow \underset{R}{\overset{R}{\diagdown\!\!\diagup}}C{=}O + 2Ag + CO_2 + H_2O$$

However, the use of an excess of the reagent is required for the reaction to proceed at a reasonable rate.*

The first step is very likely an adsorption of the substrate on the solid: hence the very important role of the solvent. Unless the compound to be oxidized (e.g., a carbohydrate) is readily bonded to Celite, which has an only moderate adsorption activity, no reaction takes place in polar solvents. For instance, the silver carbonate/Celite oxidation of androstan-3β-ol in benzene proceeds about 1000 times faster than in *t*-butanol. Except in the case of carbohydrates, benzene or toluene have been used almost exclusively.[13,14]

The second step is probably a reversible chemisorption, followed by an irreversible and concerted one-electron transfer, depicted in Fig. 1.

In particular, for the reaction to take place, the hydrogen atom which is to be oxidized into a proton, *must be close to the surface of the solid.* Moreover, it is quite reasonable to expect the C–H and O–Ag bonds to be coplanar so as to provide the best possible overlapping between the molecular orbitals which are involved in the transition state.

A *model* of the latter transition state, which has a very high predicting power, is shown in Fig. 1.

If this model is correct, no "local" steric hindrance is to be taken into account: a rigid molecule has to be taken as an individual entity, and some bulky groups *which might be far away from the hydroxyl function whose oxidation is contemplated* may slow down the reaction rate, or even, prevent the reaction from taking place. Thus, although 5α-androstan-6β-ol can be smoothly converted into the corresponding ketone, the 6α isomer remains unaffected (Fig. 2).

* A six- to tenfold excess has practically been used in most cases. However, since the oxidation of many compounds is extremely clean, the recovery of the expensive silver salt is no great problem: the inorganic solid is dissolved in nitric acid, Celite is filtered off, and some nitric acid is evaporated, until pure silver nitrate crystallizes out.

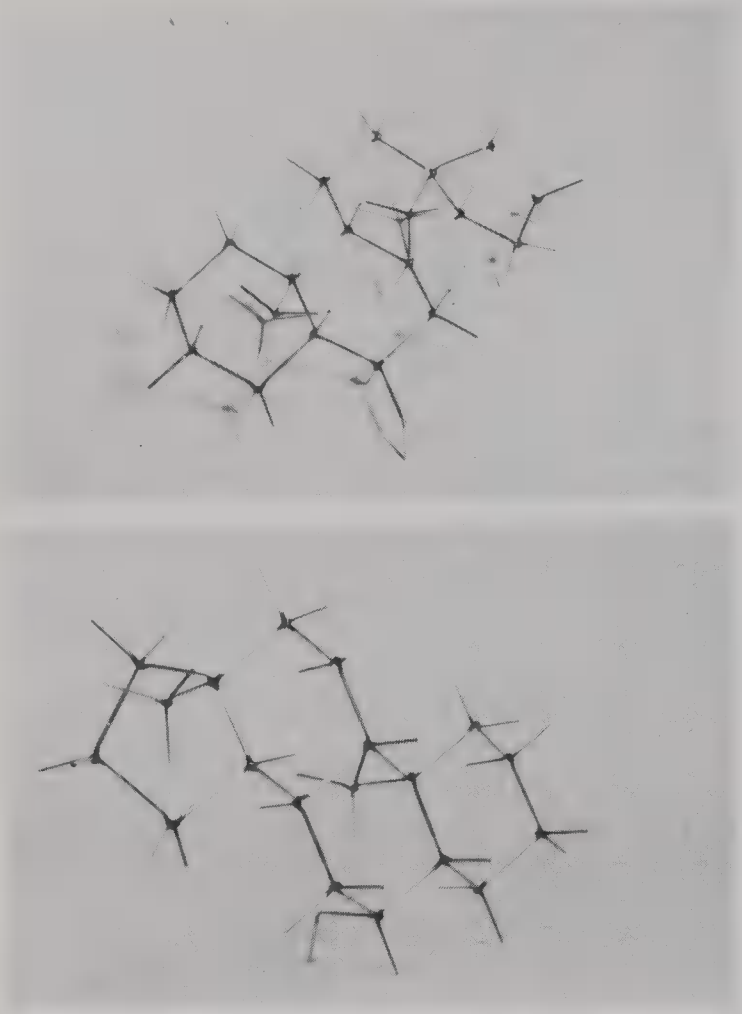
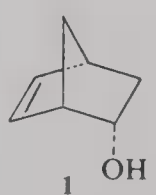


FIGURE 2. 6α-Androstanol (top) and 6β-androstanol (bottom).

These considerations may easily explain the regioselectivity of polyhydroxysteroids, as illustrated in a next section. Sunko[15] noticed that the rate of oxidation of norbornenol **1** is



1

roughly 50 times lower than that of the corresponding saturated alcohol. This may be explicated by the difference in reactivity of the "doubly anchored" substrate (O···Ag and π···Ag bonds) in which the hydrogen to be oxidized is far away from the surface of the active solid, and the more loosely "monoanchored" alcohol, in equilibrium with the latter, in which this particular hydrogen may easily be reached.

Similar observations have been made in the steroid and tropane series. Thus, it seems that the course of many related oxidations can be predicted on the basis of this simple model even if there are still some moot points.

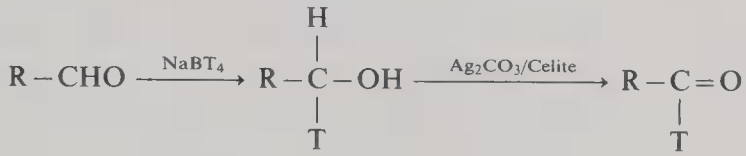
The rate-determining step of the oxidation, *once the right support/substrate relationship has been established*, is clearly α-hydrogen abstraction.

Steric decompression, which we consider as a "local" factor, seems to play a very minor part.

Some unexpected reactions may take place, especially in highly strained alcohols. Thus cyclobutanols afford mixtures of cyclobutanones *and γ-lactones.*[16] Rearrangements have also been observed.[17]

On the other hand, the isotope effect[18] is fairly high, especially for tritium.

From a practical point of view, it is interesting to note that the following reactions could easily be carried out with practically no loss of tritium[19,20]*:



3. SCOPE AND LIMITATIONS

3.1. Protecting Groups

Most of the usual OH protecting groups have no effect on the course of the reaction, and may therefore be used [e.g., formates, acetates, tetrahydropyranyl (THP), or trimethylsilyl (TMS) derivatives,...]. However, ethylene thioketal lead to much smaller yields of oxidation products.[10]

Cyanohydrins are converted back to the starting carbonyl compound.[21]

Curiously enough, ethynyl tertiary alcohols are also converted into ketones, very smoothly and in high yield.†[21] Ethynylation of ketones might well become a new method of protection of carbonyl groups, against fairly drastic basic conditions.

A case of oxidation of a secondary alcohol containing a tricarbonyl arene chromium moiety has been reported.[17] Although the other oxidizing agents brought about a rapid oxidation at the zerovalent chromium center, silver carbonate on Celite was found to oxidize the hydroxyl group faster than the metallic atom.

A case of hydrolysis of a nitrile group into an amide in the course of an oxidation has been reported.[23]

3.2. Oxidation of Monoalcohols

Primary and secondary alcohols are usually oxidized by silver carbonate on Celite into aldehydes and ketones, respectively. The yields are generally good or even virtually quantitative. Primary alcohols react more slowly than secondary ones. To get a reaction fast enough for synthetic purposes a larger amount of silver carbonate on Celite is required in case of a primary alcohol than in the case of a secondary one.

Furthermore, allylic and benzylic alcohols react faster than saturated alcohols. In benzene, the difference in oxidation rates is not high enough to permit any regioselectivity. However, in boiling methanol, 3β,17β-dihydroxyandrost-4-ene is converted into testosterone in ten minutes, whereas in benzene, a mixture of testosterone and androst-4-ene-3,17-dione is obtained.[24]

Apart from this particular case, nonpolar solvents, especially benzene, more rarely

* $NaBT_4$ represents tritiated sodium borohydride.

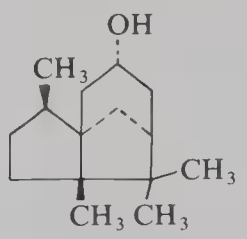
† This unexpected cleavage might well be the reason for the faiture of silver carbonate/Celite attempted oxidations of several acetylenic sugar derivatives.[22]

toluene and hexane, have been used with a ratio of 3–6 moles (respectively, 10–20 moles) of Ag_2CO_3 per mole of secondary (respectively primary) alcohol.

Functional groups, which are sensitive to acidic or basic conditions, are usually unaffected, since the medium is neutral. Some groups which are otherwise easily oxidized, are also almost inert, for instance furan, indole rings,[25] chromium tricarbonyl complexes.[17]

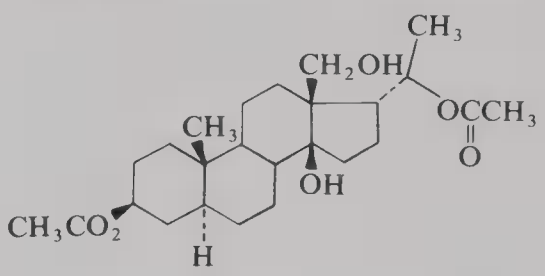
Epimerization at a carbon α to the newly formed carbonyl group is rather exceptional.[26,27]

As indicated above, the oxidation rate strongly depends on the geometry of the system adsorbed species-reagent. For instance, 15-nor-9α-cedranol, **2**, is not oxidized, even after a



2

long refluxing time,[28] since the 9β hydrogen is in a cage, and therefore inaccessible from the surface of the solid. Similarly, the 18-hydroxy-steroid **3** does not react,[29] whereas the 19-hydroxy analog **4** gives the expected aldehyde almost quantitatively.[30,31]



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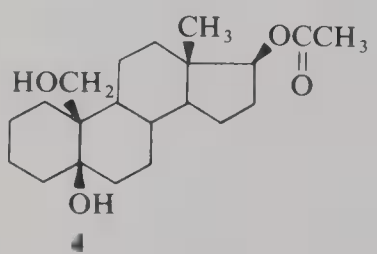

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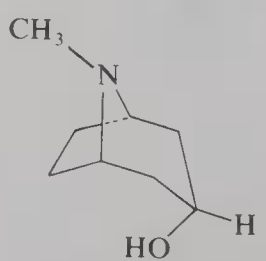
The great sensitivity to steric environment can be used for selective oxidations, especially of rigid molecules such as steroids and terpenoids.

However, it must be emphasized that *the major point is not steric hindrance in the free substrate, but the geometric characteristics of the adsorbed species.*

Thus, tropine **5** is oxidized much more rapidly than pseudotropine **6**.[32] As suggested



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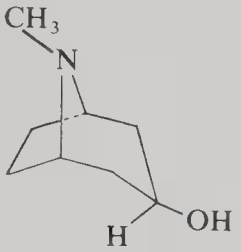
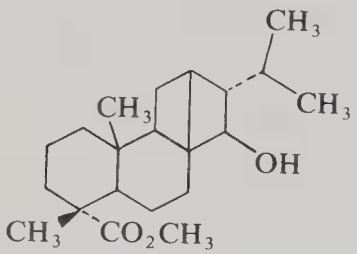


6

before, pseudotropine is essentially "doubly anchored" to the reagent, very likely through the lone pairs of electrons of both nitrogen and oxygen so that the transition state for the oxidation is not favored. In sharp contrast, tropine is bonded to the solid either with the nitrogen or the oxygen atoms. In the latter case, oxidation takes place very fast.

In strained compounds, such as **7**, insertion of oxygen between the carbonyl group and the α carbon atom has been observed, which is the equivalent of a Baeyer–Villiger oxidation.[33] The presence of traces of water may well be important in this reaction.[16]



7

Another unexpected and interesting reaction has been observed in the case of tetrahydrofurfuryl alcohol and tetrahydropyran-2-methanol, which lead to γ-butyrolactone and δ-valerolactone, respectively. No intermediate aldehyde could be detected.[25,34]

Normally, the oxidation of a primary alcohols stops at the aldehyde level, although there is one reported case of direct formation of the corresponding acid.[35]

However, when the oxidation of partly protected carbohydrates is carried out in methanol, methyl esters are isolated in fair yield (see Section 3.7), very likely because of the rapid formation of a hemiacetal, which is known to be oxidized very rapidly.[36]

The fairly strong isotope effect, mentioned previously, has been taken to advantage for the preparation of tritiated aldehydes[19] and less efficiently, of deuterated aldehydes.[18]

3.3. Lactones from Diols

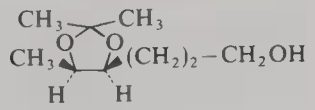
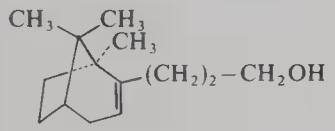
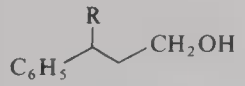
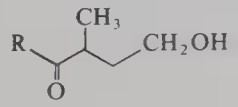
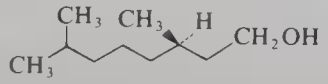
When at least one of the hydroxyl groups of a 1,4-, 1,5-, or 1,6-diol is primary, the diol is smoothly oxidized into a lactone by silver carbonate on Celite in refluxing benzene. Very likely, the key step is the formation of a lactol from the intermediate hydroxyaldehyde. In fact, when the cyclization of the intermediate hydroxyaldehyde is too sluggish, for instance in case of steric ring strain, no lactone can be detected.

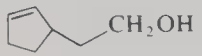
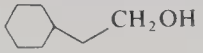
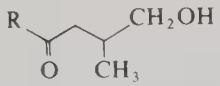
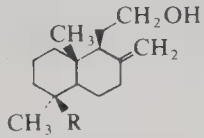
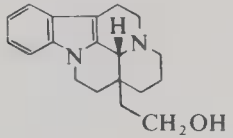
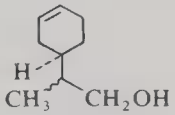
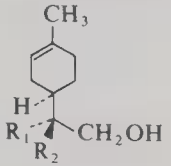
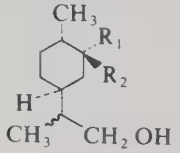
Oxidation of primary–tertiary diols is straightforward. The lactones are usually isolated in high yield.

No difficulty arises when a symmetric primary diol is submitted to the oxidation. The reaction is so mild that even a tertiary alcohol β to the carbonyl group of the obtained lactone is not dehydrated.[95]

However, oxidation of 2,3-isopropylidene-*erythro*-butane-1,2,3,4-tetrol proceeds at a rather low rate, and in modest yield, very likely because of steric ring strain.[95]

TABLE I. Oxidations of Alcohols to Aldehydes

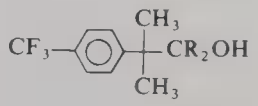
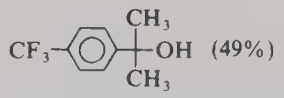
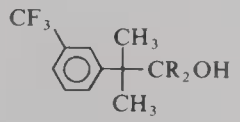
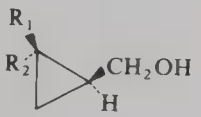
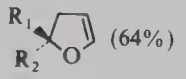
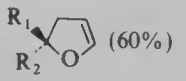
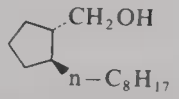
Primary alcohol		By-products (yield %)	Aldehyde yield (%)	Solvent	Reference
1-Heptanol			100	Hexane/heptane	14
n-Nonyl-C_2H_2OH			82	Benzene	20
			82	Benzene	37
$R-(CH_2)_2-CH_2OH$	R				
	Phenyl		81	Benzene	38
	4′-Pyridyl		0	Benzene	25
	2′-Methyl-5′-furyl		98	Benzene	25
$R-C(=O)-(CH_2)_2-CH_2OH$	R Phenyl		90–95	—[a]	39
	α-Furyl		90–95	—	39
			95	Benzene	40
	R				
	CH_3		82	Benzene	41
	$(CH_3)_3C$		29	Benzene	42
	R				
	Propenyl		90–95	—	39
	Phenyl		90–95	—	39
	α-Furyl		90–95	—	39
			46	Toluene	43

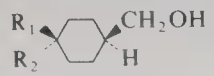
		82	Benzene	44
		90	Benzene	45
		100	Benzene (Ar)	45
	R			
	Phenyl	90–95	—	39
	α-Furyl	90–95	—	39
	R			
	CH_3	80	Benzene	46
	CO_2CH_3	96	Benzene	47
		88	Benzene	48
		78	Benzene	49
	R_1 R_2			
	CH_3 H	>62	Benzene	50
	H CH_3	—[b]	Benzene	50
	Mixture 1:1	72	Benzene	50
	R_1 R_2			
	OTHP H	—[b]	Benzene	27
	H OTHP	—	Benzene	27

[a] Solvent is not specified in Ref. 39.
[b] The product is obtained, but the yield is not specified.

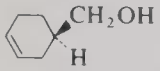
Table continued

TABLE I. *Continued*

Primary alcohol			By-products (yield %)	Aldehyde yield (%)	Solvent	Reference
	R					
	H			55	Benzene	51
	H		 (49%)	9	Toluene	51
	^{2}H			40	Benzene	51
	H			65	Toluene	51
	^{2}H			43	Toluene	51
	R_1	R_2				
	H	H		100	Hexane	14
	$CH_2=CH$	H		80	Benzene	52
	H	$CH_2=CH$		80	Benzene	52
	$C_6H_5OCH_2$	CH_3		90	Benzene	53, 54
	CH_3	$C_6H_5OCH_2$		90	Benzene	53, 54
	C_6H_5	CH_3		90	Benzene	54
	CH_3	C_6H_5		90	Benzene	54
	iso-BuO	H	 (64%)	0	Benzene	55
	CH_3O	CH_3	 (60%)	0	Benzene	55
				>52	—	56



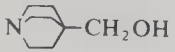
R_1	R_2
H	H
$(CH_3)_3C$	H
H	$(CH_3)_3C$

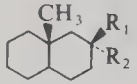


Cycloheptylmethanol

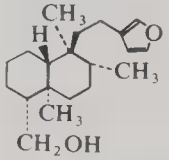
Cyclooctylmethanol

Cycloundecylmethanol





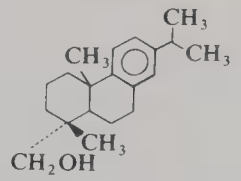
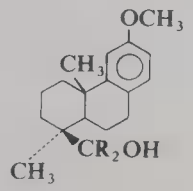
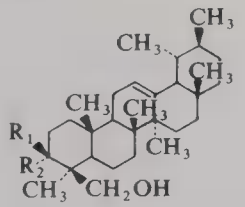
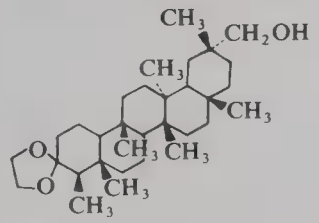
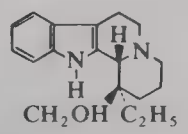
R_1	R_2
CH_2OH	H
H	CH_2OH



Cyclohexanone (2%)	97	Benzene	45
	90	Benzene	54
	90	Benzene	54
	62	Benzene	57
Cycloheptanone (12%)	50	Benzene	45
Cycloheptanone (2%)	92	Benzene (Ar)	45
Cyclooctanone (36%)	29	Benzene	45
Cyclooctanone (20%)	39	Benzene (Ar)	45
Cycloundecanone (45%)	24	Benzene	45
Cycloundecanone (13%)	60	Benzene (Ar)	45
	53	Toluene	58
	85	Toluene (N_2)	59
	90	Benzene	54
	90	Benzene	54
	42	Toluene	60

Table continued

TABLE I. *Continued*

Primary alcohol			By-products (yield %)	Aldehyde yield (%)	Solvent	Reference
				97	Benzene	61
	R					
	H			80	Benzene	61
	^{2}H			80	Benzene	61
	R_1	R_2				
	H	OTHP		52	Benzene	61
	OTHP	H		78	Benzene	61
				54	Benzene	62
				0	—	63

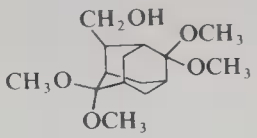
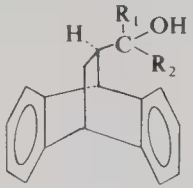
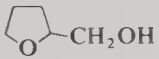
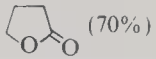
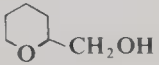
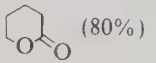
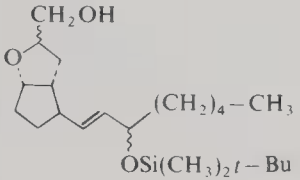
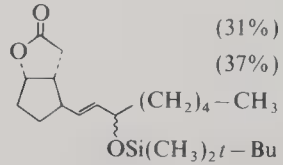
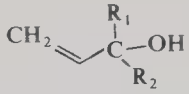
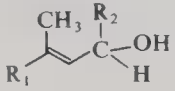
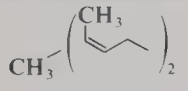
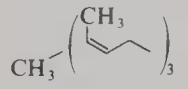
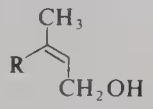
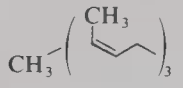
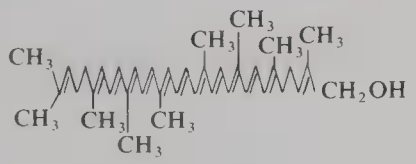
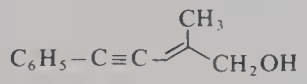
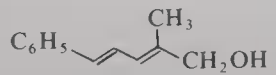
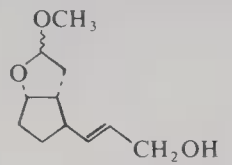
				100	Benzene	64
	R_1	R_2				
	^2H	^2H		90	Benzene	19
	^3H	H		80	Heptane	20
			 (70%)	0	Benzene	25
			 (80%)	0	Benzene	25
			 (31%)	0	Benzene	34
			(37%)	0	Toluene	34
	R_1	R_2				
	^2H	H		≃80	C_6H_5Cl	19
	^3H	H		65	C_6H_5Cl	20
	R_1	R_2				
	$CH_3-CH_2-CH_2$	H		88	Benzene	65
	$(CH_3)_2CH-(CH_2)_3$	H		90	Benzene	65
	$(CH_3)_2CH-(CH_2)_3$	^3H		>65–70	Benzene	20
Geraniol	$(CH_3)_2C=CH-(CH_2)_2$	H		100	Benzene	10, 66

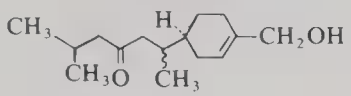
Table continued

TABLE I. *Continued*

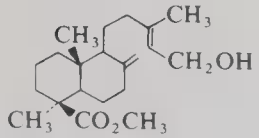
Primary alcohol		By-products (yield %)	Aldehyde yield (%)	Solvent	Reference
	R_1 R_2				
Farnesol	 H		98	Benzene	67
	 H		59	Benzene	65
	R				
	$CH_3-CH_2-CH_2$		74	Benzene	65
	$(CH_3)_2CH-(CH_2)_3$		85	Benzene	65
Nerol	$(CH_3)_2C=CH-CH_2-CH_2$		95	Benzene	10
			69	Benzene	65
		*cis* isomer (11%)	4	Benzene	66
			92	Benzene	68
			86	Benzene	68



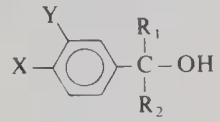
				60	Benzene	69



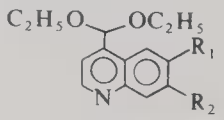
				91	Benzene	70



				100	Benzene	71



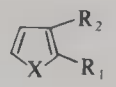
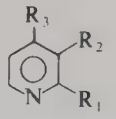
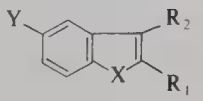
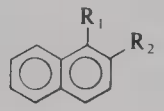
X	Y	R_1	R_2			
H	H	H	^3H	>80	Benzene	20
H	H	^2H	^2H	82	Benzene	20
H	NO_2	H	^3H	>70	Benzene	20
CH_3	H	^2H	^2H	90	Benzene	20
CH_3O	H	H	H	87	Benzene	10
CH_3O	H	H	H	92	CH_2Cl_2	10
CH_3O	H	H	^3H	>80	Benzene	20
CH_3O	H	^2H	^2H	96	Benzene	20
CH_3O	CH_3OCH_2O	^2H	^2H	94	Benzene	20
Br	H	^2H	^2H	85	Benzene	20
Cl	H	^2H	^2H	75	Benzene	20
$(CH_3)_2N$	H	^2H	^2H	100	Benzene	20



R_1	R_2			
H	CH_2OH	50	Toluene	72, 73
CH_2OH	H	—	Toluene	73

Table continued

TABLE I. *Continued*

Primary alcohol				By-products (yield %)	Aldehyde yield (%)	Solvent	Reference
	X	R_1	R_2				
	O	CH_2OH	H		80	Benzene	25
	S	CH_2OH	H		94	Benzene	25
	S	C^2H_2OH	H		97	Benzene	20
	NH	CH_2OH	H		0	Benzene	25
	NCH_3	CH_2OH	H		95	Benzene	25
	NCH_3	CHO	CH_2OH		—	—	74
	R_1	R_2	R_3				
	CH_2OH	H	H		87	Benzene	25
	H	CH_2OH	H		78	Benzene	25
	H	C^2H_2OH	H		90	Benzene	20
	H	H	CH_2OH		74	Benzene	25
	X	Y	R_1	R_2			
	NH	H	H	CH_2OH	50	Benzene	25
	NCH_3	H	CH_2OH	H	93	Benzene	25
	$C_6H_5CH_2N$	H	H	CH_2OH	97	Benzene	25
	NH	CH_3O	CH_2OH	H	87	Benzene	25
	NH	Cl	CH_2OH	H	92	Benzene	25
	NH	Br	CH_2OH	H	88	Benzene	25
	S	H	H	CH_2OH	70	Benzene	25
			R_1	R_2			
			C_2H_2OH	H	60	Benzene	20
			H	C_2H_2OH	95	Benzene	20

When the starting diol is unsymmetrical, the two expected lactones are formed, unless the formation of one of them is strongly favored (for instance when one of the hydroxyl group is allylic or benzylic), or if steric hindrance is important (Table III).

Since, generally speaking, the oxidation of a secondary alcohol proceeds much faster than the oxidation of a primary alcohol, primary–secondary diols do not lead necessarily to lactones, but to mixtures of lactones and hydroxy ketones. Here again activation of the primary alcohol or steric factors play a major role (Table III).

3.4. Lactones from Lactols

The results from oxidations of lactols to lactones by Ag_2CO_3/Celite are summarized in Table IV.

3.5. Hydroxy Ketones from Diols. Cleavages of α-Diols

Silver carbonate on Celite oxidation of α-diols leads very often to cleavages of C–C bonds, just like more classical reagents such as sodium periodate, sodium bismuthate, lead tetracetate, and others.[143,*]

However, the stereochemistry of the starting diol strongly determines the course of the reaction. In boiling benzene, *erythro* diols afford α-hydroxyketones as major products, whereas the *threo* isomers are cleaved.[144]

In the steroid series, for instance, pregnan-17α,20α-diol gives 17α-hydroxypregnan-20-one, although pregnan-17α,20β-diol leads to androstan-17-one.[145] This reflect the importance of the accessibility of the hydrogen which is later oxidized into a proton.

Under the usual reaction conditions, α-hydroxyketones are stable,[92,145,146] which means that they are not intermediates in the cleavage reaction, of which the mechanism is still largely unknown. In some cases, under prolonged treatment with silver carbonate on Celite, diones are formed, albeit in small yield.

The oxidations of β-diols with many oxidizing agents are rather delicate to carry out, since the resulting β-hydroxyketones are very easily dehydrated. With silver carbonate on Celite, it seems that the rate of dehydration is very low. On the other hand, retroaldolization has rarely been observed.[147,148] Some β-diols have been successfully oxidized into β-hydroxyketones (Table V).

For other diols, such as cyclohexane-1,4-diol, the oxidation to 4-hydroxycyclohexanone is much faster than the subsequent oxidation to cyclohexane-1,4-dione. It is thus practically possible to stop the reaction at the hydroxyketone stage.[149]

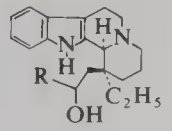
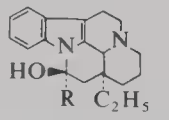
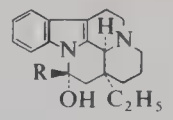
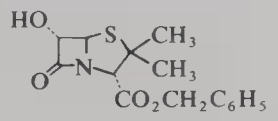
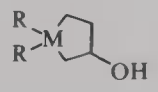
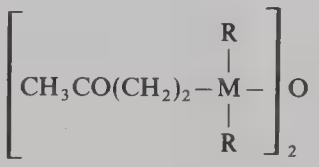
3.6. Steroids. Di- and Triterpenes

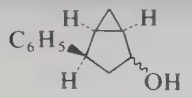
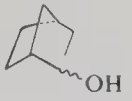
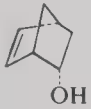
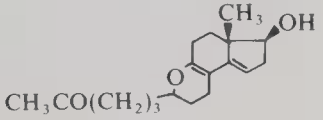
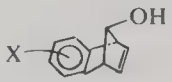
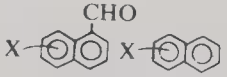
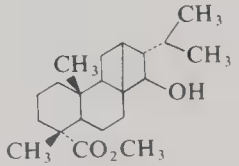
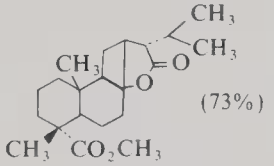
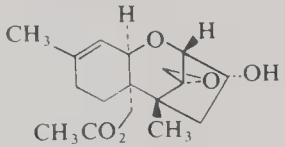
The oxidation of alcohols in the steroid, di-, or triterpene series is a special case owing to the rigidity of the carbon skeleton of most of these molecules. In particular the oxidation of polyols is quite generally highly regioselective. On the basis of the proposed mechanism, it is easy to predict that androstan-2β-ol, androstan-3β-ol, or androstan-17β-ol can easily be oxidized to the corresponding ketones. However, as soon as the geometry of the system "adsorbed substrate/reagent"[†] does not allow the formation of the postulated transition state, the oxidation does not take place, or becomes very sluggish, as shown, for instance, by androstanols when the hydroxyl group is at position 1α, 1β, 6α, 7α, 15β,...[168] even if this hydroxyl group is allylic.[169]

* The case of carbohydrates will be discussed in Section 3.7.

† The reagent is always considered as a plane.

TABLE II. Oxidations of Alcohols to Ketones

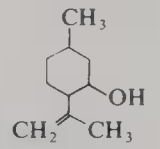
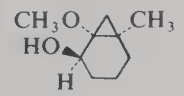
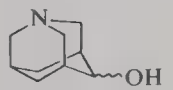
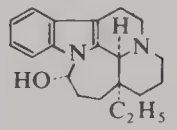
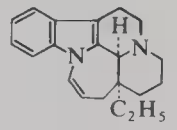
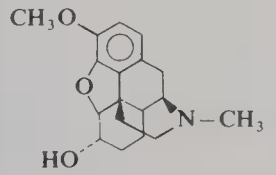
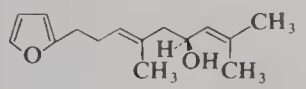
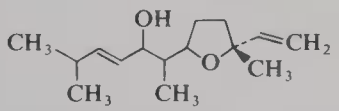
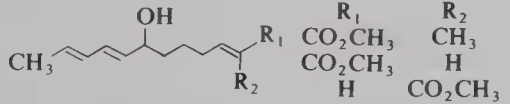
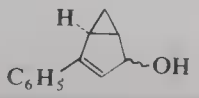
Secondary alcohols		By-products (yield %)			Ketones (yield %)	Solvent	Reference
							
	R						
	CO_2CH_3	—	+	(50%)	0	Benzene (N_2)	75
	CO_2CH_3	(80%)	+	(20%)	0	Xylene (N_2)	75
	CO_2CH_3	(65%)	+	—	0	Toluene (N_2)	75
							
	R						
	OH endo			(29%)	71	Benzene	16
	OH endo			(69%)	31[a]	Benzene	16
	OH exo			(29%)	71	Benzene	16
					0	—	76
	M	R					
	Ge	C_2H_5	(84%)		0	Benzene	77
	Ge	C_6H_5	—		0	Benzene	78
	Si	C_6H_5	—		0	Benzene	78

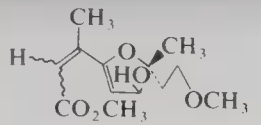
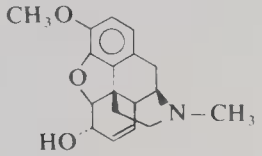
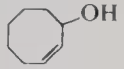
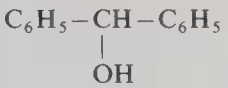
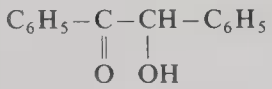
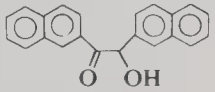
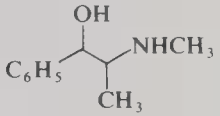
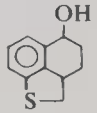
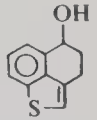
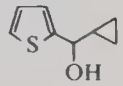
			96	Benzene	79
	Endo		>90	Benzene or heptane	15
	Exo		>90	Benzene or hexane	15
			90	Benzene	15
			88	Benzene	80
			47	Xylene	81
	No complex	 (67%) + (17%)	0	Benzene	17
	Endo complex X = $Cr(CO)_3$	(69%) + (3%)	0	Benzene	17
	Exo complex X = $Cr(CO)_3$	(53%) + (0.4%)	0	Benzene	17
		 (73%)	0	Benzene	33
			70	Toluene	82

[a] Moistened reagent.

Table continued

TABLE II. *Continued*

Secondary alcohols	By-products (yield %)	Ketones (yield %)	Solvent	Reference
		0	Benzene	14
		90	Benzene	83
		80	Xylene	84
	 (−%)[a]	—[a]	Xylene	85
		75	Benzene	25
		86	Benzene	86
		>70	—	87
		97 98 94	Benzene Benzene Benzene	88 88 88
		—	Benzene	79

		68	Benzene	89
		91	Benzene	25
		84	Benzene	90
		100	Benzene	14, 91
		90	Benzene	10
		97	Benzene	92
	C_6H_5-CHO (—%)[a]	33	Benzene	93
		80	Benzene (N_2)	94
		52	Benzene (N_2)	94
		98	Benzene	25

[a] Unspecified yield.

TABLE III. Oxidations of Polyols to Lactones

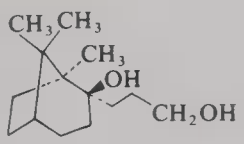
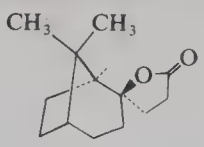
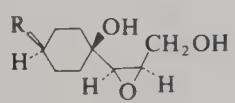
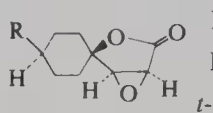
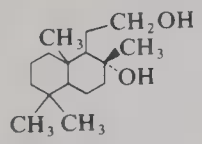
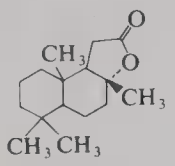
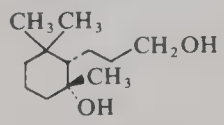
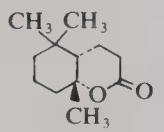
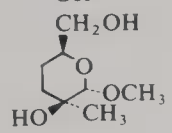
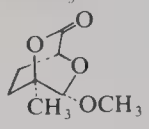
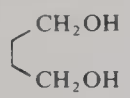
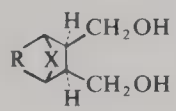
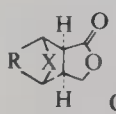
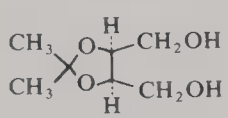
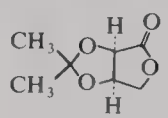
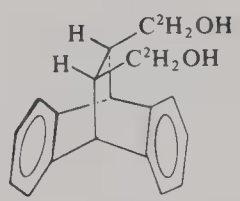
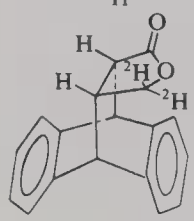
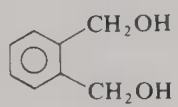
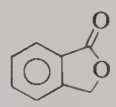
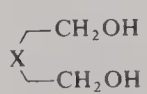
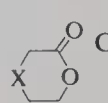
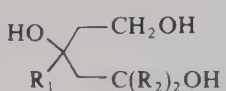
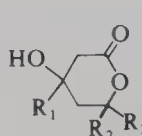
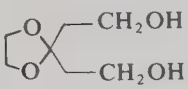
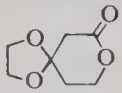
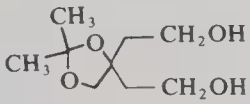
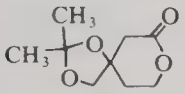
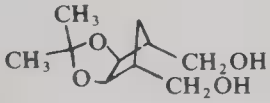
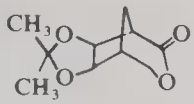
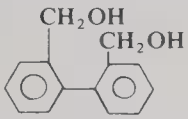
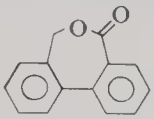
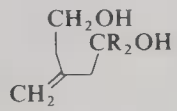
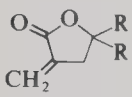
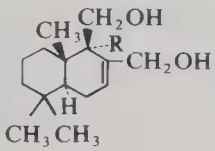
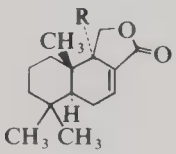
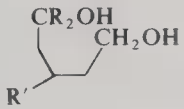
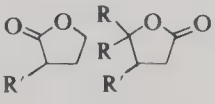
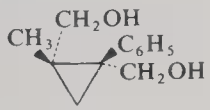
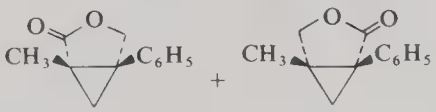
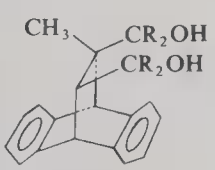
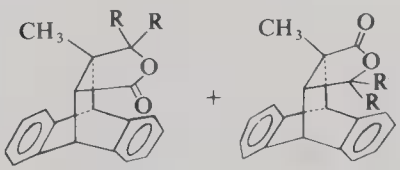
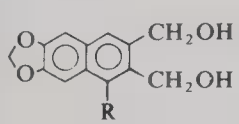
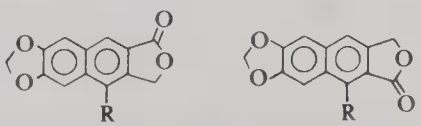
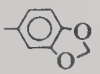
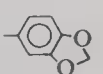
Polyols	Lactones			Lactones yield (%)	Solvent	Reference
				100	Benzene	40
		R				
		H		70	Benzene	96
		t-Bu		80	Benzene	96
				100	Benzene	95
				86	Benzene	97
				73	Toluene	98
				90	Benzene	95
		R	X			
		CH=CH	CH_2	96	Benzene	95
		CH_2-CH_2	O	85	Xylene	99
				50–65	Benzene	95
				60–75	Benzene	100
				95	Benzene	95
		X				
		CH_2		94	Benzene	95
		O		95	Benzene	95
		S		9	Benzene	95
		R_1	R_2			
		$H^2H^3H^{14}C$	H	20	Benzene	101
		CH_3	H	74	Benzene	95
		C^2H_3	H	70	Benzene	95
		CH_3	H	15	Benzene	102
		C^2H_3	^2H	70	Benzene	103

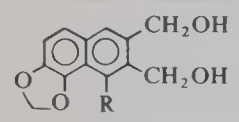
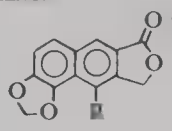
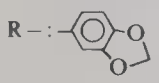
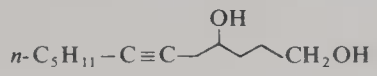
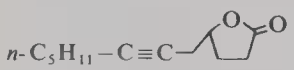
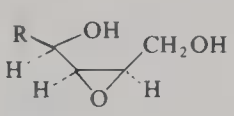
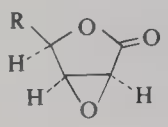
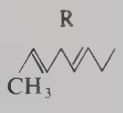
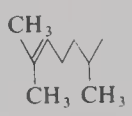
TABLE III. *Continued*

Polyols	Lactones		Lactones yield (%)	Solvent	Reference
			79	Benzene	95
			77	Benzene	95
			98	Benzene	104
Hexane-1,6-diol	ε-Caprolactone		96	Benzene	95
			100	Benzene	14
		R H ^2H	80 —	Benzene Hexane	95 100
		R H OH	100 98	— Benzene	105 106
		R R′ 70% + 30% H CH_3 40% + 60% H n-C_5H_{11} 10% + 90% ^2H n-C_5H_{11}	94 96 —	Benzene Benzene Benzene	95 95 95
		75% + 25%	—	Benzene	107
 R = ^2H	 82% + 18%		>80	Benzene	100
					
R –: 	80% (24%)[a]	20% (6%)[a]	80	Benzene	108
R –: 	85% (36%)[a]	15% (7%)[a]	100	Benzene	109

[a] Crystallized product.

Table continued

TABLE III. *Continued*

Polyols	Lactones	Lactones yield (%)	Solvent	Reference
				
	55%	8%	—	Benzene	110
		73	Benzene	111
			50	Benzene	96, 112
			20	Benzene	96
		n-C_7H_{15}	60	Benzene	96
			50	Benzene	96
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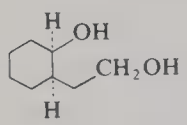
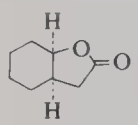
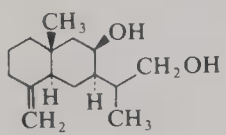
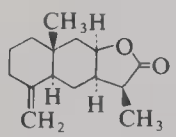
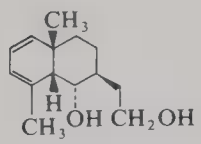
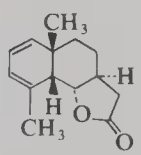
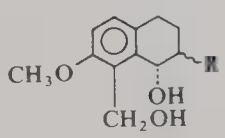
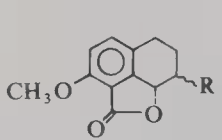
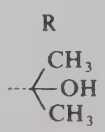
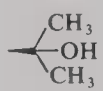
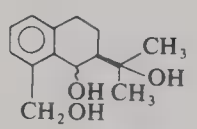
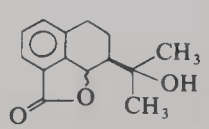
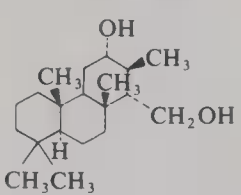
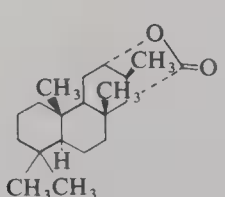
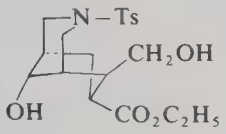
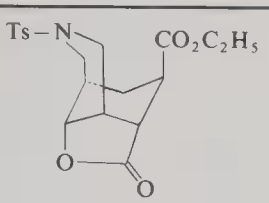
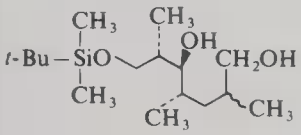
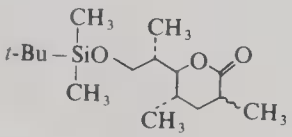
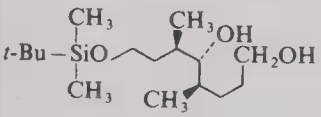
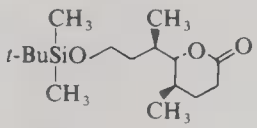
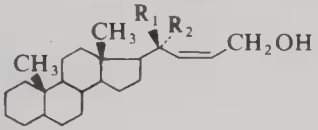
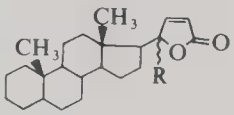
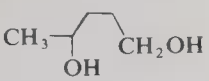
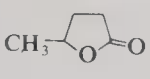
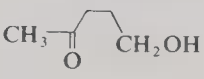
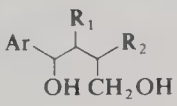
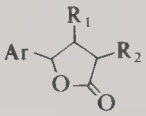
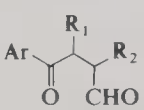
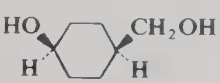
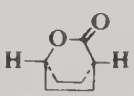
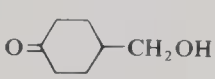
		—	Benzene	113
		100	Benzene	114
		52	Benzene	115
			55	Benzene	116
			69	Benzene	116
		51	Benzene	117
		88	Benzene	118

TABLE III. *Continued*

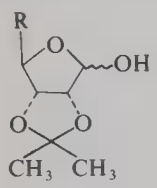
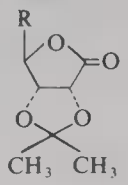
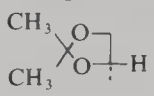
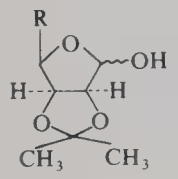
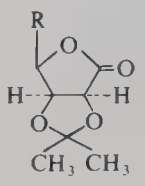
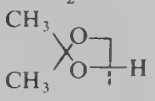
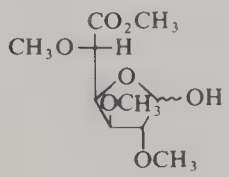
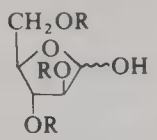
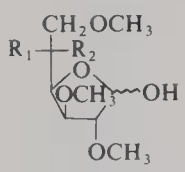
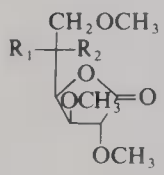
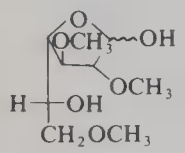
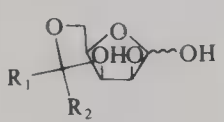
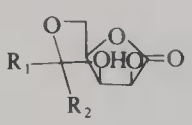
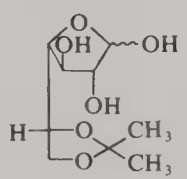
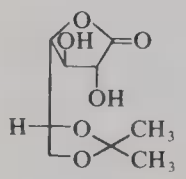
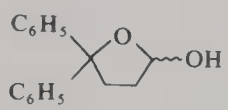
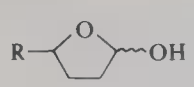
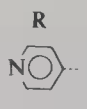
Polyols	Lactones	Lactones yield (%)	Solvent	Reference
		—	Xylene	119
		90	Benzene	120
		86	Benzene	121
	 R = H: OH, H, ···H	44	Benzene	122
	R = OH: H, H, ◄H	50	Benzene	122

Polyols	Lactones yield (%)	Ketols or Diones yield (%)	Solvent	Reference
				
	45%	55%	Benzene	95
	10%	90%	$CHCl_3$	95
				
Ar: phenyl or α-furyl; R_1: H, CH_3, H; R_2: H, H, CH_3	45% / 90% / 30%	55% / 10% / 70%	Benzene	39
				
	60%	40%	Benzene	95
	15%	85%	$CHCl_3$	95

Thus, a very remarkable regioselectivity is expected in polyhydroxy-steroids. In the bile acid series, even after a prolonged reaction time (up to 3 weeks)[170] or in toluene instead of benzene,[171] oxidation affords the 3-keto derivative only.[172,173] Similar results have been reported in other series.[174–176]

However, as emphasized previously, all the polar groups of the molecule participate in its adsorption, so that rules which are quite reliable for monohydroxylated compounds are not necessarily useful when more complex molecules are taken into consideration.

TABLE IV. Oxidations of Lactols to Lactones

Starting material	Products[a]		Lactones yield (%)	Solvent	Reference
		R H CH_2OH 	 82 80 92	 Benzene Benzene Benzene	 123 124 124
		R H CH_2OH 	 65–70 >58 98	 Benzene Benzene Benzene	 125, 124 126 124
			64	Benzene	26
		R $C_6H_5CH_2$	 91	 Benzene	 26
		R_1 R_2 H OH OH H	 >38 100	 Benzene Benzene	 127 128
			92	Benzene	128
		R_1 R_2 CH_3 CH_3 C_6H_5 H	 70 —	 Benzene Benzene/toluene	 126 129
			75	Benzene	126
			71	Benzene	130
		R	48	Xylene	130
			55	Xylene	130

[a] Indicated only in case of ambiguity.

Table continued

TABLE IV. *Continued*

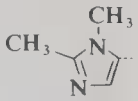
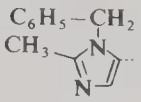
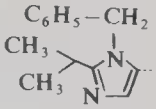
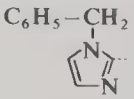
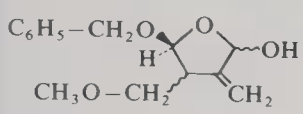
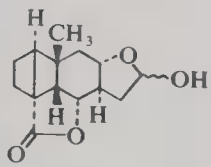
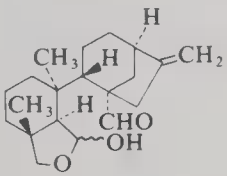
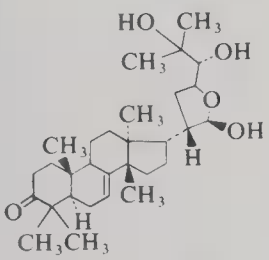
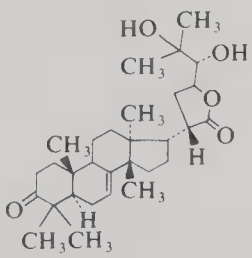
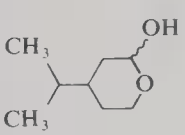
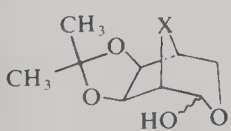
Starting material	Products[a]	Lactones yield (%)	Solvent	Reference
		22	Xylene	130
		49	Xylene	130
		61	Xylene	130
		51	Xylene	130
		25	Xylene	130
		77	Benzene	131
		88	Benzene	132
		80	Benzene	133
		—	Benzene	134
		93	Benzene	135
	X CH_2 O	70 70	Benzene Benzene	104 136

Table continued

TABLE IV. *Continued*

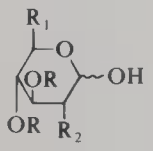
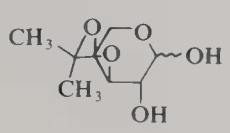
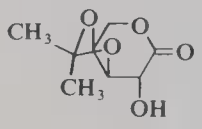
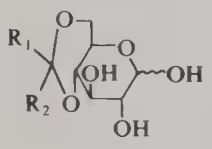
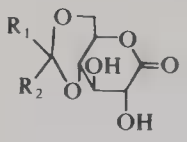
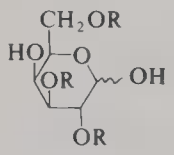
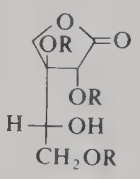
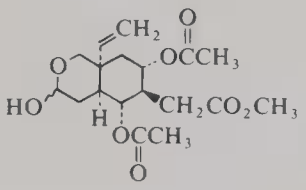
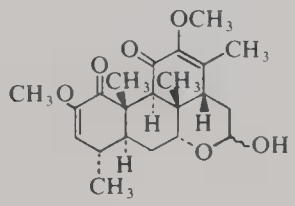
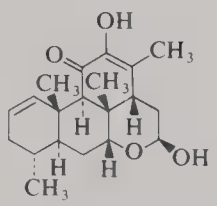
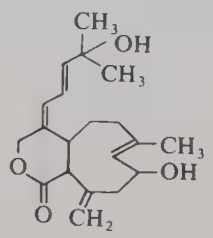
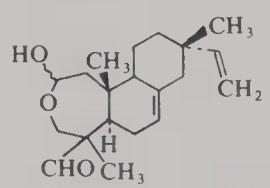
Starting material	Products[a]			Lactones yield (%)	Solvent	Reference
	R	R_1	R_2			
	CH_3	H	OR	85	Benzene	128
	CH_3	CH_2OR	OR	93	Benzene	128
	$C_6H_5-CH_2$	CH_2OR	OR	72	Benzene	26
	$C_6H_5-CH_2$	CO_2R	OR	42	Benzene	26
	$C_6H_5-CH_2$	CH_2OR	$NHCOCH_3$	61	Benzene	26
				48	Benzene	124
		R_1	R_2			
		C_6H_5	H	49	Benzene/DMF	129
		CH_3	H	71	Benzene	129
		CH_3	CH_3	72	Benzene	129
		R				
		H		Good	H_2O	137
		CH_3		100	Benzene	128
				48	Benzene	138
				77	Benzene	139
				>73	Benzene	140
				33	Toluene	141
				97	Benzene	142

TABLE V. Oxidations of Polyols to Ketols or Diketones

Starting material		Products: A yield (%)	B yield (%)	Cleaved yield (%)	Dione yield (%)	Solvent	Reference
$R-CH(OH)-CHR'(OH)$		$R-C(=O)-CH(OH)-R'$	$R-CH(OH)-C(=O)-R'$	Cleaved	$R-C(=O)-C(=O)-R'$		
R	R′						
(E) $CH_3-CH=C(CH_3)$ *dl*;	R	0		Only		Benzene	144
(E) $CH_3-CH=C(CH_3)$ *meso*;	R	80		—		Benzene	144
(E) $CH_3-CH=C(CH_3)$;	(Z) $CH_3-CH=C(CH_3)$	80	20	—		Benzene	144
Mixture threo 57%–58% + erythro 43%–42%:							
$CH_2=C(CH_3)$;	*p*-Cl$-C_6H_4$	80	20	—		Benzene	144
$CH_2=C(CH_3)$;	C_6H_5	44	56	—		Benzene	144
$CH_2=C(CH_3)$;	*p*-$CH_3-C_6H_4$	40	60	—		Benzene	144
$CH_3-CH=CH$;	C_6H_5	80	20	—		Benzene	144
$CH_3-CH=CH$;	*p*-$CH_3C_6H_4$	62	38	—		Benzene	144
$CH_3-CH=CH$;	*p*-$CH_3OC_6H_4$	58	42	—		Benzene	144
Mixture in various proportions:							
$CH_2=C(CH_3)$;	*p*-$CH_3C_6H_4$						
threo	erythro						
100%	0%	0	0	85	0	Benzene	144
90%	10%	4	3	76	3	Benzene	144
58%	42%	20	14	43	3	Benzene	144
34%	66%	32	22	36	4	Benzene	144

Table continued

TABLE V. *Continued*

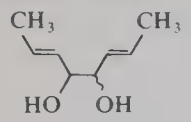
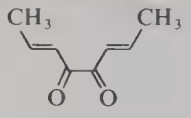
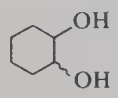
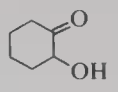
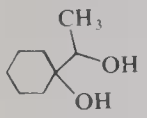
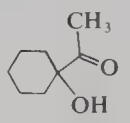
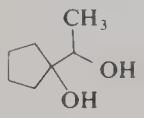
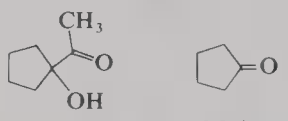
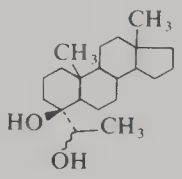
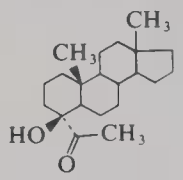
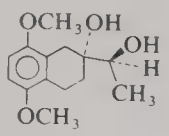
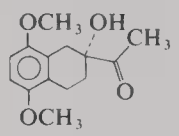
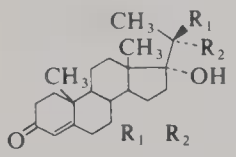
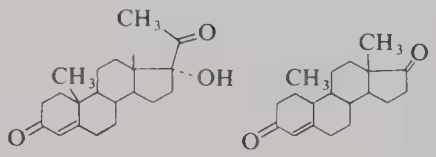
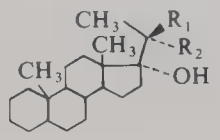
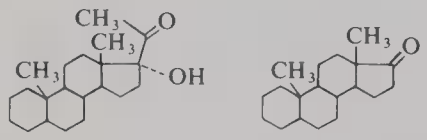
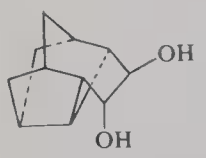
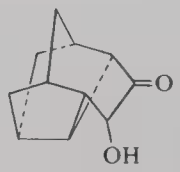
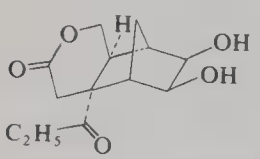
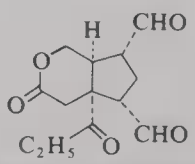
Starting material	Products	Yield (%)	Solvent	Reference
		32	Benzene	150
		45	Benzene	149
		85	Benzene	145
	 —% Major		Benzene	151
		70	Benzene	145
		90	Benzene	152
				
R_1 R_2				
H OH	54%	11%	Benzene	145
OH H	27%	63%	Benzene	145
				
R_1 R_2				
H OH	75%	3%	Benzene	145
OH H	—	80%	Benzene	145
		85	Benzene	146
		Major	Benzene	153

Table continued

TABLE V. *Continued*

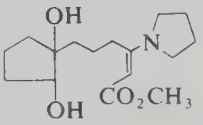
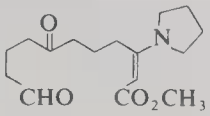
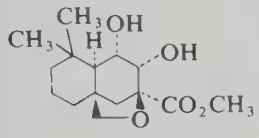
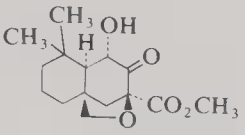
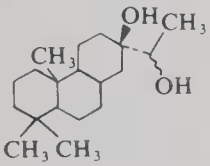
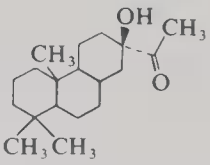
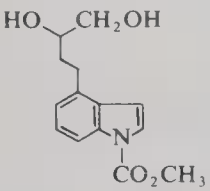
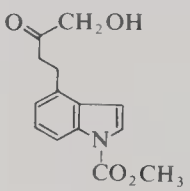
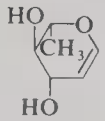
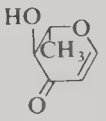
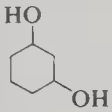
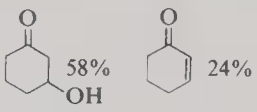
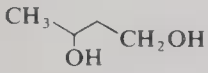
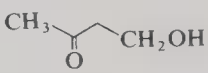
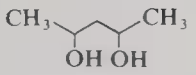
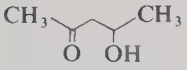
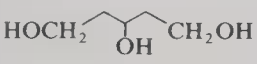
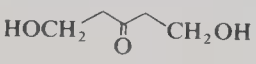
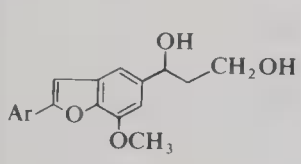
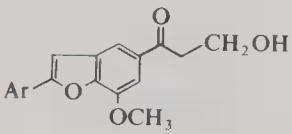
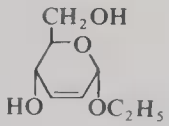
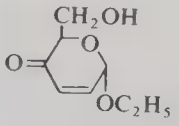
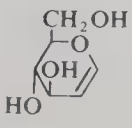
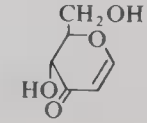
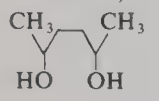
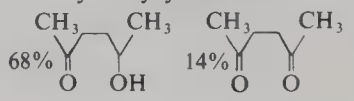
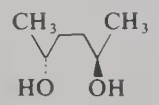
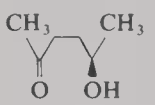
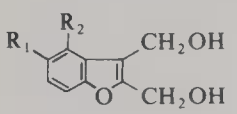
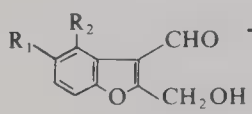
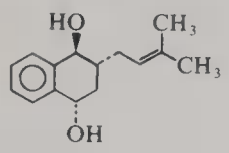
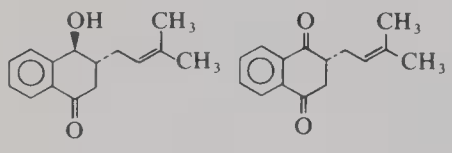
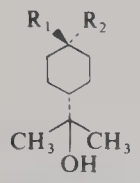
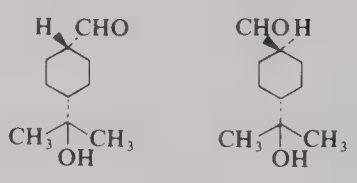
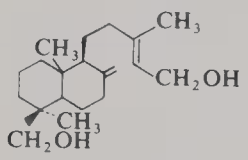
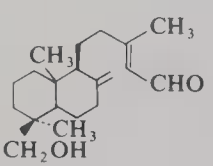
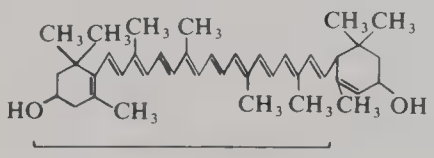
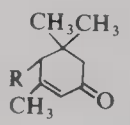
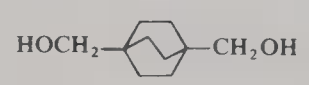
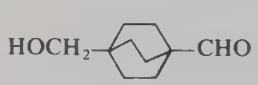
Starting material	Products	Yield (%)	Solvent	Reference
		65–75	Benzene	154
		<33 Major	Benzene Toluene	155 155
		90	Benzene	46
		40	Benzene	156
		59	Benzene	157
			Benzene	149
		80	Benzene	149
		83	Benzene	149
		43 82	Benzene $CHCl_3$	149 158
		59	Benzene	159
		85	Benzene	160
		70	Benzene	161

Table continued

TABLE V. *Continued*

Starting material	Products	Yield (%)	Solvent	Reference
Cyclohexane-1,4-diol	4-Hydroxycyclohexanone	80	Benzene	149
			Benzene	158
		46	Benzene	162
				
	R_1 = H, R_2 = H	85	Ethyl acetate	163
	R_1 = CH_3, R_2 = H	85	Ethyl acetate	164
	R_1 = H, R_2 = CH_3	62	Ethyl acetate	164
				
	71% 2%		Benzene (N_2)	165
				
R_1 = CH_2OH, R_2 = H	0% only		Benzene	27
R_1 = H, R_2 = CH_2OH	65% 6%		Benzene	27
		60	Methanol	166
		25	Benzene	66
		75	Benzene	167

For instance, in boiling benzene, androstane-3β,5α,6β-triol is oxidized at C-6 essentially, although androstane-6β-ol is unaffected under the same conditions.

The only accessible hydrogen atom, later oxidized into a proton, in the "trianchored" adsorbed state, is the 6α one (Fig. 3). Addition of chloroform increases the proportion of less strongly adsorbed (i.e., "monoanchored") steroid, thus increasing the rate of formation of the 3-keto compound.[177] In sharp contrast androstane-3β,5α,6α-triol is normally oxidized into the 3-ketosteroid. No trace of 6-keto derivative could be found, in agreement with the simplified mechanism proposed.

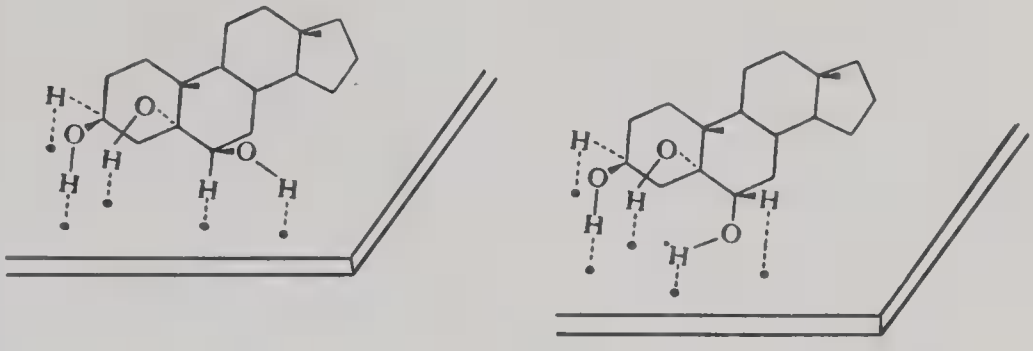


FIGURE 3

Similarly[168] 5α-androstane-3β,6β-diol is preferentially oxidized in benzene at C-6, although, under the same conditions, the rate of oxidation of androstane-3β-ol is about 9 times larger than that of androstane-6β-ol.[13] In chloroform, more polar than benzene, the proportion of "monoanchored" steroid is much higher, and oxidation takes place at C-3.[168]

Generally speaking, a primary alcohol is oxidized more slowly than a secondary one. Examples of a reversed order of reactivity have been reported[178] for which the same explanation as above may be provided.

The very striking difference of reactivity of pregnane-17α,20α-diol and pregnane-17α,20β-diol which have been indicated previously may also be explained on the basis of the same mechanism. The oxidation of cholesterol is very unspecific, leading to many products, even when the reaction is carried out under argon. This is due to the instability of the intermediate cholest-5 ene-3 one, since 4,4-dimethyl-cholesterol undergoes the expected oxidation of the OH group.[179]

Double bonds farther away from the hydroxyl group do not seem to have any measurable effect on the oxidation rates.

TABLE VI. Oxidations in the Steroid, Di- or Triterpene Series

Starting material		Ketone or aldehyde yield (%)	Solvent	Reference
Monohydroxy-	*Compounds*			
2α-	5α-androstane	—	Benzene	13
2α-	A-Nor-5α-androstane	95	Heptane	158
2β-	5α-androstane	99	Benzene	180
3α-	5α-androstane	96–97	Benzene	181
3α-	2β[2]H-5α-androstane	85	Heptane	158
3α-	5α-androst-16-ene	93–95	Benzene	181
3α-	21-acetoxy-5α-pregnane-11,20-dione	50	Benzene	182
3α-	methyl 5β-cholan-24-oate	High	Benzene	172
3β-	5α-androstane	87	Benzene	10
3β-	4-androstene	95	Benzene	24
		96	Methanol	24
3β-	5-androstene	0	Benzene	168

Table continued

TABLE VI. *Continued*

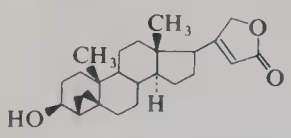
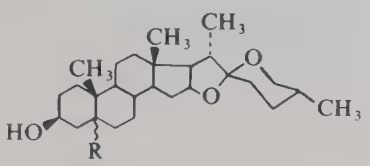
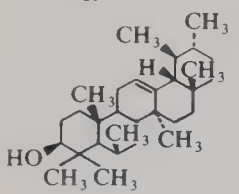
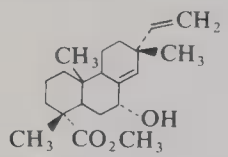
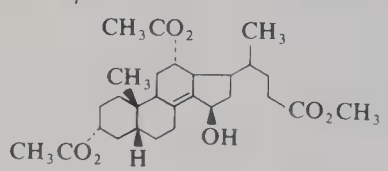
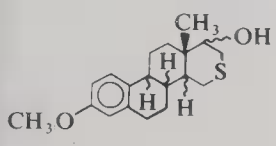
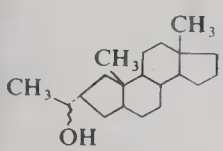
Starting material		Ketone or aldehyde yield (%)	Solvent	Reference
Monohydroxy-	*Compounds*			
3β-	5α-androst-6-ene	100	Benzene	183
3β-	4β[2]H-5α-androst-6-ene	75	Benzene	183
3β-	5α[2]H-androst-6-ene	75	Benzene	183
3β-	5α-androst-16-ene	95–98	Benzene	181
3β-	5α,13α-androstane	95	Benzene	181
3β-	17a,17a-dimethyl-D-homo-5α-androstane	92	Benzene	184
3β-	5β-androstane	93–96	Benzene	181
3β-	5β-androst-16-ene	93–96	Benzene	181
3β-	7,7-ethylenedithio-5α-cholestane	61	Benzene	10
3β-	4,4,14α-trimethyl-5α-cholest-8-ene	95	Benzene	185
3β-	21-Nor-5α-cholest-17 → 20-ene	90	Benzene	186
3β-	24-methyl-5β-cholesta-8,22-diene	77	—	187
3β-	methyl 12-keto-5β-cholan-24-oate	94	Toluene	10
		75	Toluene	188
	R			
	5α-H	93	Benzene	185
	5β-H	94	Benzene	10
	(α-amyrine)	98	Benzene	185
6α-	5α-androstane	5	Benzene	180
6α-	3α,5α-cyclocholestane	70	Benzene	180
6β-	5α-androstane	94	Benzene	180
6β-	3α,5α-cycloandrostane	100	Benzene	189
6β-	17β-OTs-3α,5α-cycloandrostane	45	Benzene	180
7α-	5α-androstane	0	Benzene	13
		0	Benzene	169
7β-	5α-androstane	—	Benzene	13
		0	Benzene	170

TABLE VI. *Continued*

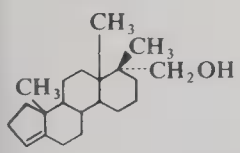
Starting material		Ketone or aldehyde yield (%)	Solvent	Reference
Monohydroxy-	*Compounds*			
17α-	5α-androstane	98	Benzene	180
17α-	3β-acetoxy-13α-androst-5-ene	80	Benzene	180
17β-	5α-androstane	98,5	Benzene	10
		99,5	Acetone	10
17β-	3,3-ethylenedioxy-5α-androstane	95	Benzene	24
17β-	1,4-androstadien-3-one	99	Benzene	158
17β-	3β-acetoxy-13α-androst-5-ene	97	Benzene	180



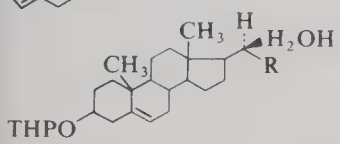
9-H	8-H	14-H	17a-OH			
α	β	β	α	44 (68,5)[a]	Toluene (N_2)	190
α	α	β	α	68	Toluene (N_2)	190
α	β	α	β	28 (68)[a]	Toluene (N_2)	190
dehydro		α	β	40 (52)[a]	Toluene (N_2)	190
dehydro		β	α	57	Toluene (N_2)	190



95	Heptane	158

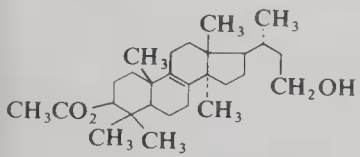


96	Benzene	184

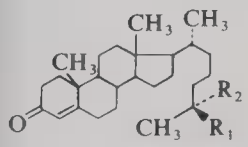


R			
CH_3	98	Benzene	191
$(CH_3)_2CH-(CH_2)_3-$	67[b]	Benzene	191

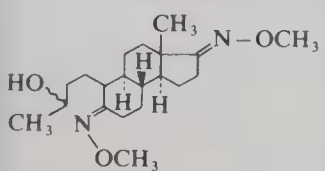
20β-	3β-acetoxy-5-pregnene	97	Benzene	185



67	Benzene	192
94,5	Benzene	10
91	Benzene	193
81	Benzene	193



R_1	R_2			
H	CH_2OH	—	Benzene	194
CH_2OH	^3H	—	Toluene	195

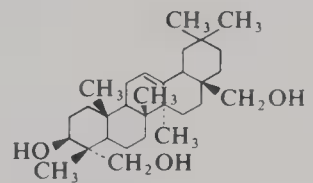
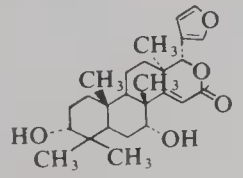


70	Xylene (N_2)	196

[a] Yield (%) based upon the recovered starting material.
[b] After recrystallization.

Table continued

TABLE VI. *Continued*

Starting material		Products	Yield (%)	Solvent	Reference
Dihydroxy	*Compounds*				
1α,17β-	5α-androstane	1α-OH 17-one(+ 1,17-dione 6%)	70	Toluene	197
1β,17β-	5α-androstane	1β-OH 17-one	73	Toluene	197
		3β-OH 4-CHO	90	Benzene	178
3β,5α-	androstan-6-one	3-one 5α-OH + 4-androstene-3,6-dione 80% / 20%	75	Benzene	177
3α,6α-	methyl 5β-cholan-24-oate	3-one 6α-OH	90	Benzene	170
3β,6α-	5α-androstane	3-one 6α-OH	87–94	Benzene	168
3β,6β-	5α-androstane	3-one 6β-OH + 3β-OH 6-one + 3,6-dione 29% 43% 15%		Benzene	168
		68% 31% 15% (?)		$CHCl_3$/benzene	168
3α,7α-	methyl 5β-cholan-24-oate	3-one 7α-OH	84	Toluene	171
			High	Benzene	172
			100	Benzene	173
		3-one 7α-OH	57	Benzene	198
3α,7β-	methyl 5β-cholan-24-oate	3-one 7β-OH	87	Benzene	170
			90	Toluene	171
3β,7α-	5α-androstane	3-one 7α-OH	65	Benzene	199
3β,7α-	17,17-ethylenedioxy-5α-androstane	3-one 7α-OH	77	Benzene	168
3β,7β-	5α-androstane	3-one 7β-OH	77	Benzene	199
3β,7β-	17,17-ethylenedioxy-5α-androstane	3-one 7β-OH	89	Benzene	199

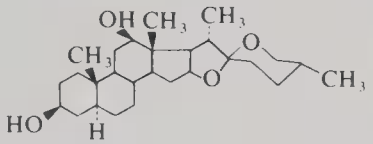
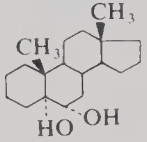
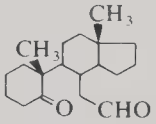
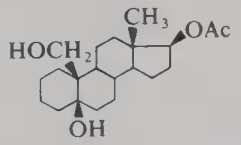
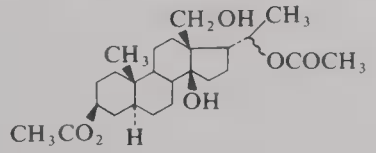
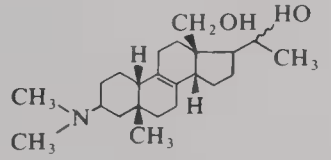
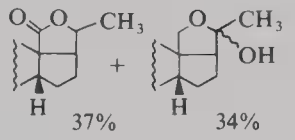
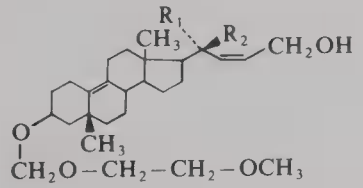
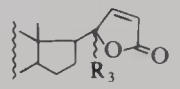
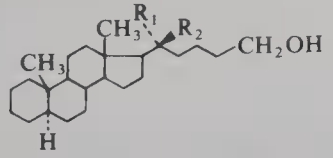
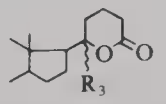
3β,11α-	5α-androstane	3-one 11α-OH	92	Benzene	168
3β,11α-	D-homo-5α-androstane	3-one 11α-OH	94	$C_6H_6/CHCl_3$	174
3β,11β-	5α-androstane	3-one 11β-OH	95	Benzene	168
3α,12α-	methyl 5β-cholan-24-oate	3-one 12α-OH	100	Benzene	170
			90	Toluene	171
3β,12α-	5α-androstane	3-one 12α-OH	80	Benzene	168
3β,12β-	5α-androstane	3-one 12β-OH	80	Benzene	168
		3-one 12β-OH	98	Benzene	24
3β,15α-	5α-androstan-11-one	3-one 15α-OH	60	Benzene	200
3β,15α-	5α-cholestane	3-one 15α-OH	88	Toluene	201
3β,15α-	5α-cholest-7-ene	3-one 15α-OH	89	Toluene	202
3β,15α-	5α-cholest-8-ene	3-one 15α-OH	90	Toluene	202
3β,17β-	5α-androstane	3-one 17β-OH + 3,17-dione 51% 26%		Benzene	24
3β,17β-	4-androstene	3-one 17β-OH	95	Acetone	10
			90	Methanol	24
3α,24-	5β-cholane	3-one 24-OH + 3α-OH 24-al + 3-one, 24-al 54% 12% 25%		Benzene	158
3β,24-	4,4,14α-trimethyl-5α-cholest-8-ene	3-one 24-OH + 3β-OH 24-one + 3,24-dione 3% 33% 38%		Benzene	158
			Major	Benzene	177
5α,6β-	androstane	5α-OH 6-one	100	Benzene	177
5α,6β-	androstan-3-one	5α-OH + 3-one-6β-OH 3,6-dione 5-androstene 25% / 75%	50	Benzene	177

Table continued

TABLE VI. *Continued*

Starting material		Products	Yield (%)	Solvent	Reference
Dihydroxy-	*Compounds*				
		5β-OH 19-al	90	Benzene	30, 31
6α,17β-	4,4-dimethyl-5α-androstane	6α-OH 17-one	94	Benzene	184
11β,17β-	5α-androstane	11β-OH 17-one	98	Benzene	168
12β,15α-	5α-androstane	12-one 15α-OH	63	Benzene	176
		14β-OH 18-al	0	Benzene	29
15β,17β	5α-androstane	15β-OH 17-one	85	Benzene	176
		 37% 34%		Benzene	203
					
		R1 R2 R3			
		OH H ---H	43	Benzene	204
		H OH ◄H	58	Benzene	204
					
		R1 R2 R3			
		OH H ---H	40	Benzene	205
		H OH ◄H	73	Benzene	205

Trihydroxy-	*Compounds*				
3β,5α,6α-	androstane	3-one + 3-one 6α-OH 5α,6α-$(OH)_2$ androst-5-ene 60% 8%		Benzene	177
3β,5α,6β-	androstane	3-one 6-one 3,6-dione 5α,6α-$(OH)_2$ 3β,5α-$(OH)_2$ 5α-OH			
		20% 55% 10%		Benzene	177
		57% 10% 12%		$CHCl_3$	177
3β,7β,11α-	5α-androstan-17-one	3-one 7β,11α-$(OH)_2$	76	Toluene	199
3α,7α,12α-	methyl 5β-cholan-24-oate	3-one 7α,12α-$(OH)_2$	90	Benzene	10
			72	Toluene	171
			High	Benzene	172
3β,7α,15α-	5α-cholest-8 → 14-ene	3-one 7α,15α-$(OH)_2$	88	Toluene	175
3β,11β,16β-	5α-androstane	3,16-dione 11β-OH (+7% 3,11,16-trione)	85	Benzene	168
3β,12β,15α-	5α-androstane	3-one 12β,15α-$(OH)_2$	82	Benzene	168
			82	Toluene	176
3α,12α,24-	5β-cholane	3-one, 24-al 12α-OH	94	Benzene	170
3α,17α,20β-	5β-pregnan-11-one	3-one 17α,20β-$(OH)_2$	70	Benzene	158
3β,17α,20-	4-pregnene	3-one 17α,20-$(OH)_2$	>90	Acetone	206
Tetrahydroxy-	*Compounds*				
3α,7α,12α,24-	25-Nor-5β-cholestane	3-one 7α,12α,24-$(OH)_3$	—	Benzene	172
3α,7α,12α,25-	5β-cholestane	3-one 7α,12α,25-$(OH)_3$	58	Benzene	172
3α,7α,12α,26-	5β-cholestane	3-one 7α,12α,26-$(OH)_3$ 40% 3α,7α,12α-$(OH)_3$ 26-al 45% 3-one, 26-al 7α,12α-$(OH)_2$ 15%	67	Benzene	207

3.7. Carbohydrates

A considerable amount of work, reviewed earlier,[208] has been devoted to silver carbonate on Celite oxidation of carbohydrates. Two major reaction types are to be noticed: regioselectivity of the reaction, and vicinal diols cleavage, leading to various degradation patterns.

3.7.1. Regioselectivity

Oxidation of the nonprotected D-glucal takes place at the allylic hydroxyl group only.[161] Similar regiospecific oxidations of related compounds have been reported.[157,160] Olefinic sugars are readily oxidized at the allylic hydroxyl group in preference to free non-allylic OH groups.[22] However, the oxidation fails completely with the corresponding acetylenic carbohydrates, which, very likely, undergo a cleavage leading to acetylene and an aldehyde, as shown by Lenz in the steroid series[21,22] (Table VII).

Obviously, when the hydroxyl group at C-1 is free, as in aldoses, oxidation takes place very readily, and the corresponding lactone is generally obtained in high yield (Table IV) *at least when benzene, toluene, or mixtures of benzene/DMF are used as solvents.* However, when there is an unprotected hydroxyl at C-2, as first noted by Morgenlie[209] *especially in methanol,* the major compound is not a lactone, but a degradation product.

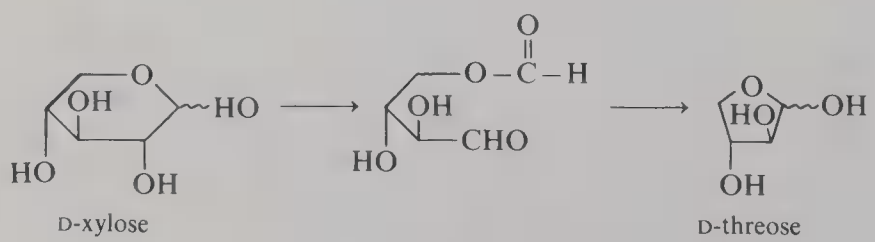
3.7.2. Degradation

3-*O*-methyl-D-glucose is oxidized by silver carbonate on Celite in methanol, but the compound which is isolated is *not* the corresponding gluconolactone. A fast cleavage occurs between C-1 and C-2, leading to the intermediate 3 and 4 formates of 2-*O*-methyl-D-arabinose,[209] which either by mild alkaline hydrolysis or prolonged treatment with the oxidizing agent affords 2-*O*-methyl-arabinose in good yield. Under these conditions, 2-*O*-methylaldopentoses are not further oxidized to lactones.

In a similar way, D-xylose was completely oxidized within 90 min at room temperature. The initially obtained formate could easily be hydrolyzed into D-threose[125] (Fig. 4).

2-Ketoses undergo a similar degradation. Thus D-fructose gives the glycolic ester of erythrose, and, after mild hydrolysis, the tetrose itself.[123] This degradation of aldoses and ketoses seems to be quite general (Table VIII). More extensive but also more sluggish degradations have also been recorded. Thus, D-fructose in methanol leads to D-glyceraldehyde and other identified products.

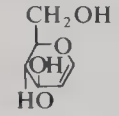
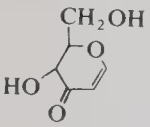
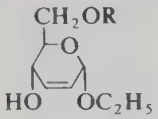
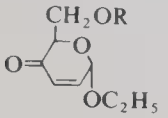
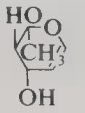
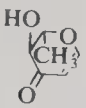
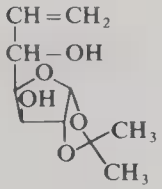
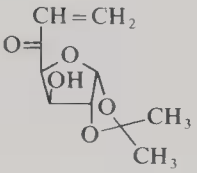
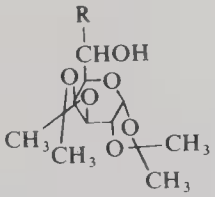
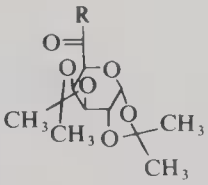
The Morgenlie degradation of aldoses can eventually be used to determine the substituent position of *O*-methyl aldoses.[210] Silver carbonate on Celite oxidation of 1,2-*O*-isopropylidene α-D-glucofuranose for 10 h in boiling methanol leads to a methyl xyluronate derivative[214] (Fig. 5). Very likely, an aldehyde is formed by cleavage of the side chain. The corresponding hemiketal is then oxidized into a methyl ester (Table IX). Under the same conditions, other α-hydroxy aldehydes, such as glycolaldehyde and glyceraldehyde



D-xylose D-threose

FIGURE 4

TABLE VII. Regiospecific Oxidation of Carbohydrates

Starting material	Products		Yield (%)	Solvent	Reference
			70	Benzene	161
		R H Ts	85 0	Benzene Benzene	160 160
			59	Benzene	157
			41	Benzene	22
		R $CH=CH_2$ $C\equiv CH$	52 0	Benzene Benzene	22 22

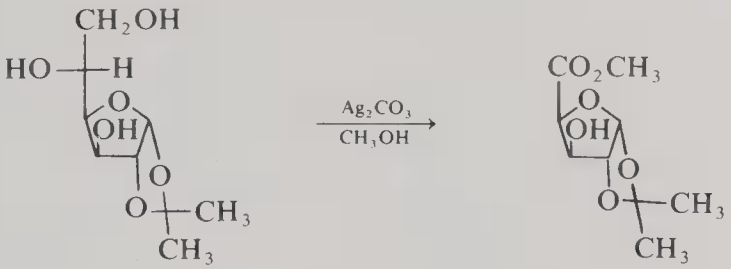


FIGURE 5

are also oxidized into the corresponding methyl esters.[215] 1,3-Dihydroxy acetone is also oxidized into methyl glycolate.*

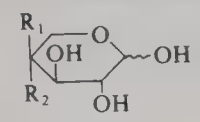
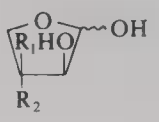
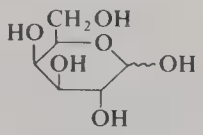
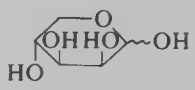
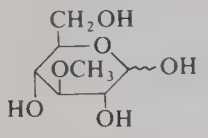
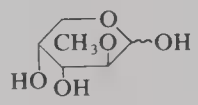
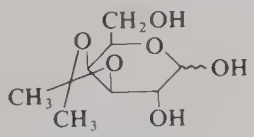
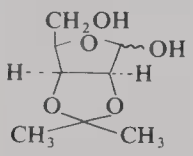
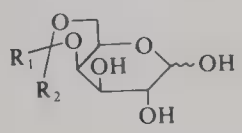
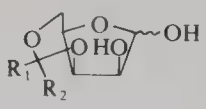
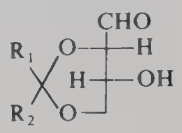
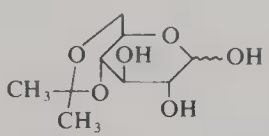
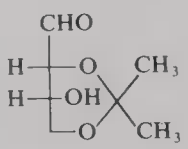
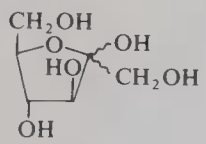
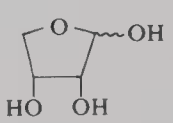
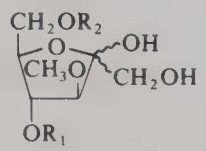
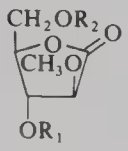
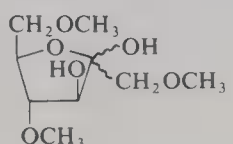
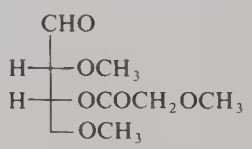
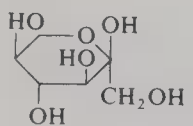
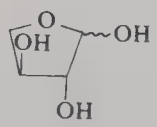
3.8. Oxidation of Phenols

3.8.1. Formation of Quinones

Silver carbonate on Celite converts hydroquinones to *p*-quinones and catechols to *o*-quinones. The reaction is nearly quantitative, at 0°C or at room temperature or in refluxing dichloromethane, within 2 h or less. Even sensitive quinones such as methoxybenzo-

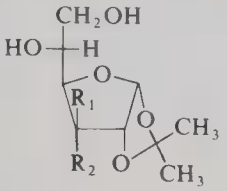
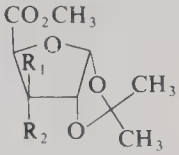
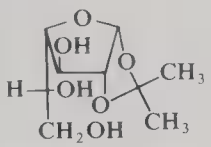
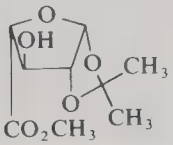
* At the very beginning of our research in this field, we also noted[185] that the *unprotected* side chain of cortisone was slowly degraded. A 17-keto steroid was obtained. However, the 21-acetate was stable towards silver carbonate on Celite in boiling benzene.

TABLE VIII. Degradation of Carbohydrates

Starting material	Product			Yield (%)	Solvent	Reference
		R_1	R_2			
		OH	H	41	Methanol	211
		H	OH	38	Methanol	211
				36	Ethanol	137
				71	Methanol	209
				>58	Methanol	126
		R_1	R_2			
		CH_3	CH_3	76	C_6H_6/DMF	126
		CH_3	H	77	C_6H_6/DMF	129
		C_6H_5	H	55	C_6H_6/DMF	129
	or 	CH_3	CH_3	—	Methanol	126
		CH_3	H	65	Methanol	129
		C_6H_5	H	59	Methanol	129
				61	Methanol	129
	 (+glyceraldehyde)			>37	Methanol	123
		R_1	R_2			
		H	H	70	Methanol	212
		CH_3	H	74	Methanol	212
		CH_3	CH_3	81	Methanol	212
				90	Methanol	212
				>39	Methanol	213

Major	Minor			
D-Tagatose	D-Threose	D-glyceraldehyde	Methanol	123
D-Psicose	D-Erythrose	D-glyceraldehyde	Methanol	123
D-altro-Heptulose	D-Ribose	D-Erythrose	Methanol	123
D-manno-Heptulose	D-Arabinose	D-Erythrose	Methanol	123
D-glycero-D-manno-Octulose	D-Altrose	D-Ribose	Methanol	123

TABLE IX. Methyl Esters from Aldehydes

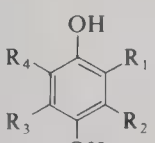
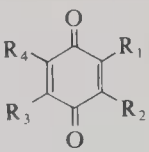
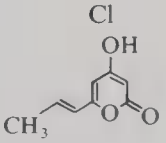
Starting material	Product	Yield (%)	Solvent	Reference
$HOCH_2-CHO$	$HOCH_2-CO_2CH_3$	55	Methanol	215
$CHO-CHO$	$CHO-CO_2CH_3$	>65	Methanol	215
$HOCH_2-CHOH-CHO$	$HOCH_2-CHOH-CO_2CH_3$	>56	Methanol	215
$HOCH_2-CO-CH_2OH$	$HOCH_2-CO_2CH_3$	>63	Methanol	215
	 R_1 = H, R_2 = OH	53	Methanol	214
	R_1 = OH, R_2 = H	68	Methanol	36
		39	Methanol	214

quinone are quantitatively obtained (Tables X and XI). "Extended" quinones such as diphenoquinones (Table XII) and stilbenequinones (Table XIII) are obtained in nearly quantitative yields. Even with an "extended" quinone the yield is very high[220] (Fig. 6). The reagent is also useful for the preparation of tropoquinone[221] (Fig. 7). Three nitrogen analogs of hydroquinones have been oxidized. In the case of *o*-aminophenol, dimerization of the intermediate radical, or of the corresponding *o*-quinone-monoanil, occurs (Figs. 8 and 9).

3.8.2. Oxidative Coupling of Phenols

Hindered phenols with a free *para*-position are quantitatively oxidized to diphenoquinones (Table XIV). When the *para* position is substituted by a methyl group, corresponding stilbene-quinones are obtained in high yields (Table XV). When the formation of "extended" quinones is impossible, the hindered phenol ($R=(CH_3)_3C-$) gives free radicals such as *A* and *B*[216] (Fig. 10).

TABLE X. *p*-Quinones from Hydroquinones

p-Hydroquinone	R_1	R_2	*p*-Quinones	R_3	R_4	Yield (%)	Solvent	Reference
	H	H		H	H	97	Benzene	216
	CH_3	H		H	H	98	Benzene	216
	CH_3O	H		H	H	100	Benzene	216
	CH_3	H		$(CH_3)_3C$	H	98	Benzene	216
	$(CH_3)_3C$	H		$(CH_3)_3C$	H	98	Benzene	216
	Cl	Cl		Cl	Cl	99	Benzene	216
	OH	H			H	32	Benzene	216
	H	H				100	Benzene	216

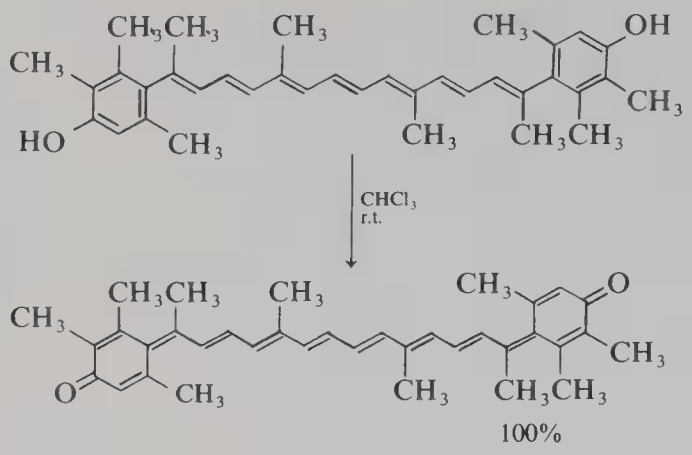


FIGURE 6

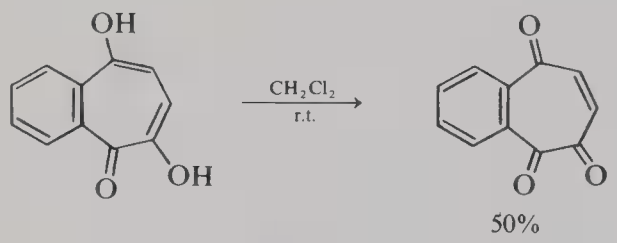


FIGURE 7

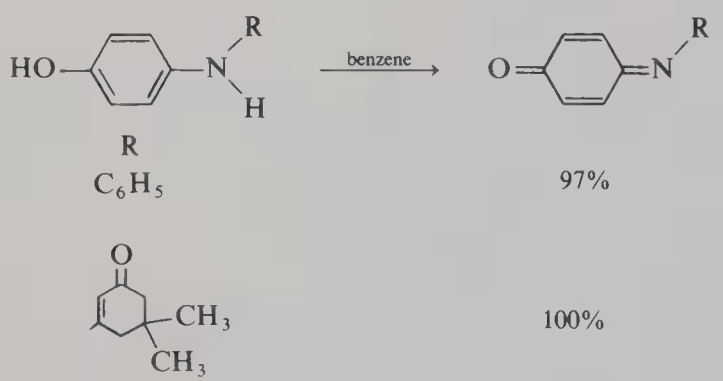


FIGURE 8

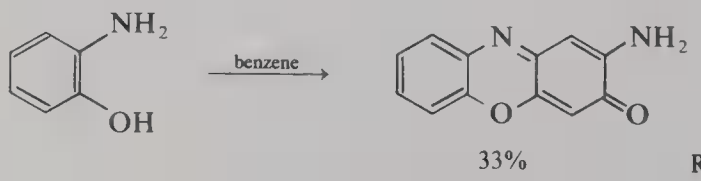
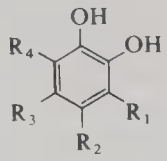
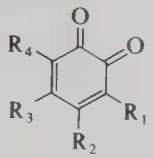
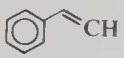
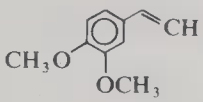
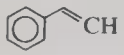
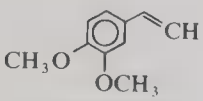


FIGURE 9

TABLE XI. *O*-Quinones from Catechols

Catechols		*O*-Quinones		Yield (%)	Solvent	Reference
						
R_1	R_2	R_3	R_4			
H	H	H	H	98	Benzene	216
H	CH_3	H	H	100	Benzene	216
H	$(CH_3)_3C$	H	H	98	Benzene	216
$(CH_3)_3C$	H	$(CH_3)_3C$	H	99	Benzene	216
H	$(CH_3)_3C$	H	Cl	33	Benzene	218
H	$CH_3-C(=O)$	H	CH_3O	65	Benzene	219
H		H	H	95	Benzene	219
H		H	H	90	Benzene	219
H		H	CH_3O	90	Benzene	219
H		H	CH_3O	89	Benzene	219

Unhindered phenols give complex mixtures, from which the expected products have been isolated in very low yields.* *p*-Nitrophenol is not oxidized.[222] When an *ortho* vinyl double bond is present, cyclization to furan derivatives may occur[223,224] along the various ways of phenol radical coupling. In some cases, the reaction requires the presence of sodium hydrogen carbonate.[225]

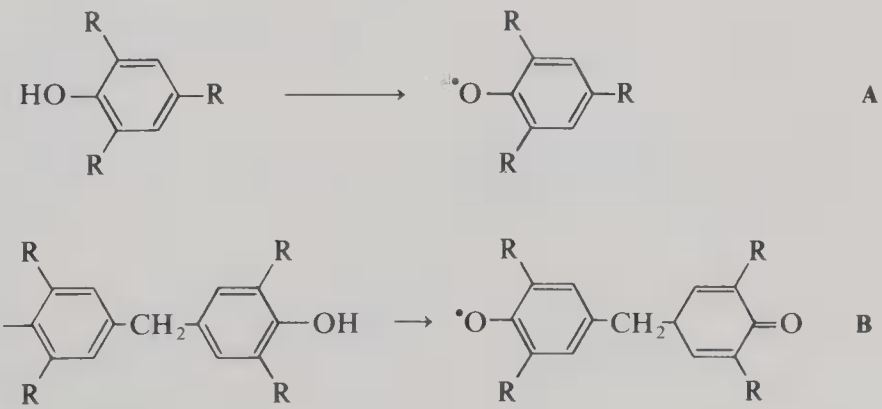


FIGURE 10

* *p*-Cresol gives Pummerer's ketone (R = CH_3, R′ = H, Fig. 11) in 10% yield.[228]

TABLE XII. Diphenoquinones from Dihydroxy-diphenyls

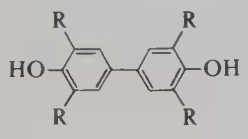
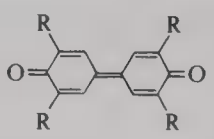
Dihydroxy-diphenyls	Diphenoquinones	Yield (%)	Solvent	Reference
				
	R			
	CH_3	98	Benzene	216
	$(CH_3)_2CH$	97	Benzene	216
	$(CH_3)_3C$	95	Benzene	216

TABLE XIII. Stilbene-quinones from *p*, *p'*-Dihydroxy-stilbenes

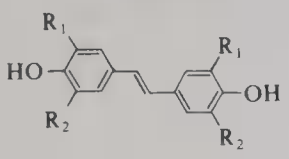
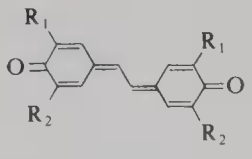
p, *p'*-Dihydroxy-stilbenes	Diphenoquinones	Yield (%)	Solvent	Reference
				
R_1 R_2				
CH_3 CH_3		83	Benzene	216
$(CH_3)_3C$ $(CH_3)_3C$		90	Benzene	216
CH_3 $(CH_3)_3C$		83	Benzene	216

TABLE XIV. Diphenoquinones from *para*-Unsubstituted Phenols

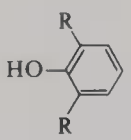
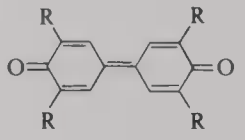
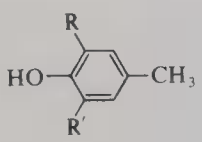
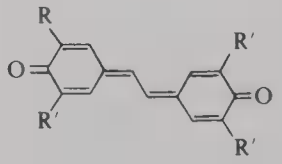
Phenols	Diphenoquinones	Yield (%)	Solvent	Reference
				
R				
CH_3		98	Benzene	216
$(CH_3)_2CH$		100	Benzene	216
$(CH_3)_3C$		99	Benzene	216

TABLE XV. Stilbene-quinones from *para*-Methylphenols

para-Methylphenols	Stilbene-quinones	Yield (%)	Solvent	Reference
				
R R′				
CH_3 CH_3		93	Benzene	216
$(CH_3)_3C$ $(CH_3)_3C$		90	Benzene	216
CH_3 $(CH_3)_3C$		97	Benzene	216

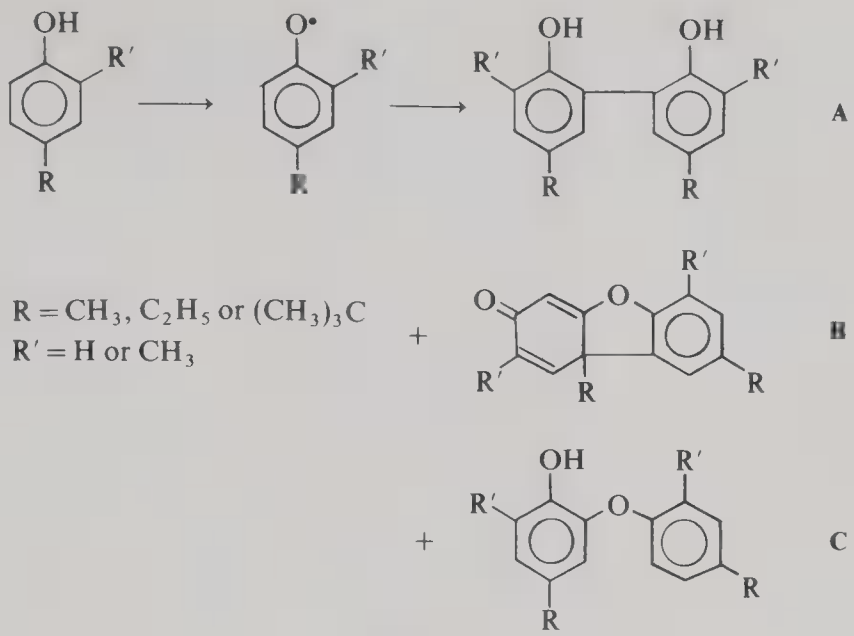


FIGURE 11

A systematic survey of oxidation of various mono- and disubstituted phenols has been made.[226–229] Under the selected conditions (large excess of phenol vs. silver carbonate on Celite) various coupling products are observed, in yields depending on temperature, solvent, and dilution. In organic solvents, *p*-cresol or 2,4-dimethylphenol give three dimeric compounds *A*, *B*, and *C* (Fig. 11).

The ketone *B* is obtained only when $R' = H$ and $R = CH_3$. The formation of *B* is favored by low temperature and polar solvent (relative yield as high as 63% of the total dimeric products has been obtained). Products of type *C* are favored by high dilution and high temperature.

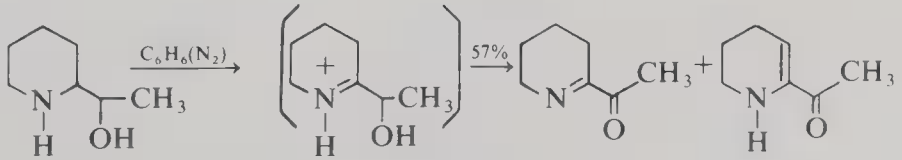
These results are consistent with the various modes of a reversible coupling of the initially formed free radical, giving a ketonic intermediate, the enolization of which is irreversible.

More complex oxidative dimerizations occur with 4-hydroxytaxodione.[230]

3.9. Aliphatic Amines

Few examples of aliphatic amines oxidations are known; moreover, in only one case was the amino-group alone in the molecule. It seems that a primary or a secondary amine is first oxidized to a protonated immonium ion, which can lose a proton to give an imine or an enamine[231] (Fig. 12).

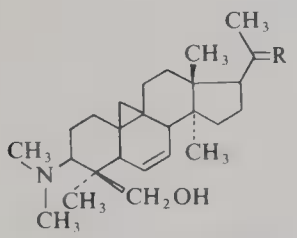
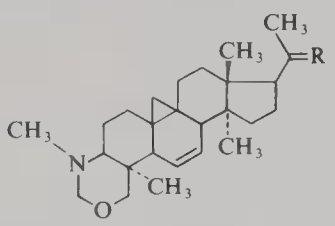
In the case of a tertiary amine, the corresponding immonium ion is cleaved[232] or it reacts with a neighboring group[233,234] (Table XVI). Similar results have been observed in the tropane series.[32]



Mixture 1/2

FIGURE 12

TABLE XVI. Aliphatic Amine Oxidations

Starting material	Products	Yield (%)	Solvent	Reference
$C_6H_5-N(CH_3)-CH_3$	$C_6H_5-NH-CH_3$; $C_6H_5-N(CHO)-CH_3$	80	Benzene	232
$C_6H_5-N(CH_3)-CH_2-C(OH)(CH_3)-CH_3$	$C_6H_5-NH-CH_3$ + $C_6H_5-N(CHO)-CH_3$ + $(CH_3)_2C=O$	100	Benzene	232
		R		
		H, OH	—	—	233
		O	42	Benzene	234

3.10. Aromatic Amines

Anilines are slowly oxidized by silver carbonate on Celite into azobenzenes; the yields are usually in the range 30%–50%, but may be occasionally very good (up to 95%). The mechanism involves probably the coupling of a nitrogen radical, followed by the dehydrogenation of the resulting hydrazobenzene. The by-products occasionally isolated are those normally expected from the various modes of radical coupling of the corresponding radicals (Fig. 13). 2,4,6-Tri-*t*-butylazobenzene was prepared (90% yield) by a mixed oxidative condensation between 2,4,6-tri-*t*-butylaniline and aniline[237] (Fig. 14).

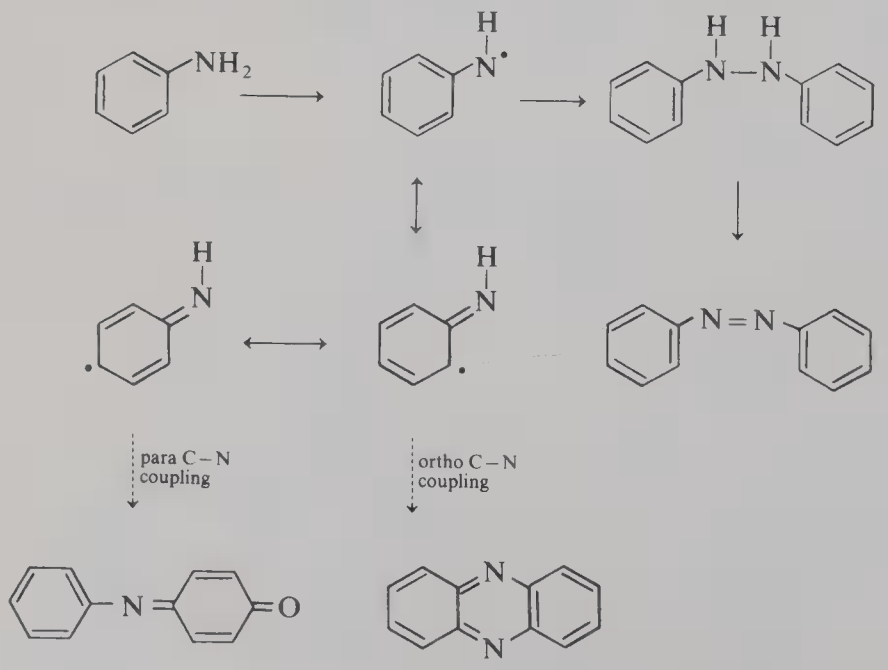
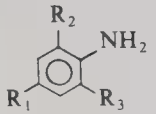
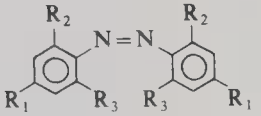
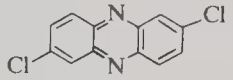
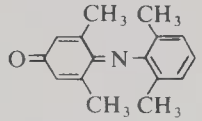
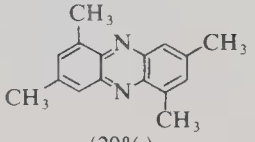


FIGURE 13

TABLE XVII. Azobenzenes from Anilines

Anilines	Azobenzene		By-products (yield %)	Azobenzene (yield %)	Solvent	Reference
						
R_1	R_2	R_3				
H	H	H		38	Benzene	235
Cl	H	H	 (8%)	35	Benzene	236
Cl	H	H		38	Benzene	235
Br	H	H		48	Benzene	235
CH_3	H	H		38	Benzene	235
CH_3O	H	H		50	Benzene	235
NO_2	H	H		5	Benzene	235
CH_3	CH_3	CH_3		75	Benzene	236
H	CH_3	CH_3	 (10%)	35	Benzene	236
CH_3	CH_3	H	 (20%)	30	Benzene	236
C_6H_5	C_6H_5	C_6H_5		95	Benzene	236
H	Cl	Cl		1	Benzene	236
Cl	Cl	Cl		No oxidation	Benzene	236
$(CH_3)_3C$	$(CH_3)_3C$	$(CH_3)_3C$		No oxidation	Benzene	236
$(CH_3)_2CH$	$(CH_3)_2CH$	$(CH_3)_2CH$		—	Benzene	237

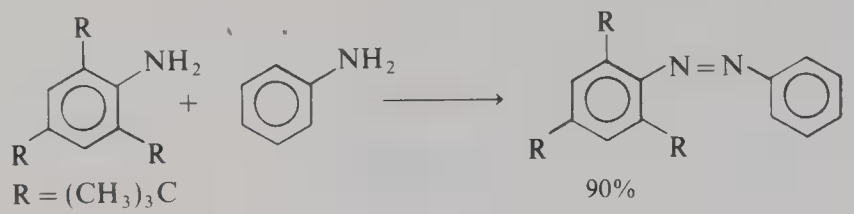


FIGURE 14

3.11. Hydrazine Derivatives

A. *Symmetrically Disubstituted Hydrazines or Hydrazides.* Symmetrically disubstituted hydrazines or hydrazides are oxidized to the corresponding azo-compounds (Table XVIII). The reaction is very fast. Phthalylhydrazide, however, is not oxidized.

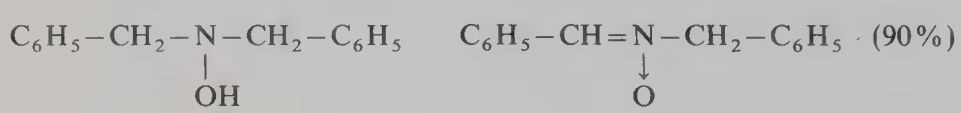
B. *N-aminopyrazole Is Not Oxidized into 1,2,3-Triazine*[238] (Fig. 15).

C. *Hydrazones.* Hydrazones are oxidized within a minute into diazoalkanes, which can be isolated by filtration. Prolonged reaction gives only a mixture of starting ketone, of diazine, and, in some cases, of the decomposition products of an intermediate carbene (Table XIX).

3.12. Hydroxylamines

Silver carbonate on Celite oxidizes monosubstituted hydroxylamines to nitroso-compounds within a few minutes, at or below room temperature and in an aprotic medium (CH_2Cl_2 of $CFCl_3$). Yields are generally much higher (84%–95%) than with other reagents, and the isomerization of primary or secondary nitrosocompounds does not occur. Some of the nitroso-compounds are obtained as *trans* dimers (Table XX).

When a suitably placed double bond is present, nitroxide radicals may be obtained[241] (Fig. 16). With *N*-disubstituted hydroxylamines, nitrones are obtained[235]:



They can undergo intramolecular cycloaddition with a suitably placed double bond[242] (Fig. 17).

3.13. Oximes

By analogy with the proposed mechanism for alcohol oxidation, a protonated nitrile oxide is the expected primary product of silver carbonate on Celite oxidation of the oxime of an aromatic aldehyde. Aromatic nitrile oxides are indeed formed, but they undergo 1,3-dipolar cycloaddition, with the precursor oxime, leading to symmetrically substituted 1,2,4-oxadiazoles. Dipolarophiles added on purpose (aceto- or propionitrile, used as solvents) afford dissymmetrically substituted 1,2,4-oxadiazoles. Ethylenic compounds give isoxazolines. Hydrolysis of the oxime occurs sometimes (Table XXI).

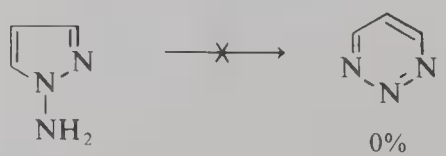


FIGURE 15

TABLE XVIII. Azo-Compound from Hydrazine Derivative

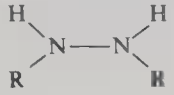
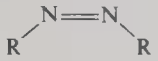
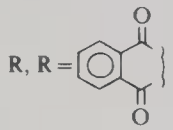
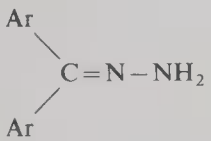
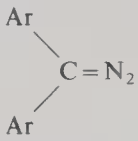
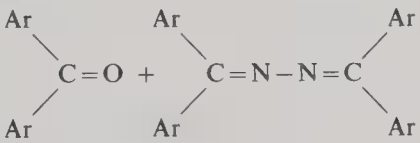
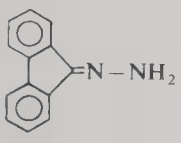
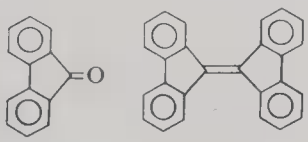
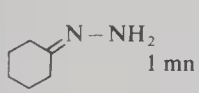
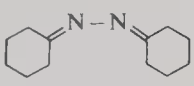
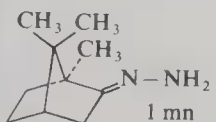
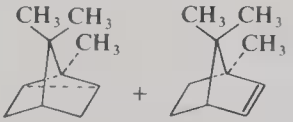
Hydrazine derivative	Azo-compound	Yield (%)	Solvent	Reference
				
R				
C_6H_5		100	Benzene	235
CO_2CH_3		80	Benzene	235
$CO_2C_2H_5$		85	Benzene	235
$CO-C_6H_5$		60	Benzene	235
		No reaction	Benzene	235

TABLE XIX. Oxidation of Hydrazones

Hydrazone	Reaction time	Products	Yield (%)	Solvent	Reference
					
Ar					
C_6H_5	5 min		88	Benzene	235
p-$CH_3O-C_6H_4$	1 min		90	Benzene	235
					
C_6H_5	5 h	(48%) (49%)	97	Benzene	235
p-$CH_3O-C_6H_4$	5 min	(44%) (48%)	92	Benzene	235
		 (91%) (4%)	95	Benzene	235
 1 mn	1 min		98	Benzene	235
 1 mn	1 min	 30 / 1	—	Benzene	235

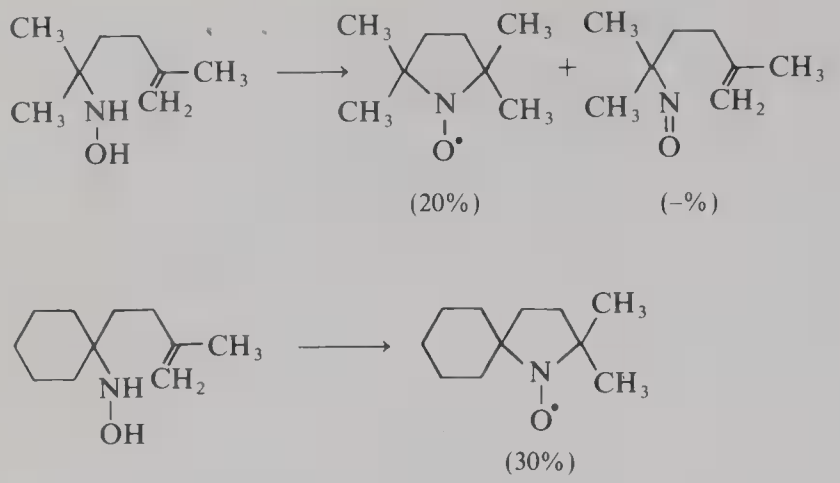
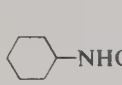
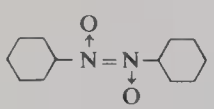
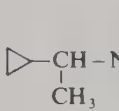
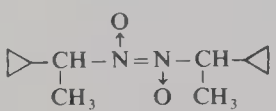
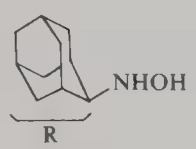
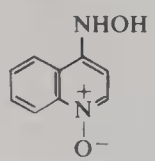
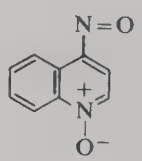


FIGURE 16

TABLE XX. C-Nitroso-Compounds from Hydroxylamines

Hydroxylamines	C-Nitroso-compounds	Yield (%)	Solvent	Reference
C_6H_5-NHOH	$C_6H_5-N=O$	85	CH_2Cl_2	239
$C_6H_5-CH_2-NHOH$	$C_6H_5-CH_2-\overset{\uparrow O}{N}=\underset{\downarrow O}{N}-CH_2-C_6H_5$	66	CH_2Cl_2	239
p-Cl$-C_6H_4-NHOH$	p-Cl$-C_6H_4-N=O$	89	CH_2Cl_2	239
		95	CH_2Cl_2	239
$(CH_3)_2CH-NHOH$	$(CH_3)_2CH-N=0$	90	CH_2Cl_2	239
$(CH_3)_3C-NHOH$	$(CH_3)_3C-\overset{\uparrow O}{N}=\underset{\downarrow O}{N}-C(CH_3)_3$	57	$CFCl_3$	239
		93	CH_2Cl_2	239
	$R-\overset{\uparrow O}{N}=\underset{\downarrow O}{N}-R$	84	CH_2Cl_2	239
		29	CH_2Cl_2	240

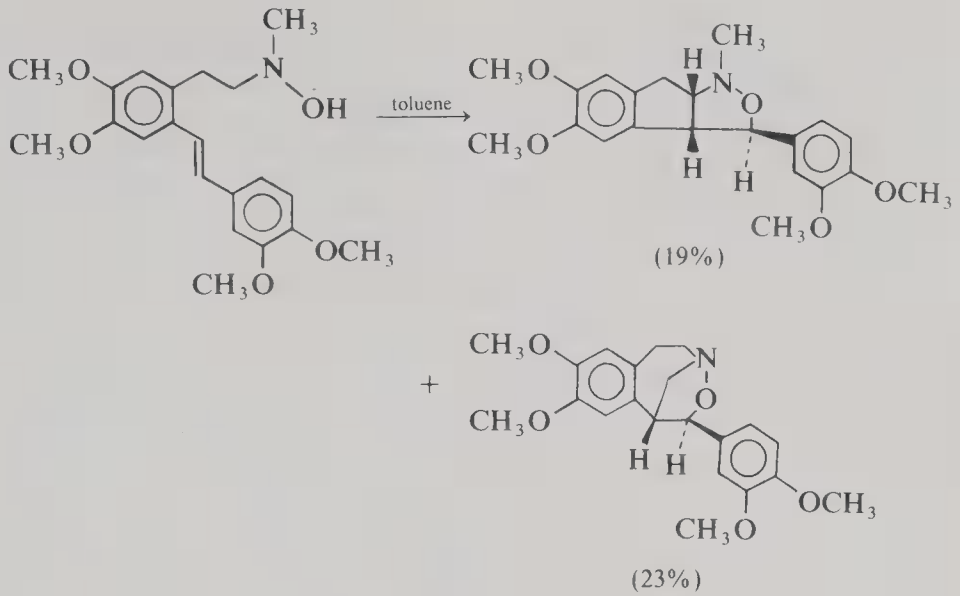


FIGURE 17

3.14. Fragmentation Reactions

Tertiary propargylic alcohols are cleaved by silver carbonate on Celite in boiling toluene into ketones and acetylene[21] in high yield. Thus, the ethynyl group might well be used as protective groups for ketones (Table XXII). Under the same conditions, the corresponding tertiary vinyl alcohols are unaffected.[243]

Cyanohydrins undergo the same type of cleavage, giving back the expected ketone very smoothly in neutral solution.[21] Acetylenic secondary alcohols in the carbohydrate series are not oxidized into ketones, but transformed into unidentified products, which might be derivatives of the intermediate fragmentation compound.[22]

3.15. Rearrangements: Halohydrins

It is well known that alicyclic bromohydrins are easily converted into epoxides, or rearranged into ketones or aldehydes in the presence of bases or metallic ions. Silver carbonate on Celite in boiling methylene chloride gives the expected compounds in high yield. Besides, they are easily isolated by filtration of the suspended solid and evaporation of the solvent (Table XXIII). However, trans-2 fluorocyclohexanol gives exclusively, albeit slowly, 2-fluorocyclohexanone.[245]

3.16. Miscellaneous Reactions

Wolfe found that the dehydroalanine derivative can be efficiently prepared from L-cysteine, in a 77% overall yield, by treating the methyl ester of carboxy benzyl cysteine with silver carbonate on Celite. Incidentally, the yield from carboxybenzyl-cysteine methyl ester is 92%, which means that virtually no oxidation of the thiol to a disulfide took place.[248]

$$C_6H_5-CH_2-OCONH-\underset{\displaystyle CO_2CH_3}{\underset{|}{CH}}-CH_2SH \xrightarrow[Ag_2CO_3/Celite]{CH_3OH} C_6H_5-CH_2-OCONH-\underset{\displaystyle CO_2CH_3}{\underset{|}{C}}=CH_2$$

TABLE XXI. Oxidation of Oximes

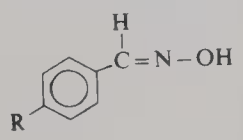
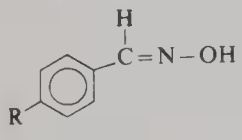
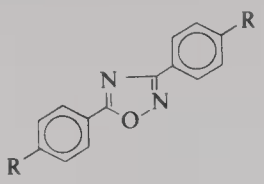
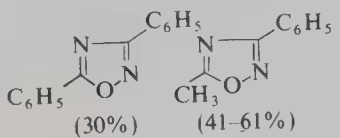
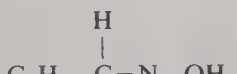
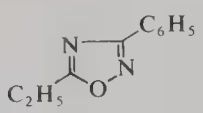
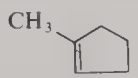
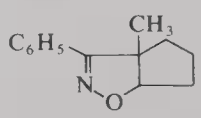
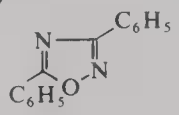
Oxime	Dipolarophile	Products	Yield (%)	Solvent	Reference
					
		R			
		H	73	Benzene	235
		CH_3O	64	Benzene	235
		C_6H_5	74	Benzene	235
	$CH_3-C\equiv N$	 (30%) (41–61%)		No	235
	$C_2H_5-C\equiv N$		37	No	235
		 (38%)			
		$+C_6H_5-CHO+$ 		No	235
		(11%) (30%)			

TABLE XXII. Tertiary Propargylic Alcohols and Cyanohydrins Cleavages

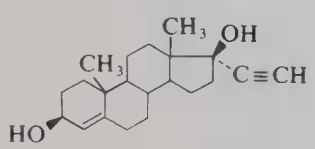
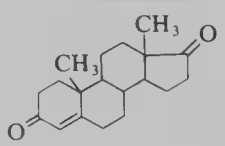
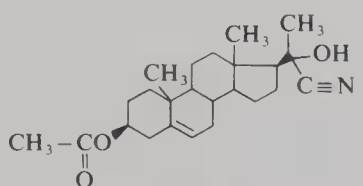
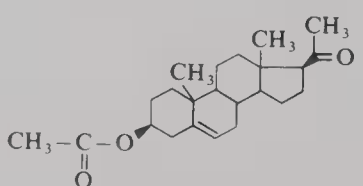
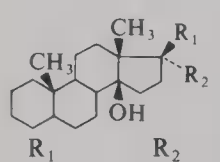
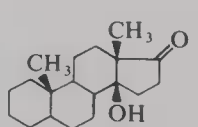
Starting material	Product	Yield (%)	Solvent	Reference
		100	Toluene	21
		100	Toluene	21
				
R_1 R_2				
OH $C\equiv CH$		—	Benzene	244
$C\equiv CH$ OH		—	Benzene	244

TABLE XXIII. Halohydrin Rearrangements

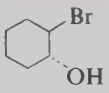
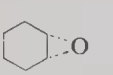
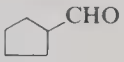
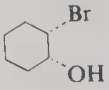
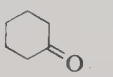
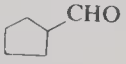
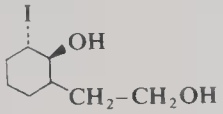
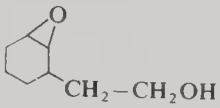
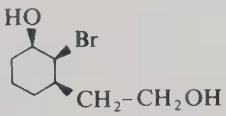
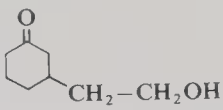
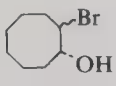
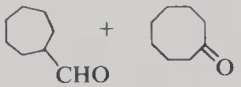
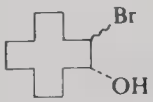
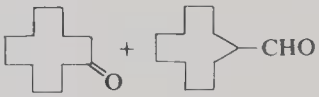
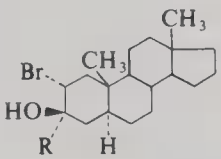
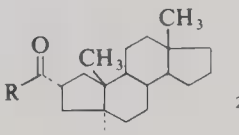
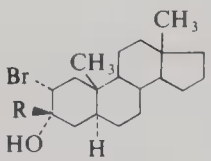
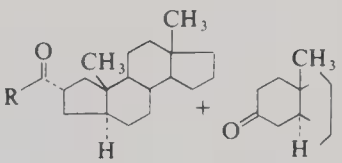
Starting material	Products	Yield (%)	Solvent	Reference
	  49% 46%		CH_2Cl_2	45
	  78% 6%		CH_2Cl_2	45
		99	CH_2Cl_2	113
		47	CH_2Cl_2	113
				
trans isomer	17% 67%		CH_2Cl_2	45
cis isomer	23% 44%		CH_2Cl_2	45
				
trans isomer	79% 11%		CH_2Cl_2	45
cis isomer	76% 1%		CH_2Cl_2	45
	 R H ^{2}H	95 98	CH_2Cl_2 CH_2Cl_2	246 158
				
R				
H	41% 50%		CH_2Cl_2	246
^{2}H	56% 36%		CH_2Cl_2	158
CH_3	96% 0%		$CHCl_3$	246
C_6H_5	100% 0%		$CHCl_3$	246

Table continued

TABLE XXIII. *Continued*

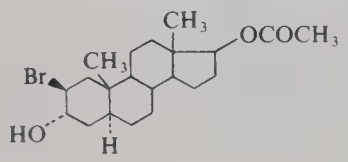
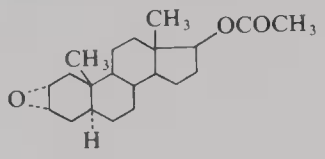
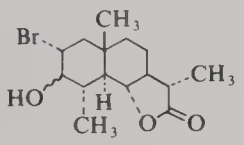
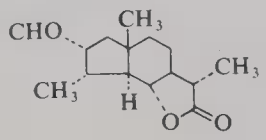
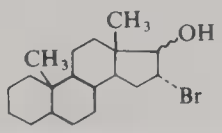
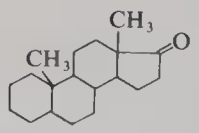
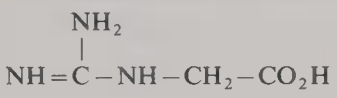
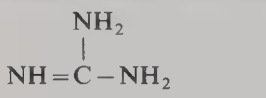
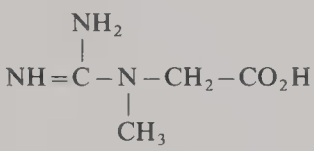
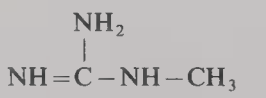
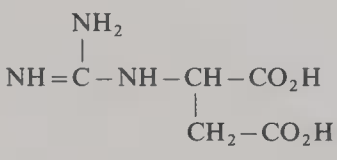
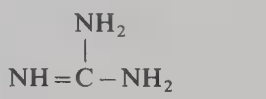
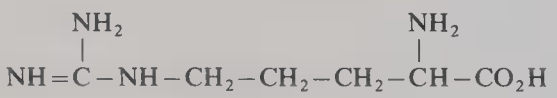
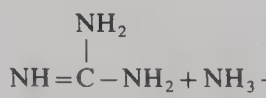
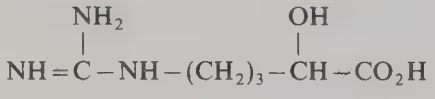
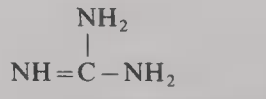
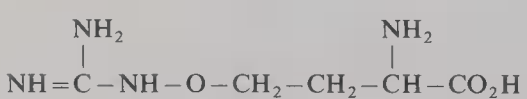
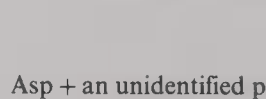
Starting material	Products	Yield (%)	Solvent	Reference
		89	CH_2Cl_2	158
		*trans* isomer *cis* isomer	81 70	Benzene Benzene	247 247
		17α-OH 17β-OH	95 97	CH_2Cl_2 CH_2Cl_2	158 158

TABLE XXIV. Guanidino Compounds Degradation

Guanidino compound	Degradation products	Yield (%)	Solvent	Reference
		—	H_2O	250
		—	H_2O	250
		—	H_2O	250
		—	H_2O	250
		—	H_2O	250
		—	H_2O	250

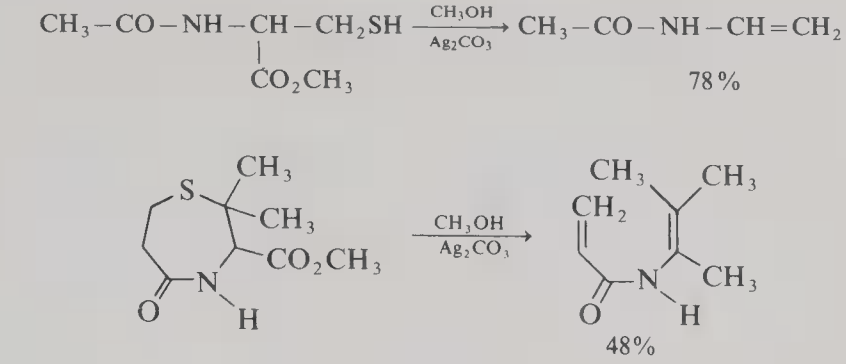


FIGURE 18

A similar reaction had been described by Gravel.[249] In this case pure silver carbonate (i.e., not coated with Celite) was used (Fig. 18).

Degradation of guanidino compounds by silver carbonate on Celite has been studied[250] when the guanidino group is α to the carboxyl function; extensive degradation was observed with isolation of guanidine or methylguanidine (Table XXIV). However, L-arginine is also degradated, whereas β and γ guanidino acids are unaffected.

According to Sukh Dev, β himachalene is slightly oxidized by silver carbonate on Celite into a mixture of several compounds, among which oxidohimachalene and an epoxide[251] (Fig. 19).

Allylic bromides have been converted to the corresponding alcohols by silver carbonate on Celite in acetone at 0°C in the prostaglandin series.[252,253] No allylic rearrangement was detected[254] (Fig. 20).

An equally successful hydrolysis of an allylic bromide has also been described. Silver carbonate on Celite gave the expected alcohol, although classical hydrolysis in the presence of K_2CO_3 led to extensive formation of a dialkyl ether.[255] *Syn* and *anti* 7-chloro 7-azabenzonorbornadiene react with silver carbonate on Celite in methanol at a very different rate. The *syn* chloride *B*, being much more reactive, is rapidly converted into *C* carbonate, which is retained on the solid. The *anti*-chloride *A* does not react, and therefore remains in solution, from which it can easily be isolated[256] (Fig. 21).

Finally, a study of the glycosidation of cardenolides (the well known Koenigs–Knorr reaction) could show that silver carbonate on Celite gives much higher yields than pure silver carbonate (Table XXV). Various other glycosidations are also described.[259,260,261]

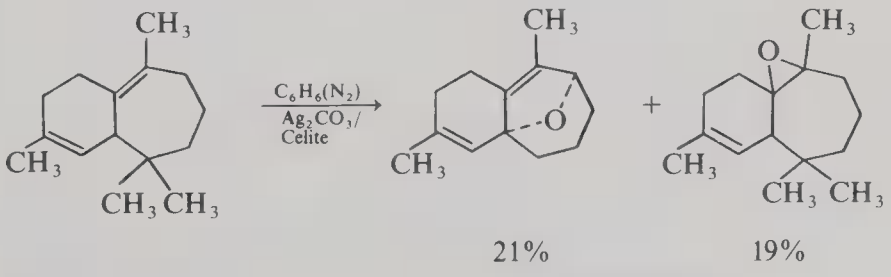
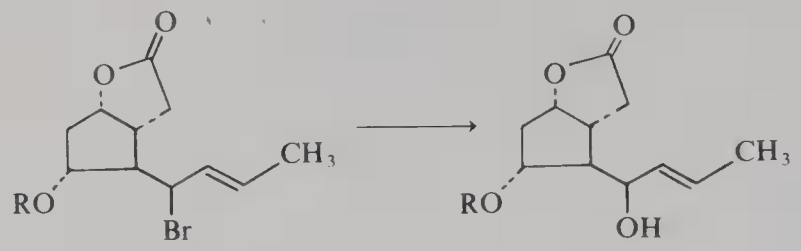


FIGURE 19



R = p-$C_6H_5-C_6H_4-CO-$ 60%

FIGURE 20

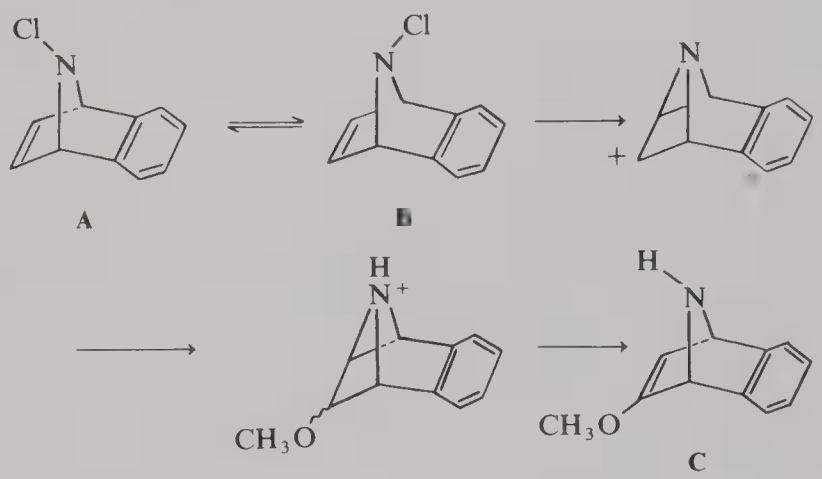


FIGURE 21

4. EXPERIMENTAL PROCEDURES

4.1. Silver Carbonate on Celite Preparation

Commercial Celite is purified by washing two times with methanol containing 10% concentrated hydrochloric acid. Afterwards, it is washed with distilled water to neutrality and then dried at 120°C.

The reagent is prepared as follows: silver nitrate (30 g) is dissolved in 200 ml of distilled water and the purified Celite (30 g) is added. The mixture is stirred magnetically. Then sodium carbonate $10H_2O$ (30 g) in distilled water (300 ml) is added slowly. After ten minutes, the yellow-green precipitate is filtered and washed to neutrality with distilled water. Finally it is dried a few hours in a rotatory evaporator on a steam bath.

The reagent can be stored in darkness for several years. 0.6 g of reagent is equivalent to roughly 1 mmol.

4.2. Recovery of Silver Nitrate

When silver carbonate on Celite oxidations are carried out on a large scale, it is convenient to recover the expensive silver salt. The following method, which has not been optimized, gave consistently good results.

A suspension of 500 g of used reagent is cautiously mixed (small portions) in a large beaker with 500 ml of fuming nitric acid and 500 ml of water, under stirring. The non-

TABLE XXV. Glycosidation of Cardenolide Steroids with Glycosyl Halides in the Presence of Silver Carbonate on Celite

Products	Yield (%)	Solvent	Reference
Strophanthidin-β-D-glucopyranosid	60	CH_2Cl_2	257
Strophanthidin-α-L-rhamnopyranosid	67	CH_2Cl_2	257
Strophanthidin-α-L-rhamnopyranosid	70–77	CH_2Cl_2	257
Digitoxigenin-α-L-rhamnopyranosid	60	CH_2Cl_2	257
Digitoxigenin-β-D-glucopyranosid	52	CH_2Cl_2	257
Digitoxigenin-3β-D-glucoside	58	Benzene	258
Digitoxigenin-3β-β-D-galactoside	58	Benzene	258
Digitoxigenin-3β-α-L-rhamnoside	62	Benzene	258
Uzarigenin-3β-β-D-glucoside	60	Benzene	258

dissolved solid, which consists of Celite, is filtered off, washed with water. The clear solution is then slowly evaporated until silver nitrate crystallizes out. At least 60%–70% of silver nitrate can thus be recovered.

4.3. Oxidation of 2-(3-Cyclohexenyl)-1-Propanol[49]

Silver carbonate on Celite (10 g, 17.5 mmol) was added to a solution of 2-(3-cyclohexenyl)-1-propanol (224 mg, 1.6 mmol) in 90 ml of benzene. Benzene–water (5 ml) was azeotropically distilled off and the reaction mixture was refluxed for 12 h. The progress of the oxidation was followed by gas–liquid chromatography. The reaction suspension was filtered and the benzene solution was evaporated under reduced pressure giving 172 mg (78% yield) of 2-(3-cyclohexenyl)propanal.

4.4. Oxidation of 4-Hydroxydendrolasin to (E)-9-(Furan-3′-yl)-2,6-dimethylnona-2,6-dien-4-one[86]

4-Hydroxydendrolasin (100 mg) was heated under reflux in benzene (15 ml) with silver carbonate on Celite (0.5 g).* After oxidation for 6 h thin layer chromatographic analysis showed the presence of one major product. Purification by preparative thin layer chromatography (ether/hexane 1:9) gave E-9-(furan-3′-yl)-2,6-dimethylnona-2,6-dien-4-one (85 mg, 86%).

4.5. Oxidation of 3-Methylpentane-1,3,5-triol to Mevalonolactone

To 128 g of silver carbonate on Celite reagent suspended in boiling benzene (500 ml) is added a solution of 3-methylpentane-1,3,5-triol (1.5 g)† in methanol (25 ml). The methanol is evaporated by azeotropic distillation with benzene. Then the suspension is heated for 6 h under reflux in benzene and filtered while still hot. The solid phase is washed several times with hot methylene chloride, then the solvents evaporated. 1.22 g of the obtained yellow oil are distilled at 95–100°C under 0.01 mm. Finally 1.08 g (74%) of pure mevalonolactone is isolated.

* 2 mmol of reagent for 1 mmol of alcohol.
† 20 mmol of reagent for 1 mmol of triol.

4.6. Oxidation of 2,6-Dimethylphenol to 3,3′,5,5′-Tetramethyldiphenoquinone[216]

2,6-Dimethylphenol (1.2 g) is refluxed for 30 min in benzene (150 ml) with Ag_2CO_3/Celite reagent (25.1 g). Removal of the solid phase and evaporation of benzene leaves 1.16 g (98%) of practically pure 3,3′,5,5′-tetramethyldiphenoquinone (m.p. 217–218°C).

4.7. Oxidation of Benzaldehyde Oxime to 3,5-Diphenyl-1,2,4-Oxadiazole[235]

To 10 g of Ag_2CO_3/Celite reagent (dried by azeotropic distillation of benzene) suspended in 75 ml of benzene, are added 1.2 g of freshly distilled benzaldehyde oxime. The suspension is heated for 1 h with elimination of water (Dean–Stark), and filtered while hot. After evaporation of solvent, the oily residue is crystallized with heptane to give 0.8 g (73%) of 3,5-diphenyl-1,2,4-oxadiazole, which is recrystallized from ethanol; m.p. = 108°C.

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11

Cerium(IV) Oxidation of Organic Compounds

Tse-Lok Ho

1. INTRODUCTION

Cerium is a member of the lanthanides, whose $[Xe]4f^1 5d^1 6s^2$ electronic configuration permits its existence in tri- and tetrapositive states. A cerium(IV) solution is obtained by oxidation of Ce(III) species with peroxodisulfate or bismuthate in nitric acid, for example. As a result of the high charge, Ce(IV) ion tends to hydrate, and very frequently coordinates with counterions. This last aspect provides a rationale for the Ce(IV)/Ce(III) potential dependence on the nature of the acid medium. Thus the increase of perchloric acid concentration heightens the oxidation potential. On the other hand, the potential decreases with increasing sulfuric or nitric acid concentration.[1] As shown in Table I, Ce(IV) is a very powerful one-equivalent oxidant.

Oxidation of organic compounds with Ce(IV) species was initially studied in relation to analysis (cerimetry).[2] Later, other aspects of cerium(IV) oxidation were developed.[3] More recent results have been incorporated into two articles: one[4] of these emphasizes the reaction mechanism, whereas the other[5] focuses on the synthetic application of cerium(IV) ion to functional group oxidation.

The most widely used reagent for organic oxidation is diammonium hexakis(nitrato-*O*-) cerate, commonly known as ceric ammonium nitrate [CAN, $(NH_4)_2 Ce(NO_3)_6$]. More "exotic" Ce(IV) reagents that have been prepared and used recently include bis(triethylammonium) hexakis(nitrato)cerate[6] $(Et_3NH)_2 Ce(NO_3)_6$, bis[trinitratocerium(IV)] chromate[7] $[Ce(NO_3)_3]_2 CrO_4$, dinitratocerium (IV) chromate dihydrate[8] $Ce(NO_3)_2 CrO_4 \cdot 2H_2O$, trihydroxycerium (IV) hydroperoxide[9] $Ce(OH)_3 OOH$, and tris[trinitrato cerium (IV)] paraperiodate[10] $[Ce(NO_3)_3]_3 H_2IO_6$. These reagents have the advantage of being more soluble in nonpolar solvents; therefore they can be used to oxidize hydrophobic substrates more readily.

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TABLE I. Oxidation Potential of Cerium(IV) Ion in Acids

Ce(IV) + e = Ce(III)		
Electrolyte	Concentration (M)	E^0 (V) (vs. SCE)
H_2SO_4	1	1.20
	4	1.19
	8	1.18
CF_3COOH	1	1.36
	3	1.33
	6	1.31
HNO_3	1	1.37
	4	1.37
	8	1.32
CH_3SO_3H	1	1.40
	3	1.41
	6	1.39
$HClO_4$	1	1.46
	4	1.51
	6	1.57
	8	1.63

This survey outlines the use of cerium(IV) in organic chemistry with a brief discussion of the mechanism involved.

2. MECHANISM

2.1. General Considerations

Cerium(IV) is a typical one-equivalent oxidant which removes one electron at a time from the substrate. In this regard Ce(IV) shares certain similarities in reaction patterns with Mn(III), Co(III), and V(V), although the other three oxidants are ions of transition metals. On the other hand, a different behavior is expected from that of chromate and permangate which have reactive oxy-anions.

In the one-equivalent oxidation of neutral or anionic organic species, cation radicals or free radicals are generated. Normally these intermediates undergo rapid oxidation to afford neutral products by electron transfer (outer-sphere reaction) or by ligand transfer (inner-sphere reaction). Alternatively, oxidation occurs after its combination with a counterion such as the nitrate ion in CAN oxidations.

$$R^{\cdot} + Ce(IV) \longrightarrow R^{+} + Ce(III)$$

$$R^{\cdot} + ONO_2Ce(IV) \longrightarrow RONO_2 + Ce(III)$$

$$R^{\cdot} + ONO_2^{-} \longrightarrow RONO_2^{\cdot -}$$

$$RONO_2^{\cdot -} + Ce(IV) \longrightarrow RONO_2 + Ce(III)$$

Because Ce(IV) oxidations deal most frequently with neutral organic compounds, radical cation intermediates are encountered most of the time. The fates of these inter-

mediates depend on their structures. They may undergo C–H bond cleavage, C–C bond cleavage, hydrogen transfer, dimerization, a combination of these processes, or other reactions characteristic of free radicals.

2.2. C–H Bond Fission Reactions

The cerium(IV) ion forms red-colored complexes with alcohols.[11] The 1:1 complex formation has been confirmed by kinetic studies.[12] More recently, the formation constants of many Ce(IV)–alcohol complexes have been measured.[13] The observed isotope effect in the alcohol oxidation indicates that C_α–H bond cleavage is rate-determining[14] and that an acyclic activated complex is involved. The mechanistic implication is that the stability of the incipient free radical intermediate affects the oxidation rate. Bent transition states have been deduced[15] for Ce(IV) oxidation of alcohols by means of a temperature dependence study of isotope effects.

A kinetic study[16] of the oxidation of benzaldehyde with Ce(IV) in aqueous acetic acid indicates involvement of both 1:1 and 2:1 inner-sphere complexes. The large kinetic isotope effect ($k_H/k_D = 16$) is consistent with a rate-determining homolysis.

$$\mathrm{RCHO + Ce(IV) \rightleftharpoons RCHO \cdot [Ce(IV)] \longrightarrow R\dot{C}O + H^+ + Ce(III)}$$

$$\mathrm{R\dot{C}O + Ce(IV) + H_2O \longrightarrow RCOOH + H^+ + Ce(III)}$$

2.3. C–C Bond Cleavage Reactions

In the case where a more stable radical can be created through C–C bond repture of the primary oxidation intermediate, such a process occurs. Thus, alkyl phenyl carbinols yield a mixture of benzaldehyde and an alkyl phenyl ketone[17] in ceric ammonium nitrate (CAN) oxidation, the aldehyde/ketone ratio being 0.04, 3.30, 184, and 195 for alkyl group being methyl, ethyl, isopropyl, and *t*-butyl, respectively. This observation is reminiscent of V(V) oxidation of benzyl alcohols[18] and Co(III) oxidation of tertiary alcohols.[19]

Cyclopropylmethyl phenyl carbinol is rather unique among the primary alkyl carbinols as the ratio of its products C_6H_5CHO/C_6H_5COR, 24.4 ± 4.1, is high. Its rate constant for oxidation is similar to that of allyl phenyl carbinol.[20]

In the Ce(IV) cleavage of 2-aryl-1-phenylethanols,[21] a considerable amount of positive charge develops on the carbon atom that becomes the radical in the transition state, as suggested by the Hammett relationship ($\rho = -2.0$ against σ^+). However, the reaction is not ionic in nature. The relative rates are 4.2, 1.00, 0.63, and 0.027 for aryl = *p*-$CH_3C_6H_4$, C_6H_5, *p*-ClC_6H_4, and *p*-$O_2NC_6H_4$, respectively. Oxidation of 1-aryl-2,3-diphenylpropan-2-ols yields benzyl phenylketone and the substituted benzyl phenyl ketone.[20] These reactions are also effected by chromic acid, in which case Cr(IV) is the oxidant.

The facile degradation of *β*-(trimethylsilylethyl)phenylcarbinol by Ce(IV) to benzaldehyde, ethylene, and hexamethyldisiloxane[22] is due to the stabilizing effect of silicon on an electron-deficient atom at the *β* position.

$$\mathrm{Me_3SiCH_2CH_2\underset{\displaystyle OH}{\underset{|}{CH}}Ph \xrightarrow{Ce(IV)} Me_3SiCH_2CH_2^+ + Ph\dot{C}HOH \longrightarrow etc.}$$

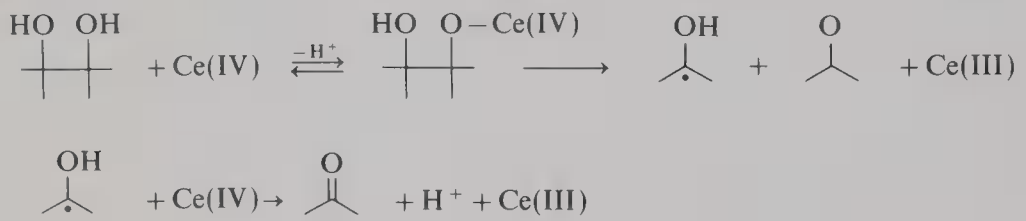
Bicyclic alcohols in which the secondary hydroxyl is attached to a carbon adjacent to the bridgehead suffer complete C–C bond fission.[23] The driving force consists of strain relief and the generation of moderately stable secondary radicals.

Cyclobutanols display a high reactivity toward one-equivalent oxidants,[24] while its two-

equivalent oxidation to cyclobutanone is not particularly fast. Interestingly, the Ce(IV) oxidation proceeds via formation of a primary radical. This radical undergoes dimerization, disproportionation, or further oxidation. Demerization is supressed by a high oxidant concentration where ligand transfer reactions, giving nitrato- and nitro-butanals, become important.

Besides cyclobutanol, only cyclopropanol and cyclopropanone hydrate and hemiacetals yield dimers.[25]

Cerium(IV) is an efficient reagent for 1,2-glycol cleavage. Contrary to the better known lead(IV) acetate oxidation, which involves the formation of a bidentate metal–glycol complex and the breakdown by a two-electron process,[26] the cerium(IV) counterpart requires metal coordination with only one hydroxy group, which is followed by a one-electron oxidation. Support for this mechanism comes from rate measurements on the oxidation of the glycols and their monomethyl ethers (similar rates),[12] radical-trapping experiments,[27,28] and parallel studies of Pb(IV) and Ce(IV) oxidations of *dl*- and *meso*-hydrobenzoins.[29] On the basis of orbital symmetry correlations,[30] a cyclic mechanism is forbidden in one-equivalent oxidation.



Almost exclusive splitting of the central C–C bond of benzoins[31] on their exposure to CAN is due to stability of aroyl radicals. Interestingly, cerium(IV) oxidation of acetoin gives biacetyl.[12]

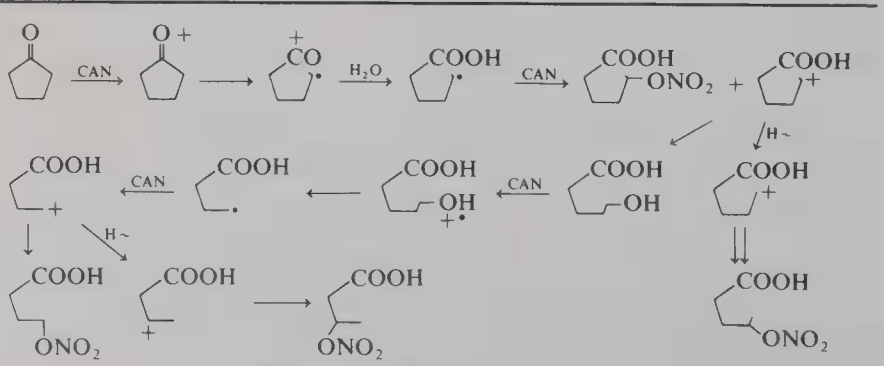
An enol mechanism[32] proposed for Ce(IV) oxidation of carbonyl compounds was refuted[33] in view of the oxidation rate of cyclohexanone with cerium(IV) sulfate being 61 times faster than enolization. Alternatively, abstraction of an α hydrogen atom in the Ce(IV)–carbonyl compound complex in the rate-determining step has been formulated.

The CAN oxidation of cyclic ketones[34] led to a mechanistic interpretation as shown in Scheme 1. Complex formation followed by electron transfer was considered to occur initially. Ring opening ensued.

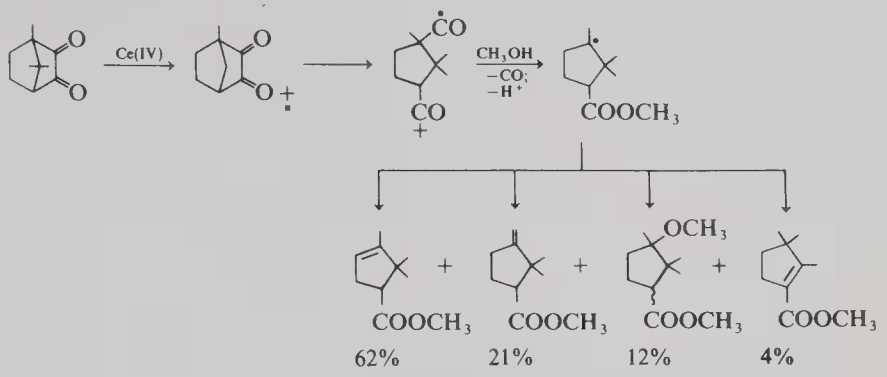
Although the degradation of triphenylacetaldehyde to triphenylmethanol was regarded as proceeding via hydrogen atom abstraction,[35] a pathway involving C–C bond rupture of the cation radical to furnish the triphenylmethyl radical and a formyl cation is equally tenable.

Exposure of camphorquinone to CAN in methanol gave rise to monocyclic esters.[36] Apparently, electron removal from the less hindered oxygen (cf. inertness of camphor)

SCHEME 1

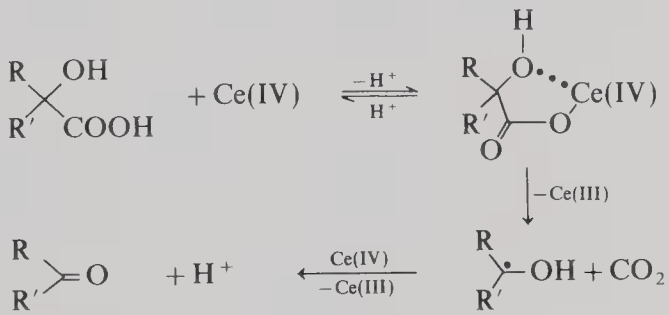


SCHEME 2



triggers the fragmentation of the central bond of the α-diketone. Interception of the resulting acylium ion by methanol and decarbonylation of the acyl radical ensue. Generation of the products from the cyclopentyl radical is easily discerned.

Simple alkanoic acids are rather resistant to Ce(IV) oxidation.[37] However, if an α-substituent which stabilizes a free radical is present, the carboxylic acid undergoes facile decarboxylation. Cases in point are 1,3,5-cycloheptatriene-7-carboxylic acid and α-hydroxycarboxylic acids. Kinetic isotope effects have been determined[38,39] for the oxidation of the latter compounds.



CAN oxidation of phenylacetic acid at 90°C in aqueous acetonitrile furnishes a mixture of benzyl alcohol, benzyl acetate, and benzaldehyde.[40] The decarboxylation proceeds via homolysis of an inner-sphere complex.

$$ArCH_2COOH + Ce(IV) \longrightarrow ArCH_2COOCe(IV) + H^+$$
$$ArCH_2COOCe(IV) \longrightarrow ArCH_2^{\bullet} + CO_2 + Ce(III)$$

The oxidation rates are abnormally high for *p*- and *m*-methoxyphenylacetic acids. These reactions might be initiated by electron transfer from the aromatic ring *(vide infra)*. The decarboxylation of Ce(IV) carboxylates, which shows hardly any rate difference among pivalate, isobutyrate, and *n*-butyrate, is best interpreted as an inner-sphere process involving homolysis of the metal–carboxylate bond.[41] This is in contrast with decarboxylation of Co(III) and Mn(III) carboxylates in which simultaneous fission of the $O-M$ and $C_\alpha-\overset{O}{\overset{\|}{C}}$ bonds occurs, and the relative rates are dependent on the stability of the alkyl radicals.[42]

Fragmentation at the central C–C bond of 2,3-dimethyl-2,3-diphenylbutane on reaction with CAN[43] proceeds via a radical cation. Cobalt(III) acetate is incapable of effecting the cleavage.

2.4. 1,5-Hydrogen Transfer

The formation of cyclic ethers[44,45] from primary alcohols correlates well with the generation of secondary radicals via specific 1,5-hydrogen transfer. Remarkably, the 1,5-hydrogen transfer was noted in the case of 5-phenyl-1-pentanol, where a more stable benzylic radical would result from a 1,6-hydrogen transfer. The transition state geometry governs the outcome of such a process.

2.5. Oxidation of Aromatic Compounds

Of particular interest in the realm of Ce(IV) oxidation is that dealing with aromatic compounds. With electron-rich aromatic compounds, quinones are usually the ultimate products. As a general rule, cation radicals are formed and react further according to reaction conditions. Such reactive species have been detected by electron spin reasonance spectroscopy.[46]

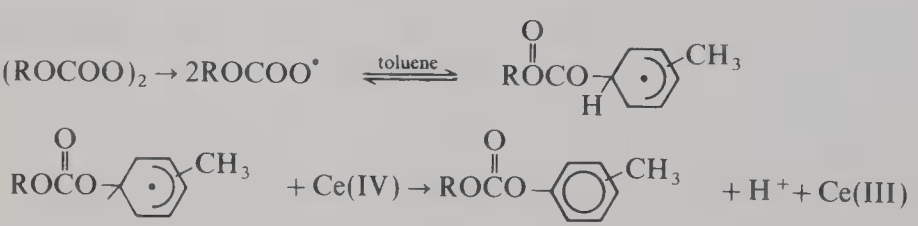
The Ce(IV) oxidation of 2,8-bis(dimethylamino)acridinium salts in either water or in the reversed micellar system of cetylpyridinium chloride-H_2O-$CHCl_3$ proceeds in two consecutive one-electron transfer steps.[47]

Nitration sometimes occurs when CAN is used as oxidant. A rather unique case (with respect to phenols) is the 4- and 6-nitration of 2-cyclopropylphenol.[48] Dimethylanilines are demethylated with concomitant nitration.[49] The nitration does not consume oxidant, and it takes place with an intramolecular rearrangement within a coordination complex of the substrate and a metal species. Inhibition of nitration by methanol suggests a competing coordination by solvent molecules.

The nitration of alkylbenzenes with CAN in acetonitrile involves nitronium ion.[50] The reactive species is formed only in the presence of the substrate; its involvement is indicated by the same product distribution as that of conventional nitration.

Nuclear acetoxylation of anisole[51] by CAN in acetic acid yields an *o/p* isomer ratio of 0.82, which correlates with the odd-electron density distribution of the anisole cation radical. The results indicate solvent capture of the cation radical.

The decomposition of dialkyl peroxydicarbonates in the presence of two molar excess of CAN in toluene leads to tolyl alkyl carbonates in 75%–90% yield.[52] CAN is stoichiometrically consumed as both halves of the peroxide are utilized in the substitution.



It is now generally accepted that side-chain oxidation of alkylarenes by Ce(IV) occurs via a radical cation. The pathway consisting of direct hydrogen abstraction has been ruled out by comparing the reaction with that of *N*-bromosuccinimide.[53] The electron transfer mechanism is consistent with the high substrate selectivity, which is related to the donor abilities of the hydrocarbons. Further investigation has indicated that the regioselectivity is substrate dependent in both CAN and electrochemical processes,[54] but not in the oxidation with cobalt(III) acetate.

$$ArCH_3 + M^{n+} \longrightarrow ArCH_3^{+\bullet} + M^{(n-1)+}$$

$$ArCH_3^{+\bullet} + B \longrightarrow ArCH_2^{\bullet} + BH^+$$

$$ArCH_2^{\bullet} + M^{n+} \longrightarrow \text{Products} + M^{(n-1)+}$$

Regarding the fate of the benzyl radical, two possibilities exist. While evidence such as common ion effect has rendered intervention of a cation via further oxidation improbable, results are well accounted for on the basis of a ligand transfer process.[55,56]

The observed isotope effect of k_H/k_D 2.3 in the CAN oxidation of perdeuterio-*p*-xylene[57] suggests the proton loss from the radical cation intermediate is, at least partly, rate determining.

In the CAN oxidation of mesitylene in oxygen-free acetic acid in the dark, a significant degree of nuclear acetoxylation has been observed.[55] The substitution pattern of the alkyl groups plays an important role in that the side-chain reaction is favored by the presence of ortho and para alkyl groups, while the meta isomer facilitates solvent capture of their radical cation species. In the ortho- or para-dialkylbenzene radical cation higher fractions of positive charge reside in the ring atoms which carry the alkyl groups, hence the loss of a proton from the corresponding benzylic positions is easier.

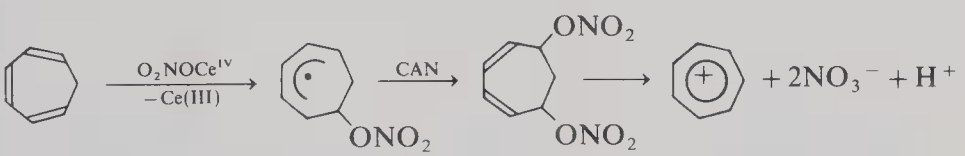
Interesting results emerged from the oxidation of benzene derivatives with cerium(IV) trifluoroacetate in trifluoroacetic acid.[58] In this reaction diaryls and diarylmethanes are the major products. The latter type of compounds arise from ion trapping by another molecule of the arene, and subsequent deprotonation. Their production is maximized in the absence of nucleophiles and solvents. In the case of mesitylene, the radical cation reacts to give dimesityl predominantly.

2.6. Additive Oxidation

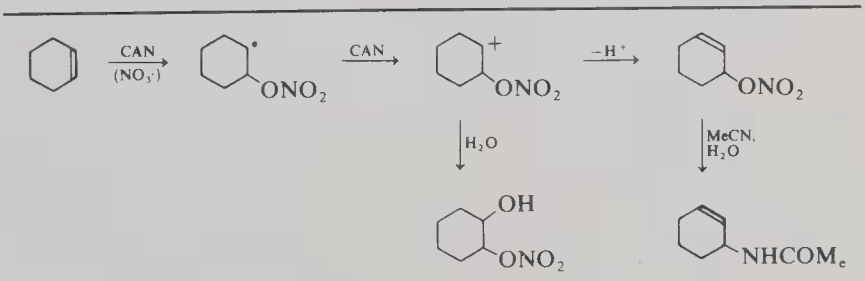
The oxidation of cyclohexene with CAN in a number of solvents has been studied.[59] In anhydrous dimethyl sulfoxide, 2-cyclohexenyl nitrate is formed, whereas in acetonitrile *N*-acetyl-2-cyclohexenylamine becomes the major product. Hydroxyl compounds are obtained when water is present in the reaction medium. A mechanism invoking the addition of a NO_3 radical to the alkene linkage as the first step accounts for the results. It has been shown that 2-cyclohexenyl nitrate undergoes solvolysis to give the amide under the reaction conditions.

Mechanistic duality in the CAN oxidation of styrenes in acetonitrile has been revealed.[60] The initial step involves electron transfer when the substrates are more reactive than styrene itself. However, a free radical addition process is favored with less reactive compounds.

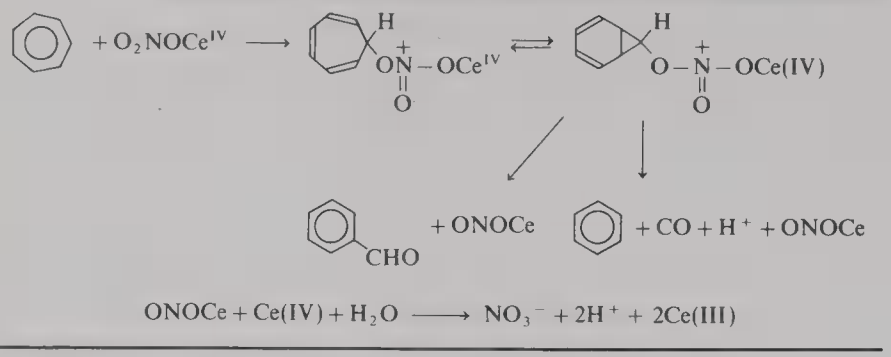
The rates of cycloalkene oxidation by CAN as determined show a dependence on the number of conjugated double bonds.[61] Direct hydrogen abstraction is unlikely in view of the absence of a kinetic isotope effect in the oxidation of cycloheptatriene-d_8. A mechanism involving addition of the NO_3 radical to the triene was presented.



SCHEME 3



SCHEME 4



The intermediacy of tropylium ion in the Ce(IV) oxidation of cycloheptatriene has been established by chemical methods.[62] Benzaldehyde, benzene, and carbon monoxide are the oxidation products when four equivalents of CAN are used. Evidence shows involvement of the nitrate ligand. Remarkably, the ratio of benzaldehyde to benzene is quite insensitive to variation of solvents [e.g., in H_2O: PhCHO 64%, PhH 11%; in CH_3CN, PhCHO 80%, PhH 18%].

2.7. Miscellaneous

Cerium(IV) oxidation of other heteroatom-containing substrates most likely involves initial *n*-electron transfer also, if a π system is absent. A scrutiny of the oxidative cleavage of 1,3-dithiane derivatives has indicated the intermediacy of bicyclic disulfonium ions.[63] The 1,3-dithiane monoxides are not generated. (For exceptions, see Ref. 137.)

The cerium(IV) ion is an efficacious agent for cleaving carbon–metal bonds (σ and π types). It is used frequently to release the organic ligands from organometallic complexes. The oxidation takes place at the metal.

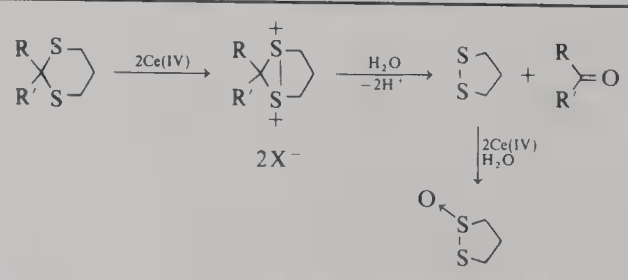
The radical cations from one-equivalent oxidation of alkyl transition-metal carbonyls such as $Cp(CO)_2$ FeR have been characterized.[64] A rapid insertion taking place immediately after the electron removal is indicated, with the generation of acylmetal cations.

3. SCOPE AND LIMITATIONS

3.1. General Aspects

The cerium(IV) ion is an extremely potent and versatile one-equivalent oxidant. Its wide application to oxidation of organic compounds had, remarkably, not been explored before

SCHEME 5



the 1960s. The oxidations are very rapid; even the generally unreactive substances such as carboxylic acids and aromatic compounds can be oxidized. By virtue of their high oxidation potentials, Ce(IV) species may be used to oxidize a broader spectrum of substrates than other one-equivalent oxidants. However, it has proved possible to achieve oxidation of certain functionalities in the presence of other reactive (but less reactive) groups.

A limitation of Ce(IV) oxidations is that acidic conditions are usually involved; therefore, it is not recommended to subject acid-sensitive compounds to such oxidation. The necessity of employing polar solvents or cosolvents also tends to restrict the versatility of the methodology.

The major drawback associated with Ce(IV) oxidations concerns, however, the large amounts of reagent required, owing to its being a one-equivalent oxidant. The situation can be alleviated by adding a cheap cooxidant which can reoxidize the spent cerium species to the active state, thereby rendering the cerium reaction catalytic. This tactic has been successfully employed in the oxidation of benzylic alcohols by the CAN/sodium bromate system.[65] This and similar dual oxidant systems[65a] should find wider use in the future.

3.2. Alcohols

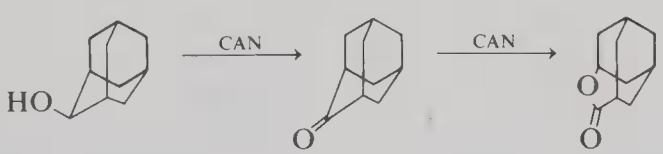
Three modes of reaction have been documented with Ce(IV) oxidation of alcohols: (a) α carbon–hydrogen bond fission resulting in aldehydes or ketones, (b) oxidative carbon–carbon bond fragmentation, and (c) cyclic ether formation.

The Ce(IV) oxidation has not found general preparative use for synthesizing aliphatic aldehydes because of further reactions. However, the oxidation of ethanol to acetaldehyde[66] in 90% yield has been reported. The conversion of propargyl alcohol to propynal[67] has also been mentioned. More useful applications concern the oxidation of cyclopropylmethanols[68] and primary benzylic alcohols.[69,70] The preparation of ^{14}C-labeled 3,6-dichloro-9-phenanthrenecarboxaldehyde[71] via CAN oxidation may be noted.

Many other effective reagents for the oxidation of benzyl alcohols have been described.[6–10] Trihydroxycerium (IV) hydroperoxide is particularly interesting because it can be readily regenerated from the spent oxidant by treatment with hydrogen peroxide, and the reaction can be carried out in benzene.

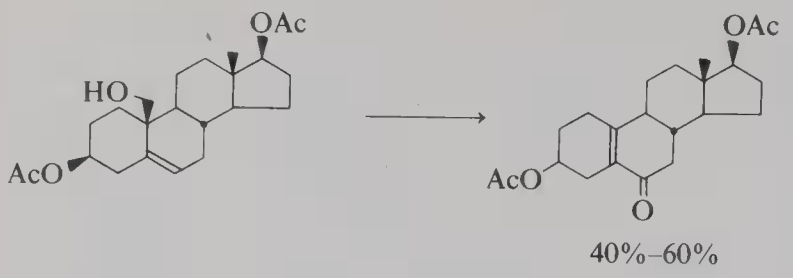
CAN adsorbed on activated charcoal is an effective catalyst for the air oxidation of benzyl alcohols.[72]

Alicyclic alcohols such as cyclopentanol and cyclohexanol have been dehydrogenated by cerium(IV).[73] 2-Adamantanol produces adamantanone and thence is converted to the corresponding lactone[34] on exposure to CAN. The overall yield is 50%.



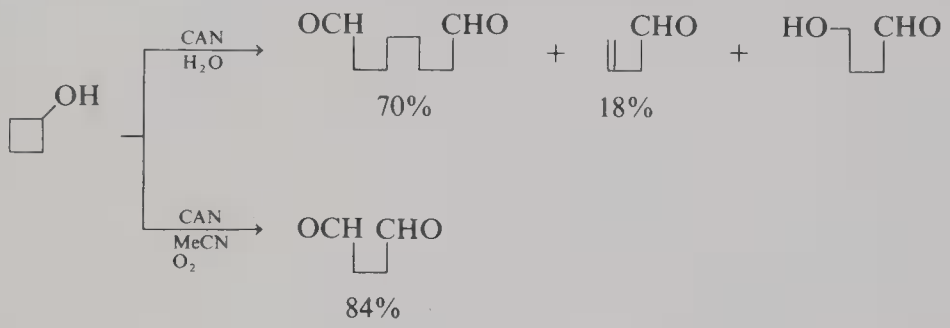
The reactions of alkyl phenyl carbinols furnish a mixture of benzaldehyde and alkyl phenyl ketone.[17] β-(Trimethylsilylethyl)-phenylcarbinol fragments readily, giving rise to benzaldehyde, ethylene, and hexamethyldisiloxane.[22] Fragmentation is also the only pathway followed by 2-aryl-1-phenylethanols,[21] where benzaldehyde and benzyl derivatives are produced.

Homoallylic alcohols are also expected to undergo C–C bond cleavage as allyl radicals are generated. An example of this type is the CAN oxidation of 19-hydroxy-3β,17β-diacetoxy-5-androstene.[74]

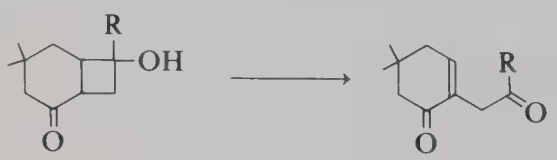


40%–60%

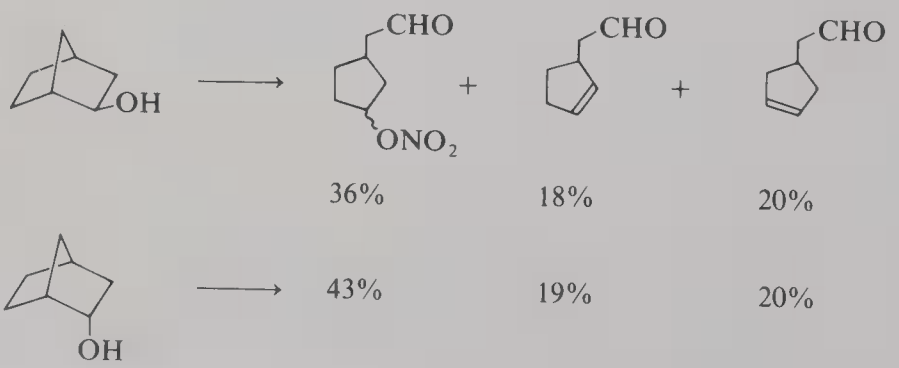
Cyclobutanol can be used as a diagnostic for determination of one- or two-equivalent oxidation pathways. One-equivalent oxidation is characterized by ring cleavage. Depending on reaction conditions, the CAN oxidation of cyclobutanol gives rise to an array of products.[24] However, good yields of dialdehydes may be obtained.



Ring-fused cyclobutanols, obtained from saponified photocycloadducts of enones with enol acetates, are transformed into α-(acylmethyl)-α,β-enones[75] by CAN. Thus, the reaction sequence constitutes a method for introducting an acylmethyl chain to the α-position of enone units.

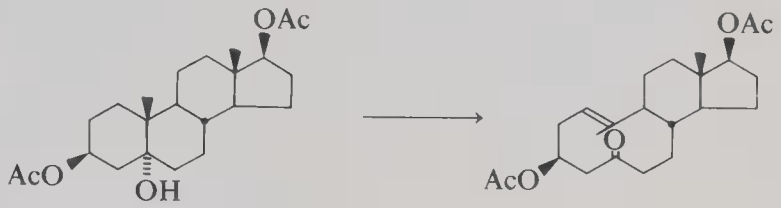


Bicyclo[x.y.z]alkan-2-ols are cleaved on exposure to CAN.[23] There is not much difference in the reaction of the epimeric pair of substrates.



The only oxidative pathway available for tertiary alcohols involves C–C bond cleavage. Ketones are obtained on treatment of *t*-alcohols with Ce(IV).[76] The direction of cleavage is

dictated by the relative stability of the ensuing free radical fragment. For example, 5α-hydroxy-3β,17β-diacetoxyandrostane reacts with CAN to afford the 5,10-secosteroid[74] in 80% yield.



Vicinal glycols and polyhydric alcohols are quantitatively broken down by the cerium (IV) ion. For example, acetone is obtained from pinacol,[27] and glucose phenylosotriazole is oxidized to 2-phenyl-1,2,3-triazole-4-carboxylic acid.[77] The equally rapid degradation of 2-methoxycycloalkanols to give dialdehydes has significant mechanistic implications *(vide supra)*.

The glycol cleavage reaction forms the basis of a quantitative method for determination[78] of aldoses and ketoses.

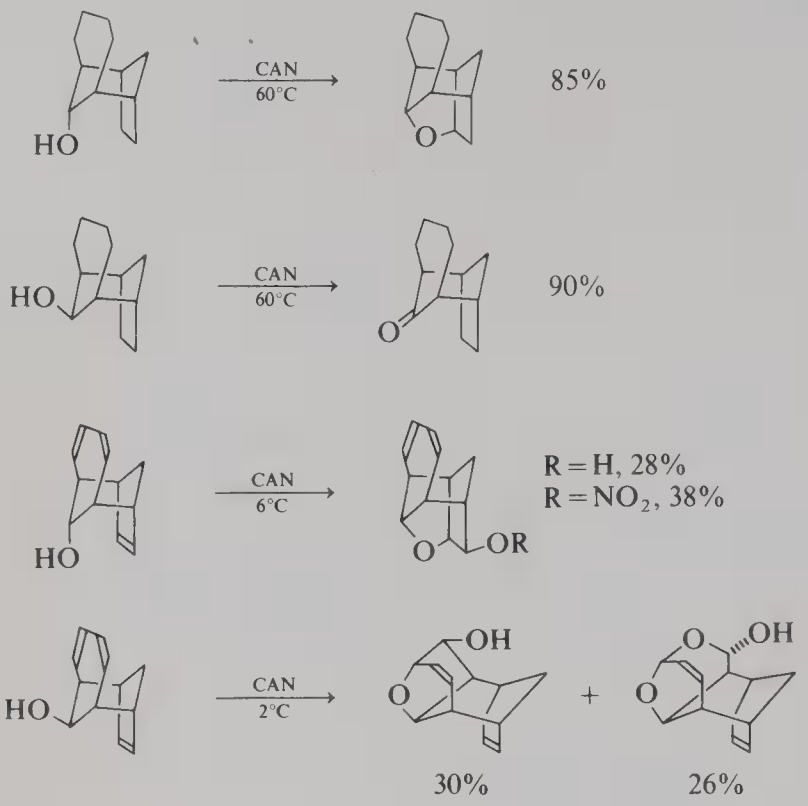
Benzoins are split into an aryl aldehyde and an aroyl radical on treatment with ceric ammonium nitrate: the radical is rapidly oxidized further to produce an arenecarboxylic acid as end product.[31] The reaction of furoin gives a very small amount of furil in addition to furoic acid, but furfural is not detectable.

Reactions of primary alkanols which possess a δ-hydrogen atom produce tetrahydrofuran derivatives.[44,45] This result is comparable with that observed from reactions with lead(IV) acetate. The lack of an α C–H bond cleavage during tetrahydrofuran formation indicates the intermediacy of an alkoxy radical (or its protonated form). This pathway is further substantiated by the specific and characteristic 1,5-hydrogen transfer even in the case of 5-phenyl-1-pentanol.

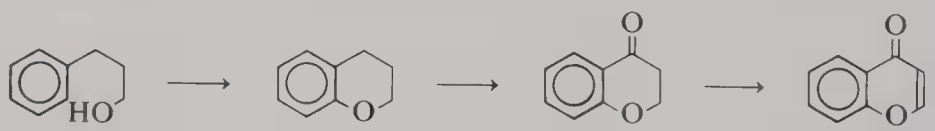
$R = CH_3$	20%
$R = C_6H_5CH_2$	40% (based on reacted alcohol)
$R = C_6H_5$	58% (based on reacted alcohol)

The formation of 6β,19-ethers[74] from 6β-hydroxy steroids on exposure to CAN is again analogous to the reaction with lead(IV) acetate. The yields decrease dramatically when the 5α-hydrogen is replaced by a halogen atom. In those cases 6-keto steroids could become the major products.

The dependence of the reaction pattern on structural features is found in the CAN oxidation of the following tricyclic alcohols[79]:



Participation of a double bond in the ether formation is clearly illustrated. A similar trapping involving the π-electrons of an aromatic ring has also been known. Thus, oxidation of 3-phenyl-1-propanol with CAN leads to chroman, which undergoes rapid and complete conversion to 4-chromanone, and eventually, chromone.[45] The absence of a δ-hydrogen for intramolecular abstraction forces the alkoxy radical species to add to the aromatic ring. The benzylic oxidation and subsequent dehydrogenation are well known *(vide infra)*.



Quite unexpected results are obtained when alcohols are oxidized with the Ce(IV)–$NaBrO_3$ system.[80] Thus, secondary alcohols are converted to ketones while primary alcoholic functions in the same molecule may be preserved. Primary 1,4-diols give δ-lactones. Substrates which undergo C–C bond fission in the presence of stoichiometric Ce(IV) react normally (dehydrogenation).

Ethers undergo oxidative cleavage to give carbonyl compounds when treated with $CAN/NaBrO_3$. Both alkyl and silyl ethers are susceptible to this reagent.[81]

3.3. Carbonyl Compounds and Derivatives

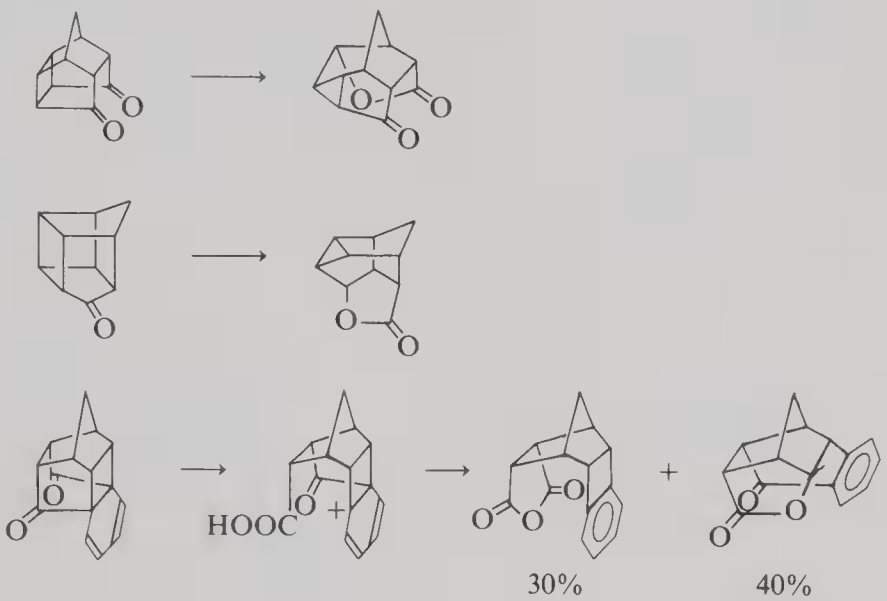
3.3.1. Aldehydes

Aldehydes and ketones are susceptible to cerium(IV) oxidation. Formaldehyde has been oxidized to formic acid in acid media,[82] while in the reaction with acetaldehyde 5.75 equivalents of cerium (IV) sulfate are consumed to produce 1.75 mol of formic acid.[83] It was reported that the reaction with triphenylacetaldehyde gave 75% triphenylmethanol together with 16% unreacted aldehyde.[35] A very stable trityl radical is formed as intermediate.

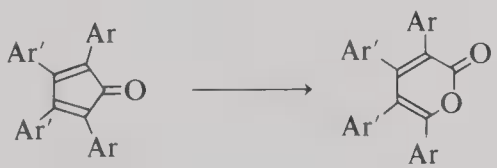
3.3.2. *Cyclic Ketones*

On treatment with CAN, cyclopentanone, cyclohexanone, and norbornanone (norcamphor) are rapidly consumed,[34] whereas camphor has been quantitatively recovered from prolonged exposure to ceric ammonium nitrate in aqueous acetonitrile at 60°C. The main products isolated from the above reactions are nitrato-carboxylic acids, indicating that an α-cleavage is involved in the major reaction pathway.

The case of adamantanone is interesting as a single lactone was obtained in good yield (73%).[34] A few other strained polycyclic ketones have also been subjected to the CAN reaction[84]; lactones were uniformly generated. However, owing to the presence of cyclobutane rings, rearrangement attends the oxidation.[85–87]



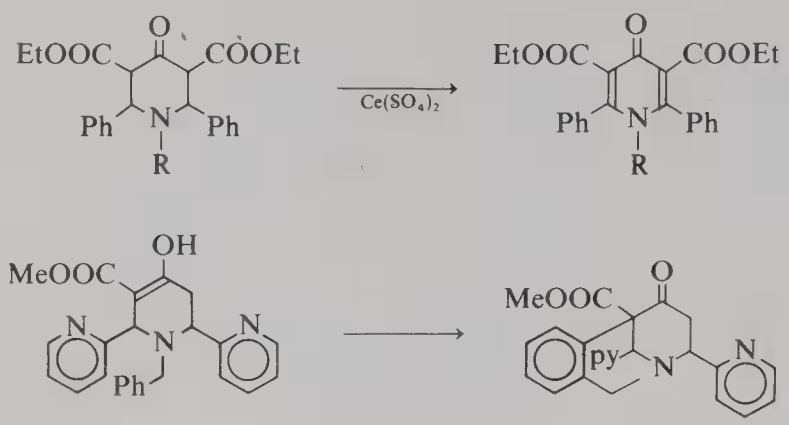
This unusual Baeyer–Villiger-type reaction is also observed in the oxidation of tetracyclones.[88] For example, tetracyclone itself has been converted to tetraphenyl-2-pyrone in 77% yield. The recovery of fluorenone after being subjected to similar experimental conditions is understandable in terms of the improbable generation of a high-energy phenyl radical intermediate. In contrast to the classical Baeyer–Villiger oxidation, the ceric ammonium nitrate reaction is extremely rapid; it is mildly exothermic and is completed within minutes at room temperature.



Although camphor is quite stable to cerium(IV), camphorquinone is easily oxidized at room temperature with ring opening and loss of one carbon atom.[36]

3.3.3. *β-Keto Esters and Stabilized Anions*

β-Keto esters are prone to generate α-radicals because of resonance stabilization. Thus, *N*-alkyl-2,6-diphenyl-4-piperidone-3,5-dicarboxylic esters undergo dehydrogenation,[89] presumably via the α-radicals. Interestingly, internal trapping of the radical generated from methyl *N*-benzyl-2,6-bis-α-pyridyl-4-piperidone-3-carboxylate[90] has been observed. It might be due to a higher population of the molecule existing in the axial *N*-benzyl conformer.

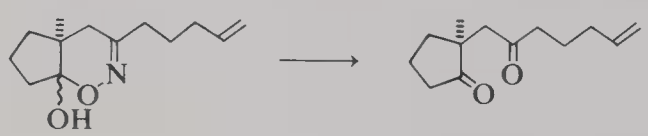


Stabilized carbanions are oxidatively dimerized on exposure to CAN. For example, tetramethyl sodiopropene-1,1,3,3-tetracarboxylate and potassium pentacarbomethoxylcyclopentadienide undergo self-coupling[91] in 90% and 84% yield, respectively.

3.3.4. Oximes and Semicarbazones

At low temperatures, oximes and semicarbazones are cleaved by CAN to regenerate the parent carbonyl compounds.[92] The oxidation at nitrogen is so fast that alcohols may be used as solvent. From the ten derivatives studied, only the reaction of camphor oxime was sluggish (27% yield), the rest giving good yields (71%–90%).

In a synthesis of the 9β isomer of 11-ketoestrone a removal of the 11-ketoxime group was required. This step was effected by CAN in methanol,[93] albeit in moderate yield (37%). The synthetic attempt of the sesquiterpene isocomene[94] also incorporated the unraveling of a 1,4-diketone unit from its monoxime which exists in the form of a hydroxazine ring.

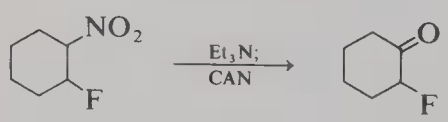


45%

Cinnamaldoxime behaves differently on exposure to Ce(IV). It undergoes oxidative dimerization at the nitrogen atom to give a dinitrone.[95]

3.3.5. Nitronates

Although nitronates are not truly carbonyl derivatives, their reaction with the Ce(IV) ion involves oxidative cleavage of the C–N bond. It has been reported that exposure of nitronates to CAN leads to carbonyl compounds.[96]



Keto macrolides are conveniently synthesized[97] by a ring expansion route from α-nitrocycloalkanones. While the Nef reaction is not suitable for converting the nitro group to the carbonyl function, the CAN/Et_3N combination serves admirably.

3.3.6. Carboxylic Acids and Derivatives

Simple aliphatic acids[37] and benzoic acid in the dark[98] are resistant to Ce(IV) sulfate oxidation in refluxing dilute sulfuric acid. However, cerium(IV) perchlorate in 4 *M* perchloric acid is capable of attacking formic and acetic acids.

The reaction of cycloheptatriene-7-carboxylic acid with ceric ammonium nitrate[99] gives the tropylium salt in 30% yield as the only isolable compound.

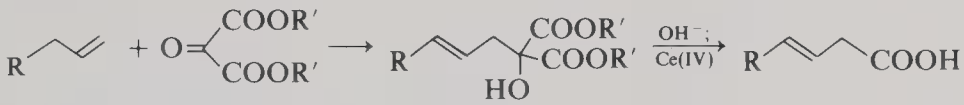
This oxidative decarboxylation is rather unique as oxidation with neutral potassium permanganate yields benzaldehyde, with alkaline permanganate, terephthalic acid, with acidic permanganate, ditropyl ether, whereas with nitric acid and with chromium(VI) oxide, both benzaldehyde and terephthalic acid are obtained.

The success of oxidative degradation of carboxylic acids depends on the stability of the decarboxylated fragments. Thus diphenylacetic acid is converted to benzophenone (90% yield) by the action of dinitratocerium (IV) dichromate dihydrate.[8]

Oxalic acid[100,101] and malonic acid[37] are readily oxidized by the cerium(IV) ion to carbon dioxide and water. Higher homologues such as succinic, maleic, and fumaric acids are found to be stable.

α-Hydroxycarboxylic acids are degraded by cerium(IV) sulfate to carbonyl compounds having one less carbon atom.[102]

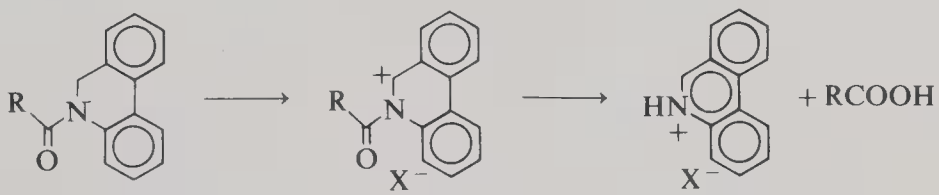
A synthetic application has been found in the degradation of tartronic acids (α-hydroxymalonic acids) which are obtainable from the ene reaction of alkenes with diethylmalonate and subsequent hydrolysis.[103] The cerium(IV) oxidation works well when sodium periodate fails. The whole process represents a transpositional allylic carboxylation of alkenes.



A solution of carboxylic acid hydrazide evolves gases vigorously on contact with CAN. The carboxylic acid can be isolated in good yields.[104] The reaction of benzilic acid hydrazide gives benzophenone (67%). This oxidation does not appear to involve any complex formation as the orange reagent is bleached immediately.

As a whole, the ceric oxidation of acid hydrazides resembles that using lead(IV) acetate,[105] although the mechanism must be different. It has been shown that N–Pb intermediates are formed during the latter process.

Protection of carboxylic acids in the form of carboxamides derived from 5,6-dihydrophenanthridine has been proposed.



Deprotection is best carried out with CAN oxidation.[106] It is likely that deprotection proceeds via cation-radical generation, loss of benzylic hydrogen, and amide bond fission.

Transacylation can be achieved by submitting the amide, an amine in anhydrous solvents, to oxidation with cerium(IV) pyridinium chloride (py_2CeCl_6) and copper(II) oxide.[107]

2,6-Di-*t*-butyl-4-methoxyphenyl esters are useful for *threo*-selective aldolization.[108] The carboxylic acids are recovered by treatment of the esters with CAN. Oxidation takes place at the aromatic ring.

3.4. Amines

Product characterization has been the major problem in Ce(IV) oxidations of aliphatic amines, with the exception of benzylamine, which gives benzaldehyde in quantitative yield on

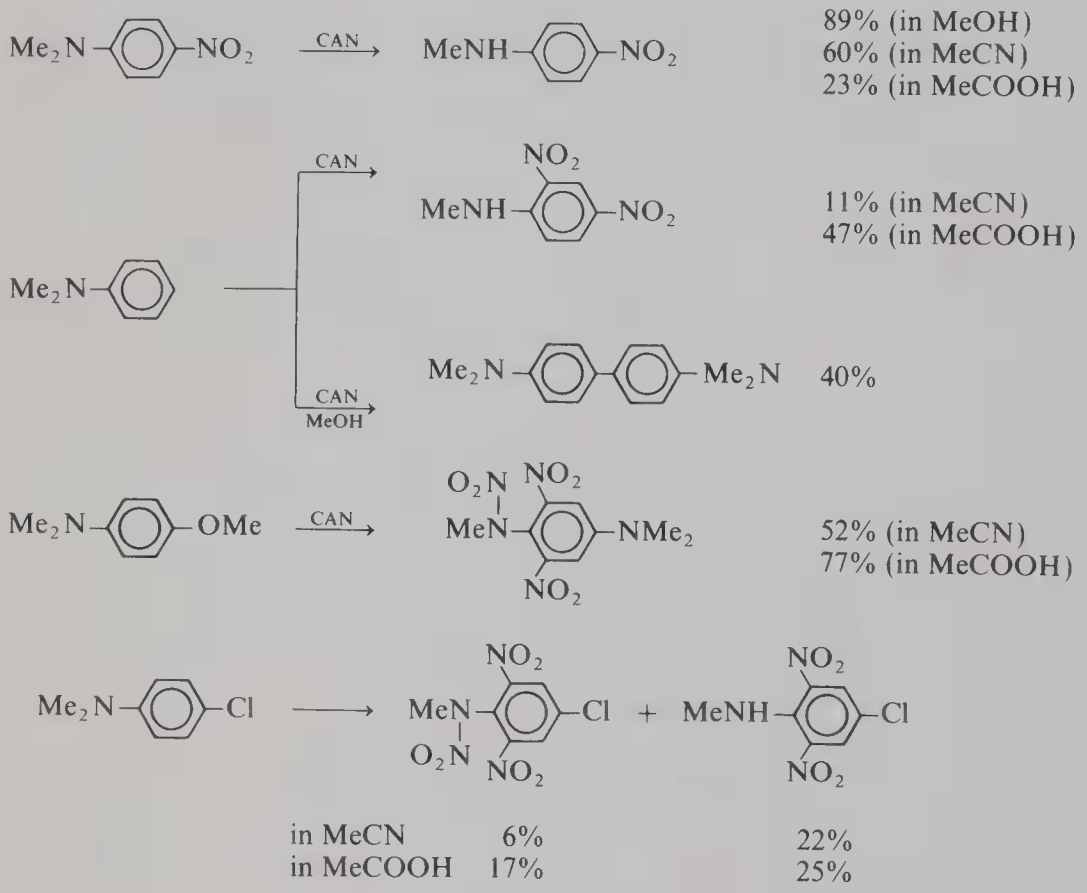
its reaction with dinitratocerium (IV) chromate dihydrate.[8] Consequently, most studies deal with aromatic amines.

Leuco malachite green is converted to malachite green by exposure to Ce(IV).[109] Control experiments confirmed that the triarylmethanol is not an intermediate.

4,4′-Bis[*N*,*N*-diethylamino]azobenzene undergoes a double one-equivalent oxidation.[110] Other 4-substituted 4′-(dimethylamino)azobenzenes[111] are either demethylated or have the 4-substituent replaced by a hydroxyl group on cerium (IV) oxidation.

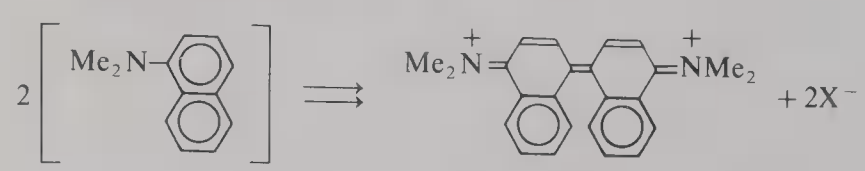
Higher *N*-alkyl groups of 2,4-dinitroanilines,[112] such as $CH_2CH_2SO_3K$, $(CH_2)_3SO_3H$, $CH_2CH_2NMe_2$, $CH_2CH_2\overset{+}{N}Me_2(CH_2)_3SO_3^-$, are lost during oxidation.

Demethylation takes place in the CAN oxidation of dimethylanilines.[113] Nitration follows the demethylation in some cases.

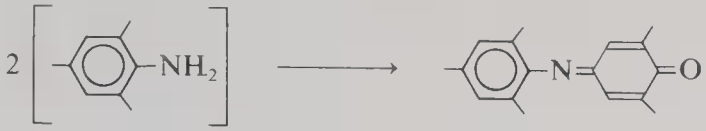


Further studies on the CAN reaction of *N*-alkyl-*N*-methyl anilines indicate that the ratio of dealkylation vs. demethylation depends on the nature of nuclear substituents.[114] On the other hand, demethylation is always preferred with the weaker oxidant thallium(III) nitrate. The nuclear nitration appears to correlate with the electrophilicity of the bidentate nitrato ligand-bearing species.

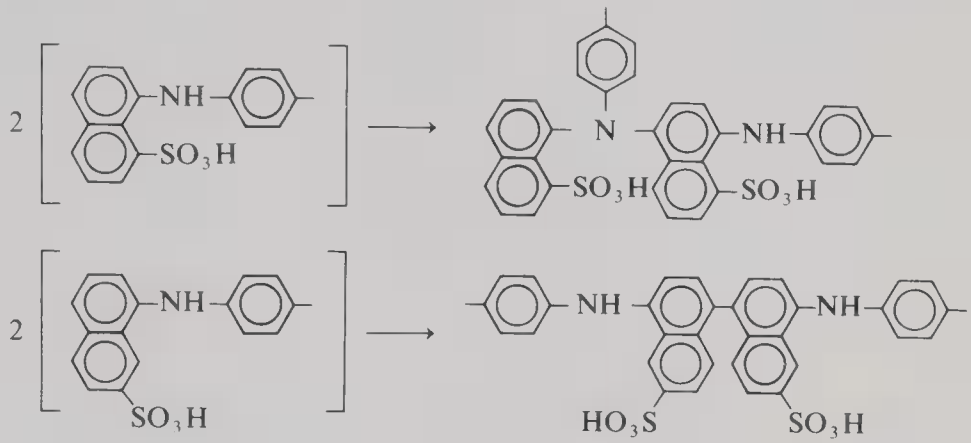
1-Dimethylaminonaphthalene undergoes self-coupling at C-4.[115] In the presence of excess oxidizing agent, the quinodiimonium salts are formed.



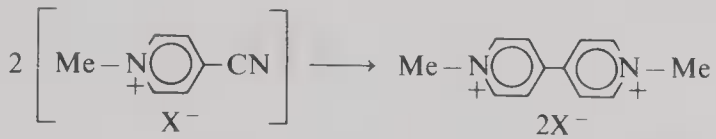
Mesidine has been oxidized to a dimeric quinoneimine in 70% yield with cerium(IV) sulfate, whereas under aprotic conditions trihydroxycerium(IV) hydroperoxide converts *p*-toluidine into 4,4′-dimethylazobenzene (55%–65% yield).[9]



1(-*p*-Toluidino)naphthalenesulfonic acids dimerize in different ways on oxidation with cerium(IV) sulfate,[117,118] according to the positioning of the sulfonic acid group.

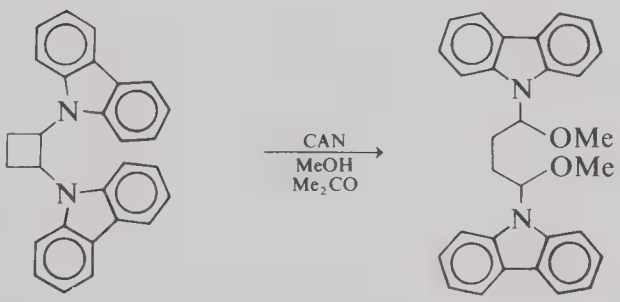


N-Alkyl-4-cyanopyridinium salts are reported to give dimers by base treatment with alkali and then with oxidizing agents including cerium(IV) sulfate.[119]



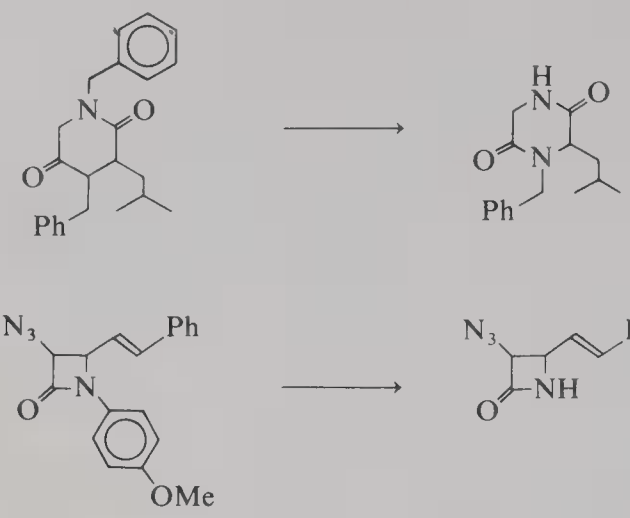
1-(Diphenylphosphoryl)-3.5-diacetyl-1,4-dihydropyridine undergoes P–N bond scission to give 3,5-diacetylpyridine and a phosphate ester when oxidized with CAN in an alcohol.[120]

Methanolytic ring fission of 1,2-di(carbazol-9-yl)cyclobutane[121] is promoted by CAN in methanol.

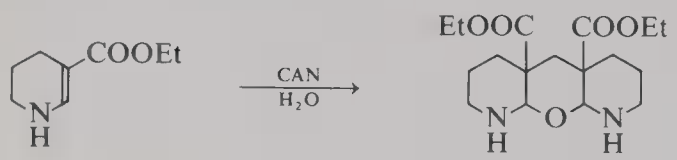


Benzyltetrahydroisoquinoline alkaloids including laudanosine, tetrandrine, hernandezine, and *O*-methylmicranthine have been degraded into a benzaldehyde and a dihydroisoquinolinium ion with CAN in buffered acetic acid in excellent yields.[122]

Secondary amides may be protected as *p*-methoxybenzyl or *p*-anisyl derivatives. By virtue of their selective deblocking with the Ce(IV) ion *N*-(*p*-methoxybenzyl)-diketopiperazines[123] and *N*-(*p*-anisyl)monobactams[124,125] have been successfully employed as synthetic intermediates. Again it should be noted that the oxidation occurs at the aromatic ring and not at the nitrogen atom.

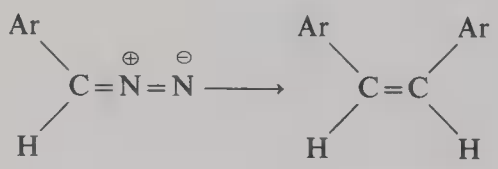


Hydrative dimerization[126] occurs when ethyl tetrahydronicotinate is exposed to CAN in a two-phase system ($H_2O-CHCl_3$).



Cerium(IV) salts cause a change in color of a chlorophyll solution from green to yellow.[127] This transformation can be reverted by reducing agents.

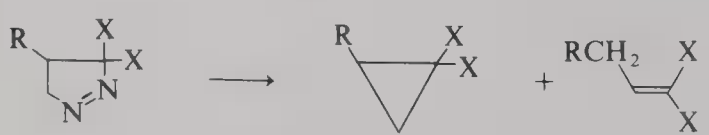
Cerium(IV) ion-catalyzed decomposition of aryldiazomethanes[128] leading to the formation of *cis*- and *trans*-stilbenes has been described; the *cis*-isomers are the predominant products. Strong electron-withdrawing groups inhibit the reaction.



(major)

Cyclopropanes, in some cases together with alkenes, are obtained from pyrazolin-3,3-dicarboxylic esters[129] on treatment with catalytic amounts of CAN.

The dehydrogenation of substituted dibenzylhydroxylamines[130] to isomeric nitrones can be accomplished with various oxidizing agents, including CAN.



X = COOMe

3.5. Organosulfur Compounds

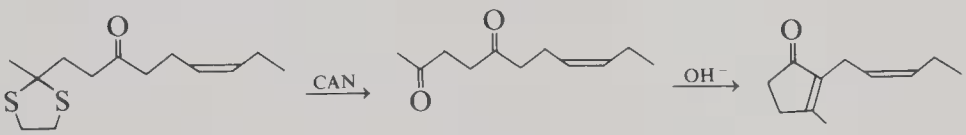
Ceric ammonium nitrate promotes selective oxygenation of diaryl sulfides to sulfoxides[131] at room temperature in excellent yields. Even in the presence of excess oxidant, sulfones are not formed. However, bis-[4-methoxyphenyl] sulfoxide can be further oxidized

to the sulfone under more vigorous conditions[132]; on the other hand, bis-[4-chlorophenyl] sulfoxide is completely stable.

This method is not particularly suitable for the oxidation of aliphatic sulfides, presumably because the products are prone to Pummerer rearrangement. Nevertheless, mass spectral analysis indicated that the reaction of di-*n*-butyl sulfide provides predominantly the sulfoxide.

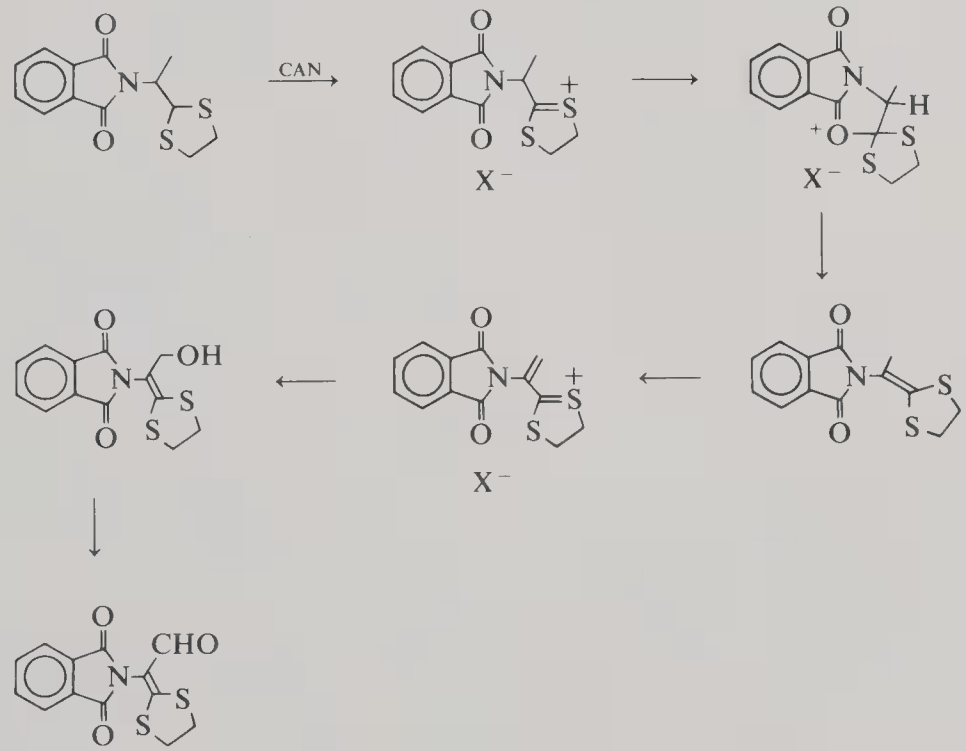
More recent work has shown that a dual oxidant system containing catalytic amounts of CAN can be used to oxidize sulfides to advantage. The essentially nonacidic conditions permit the acquisition of dialkyl sulfoxides in high yields.[133]

It is of interest to note that 1,3-dithiolanes and 1,3-dithianes are readily degraded to their parent carbonyl compounds.[134] The mild experimental conditions and broad applicability of this reaction should prove invaluable to extending the use of dithioacetal protecting grous in organic synthesis. The dethioacetalization constitutes a step in a synthesis of *cis*-jasmone[135] and in C-formylation of carbohydrates.[136]

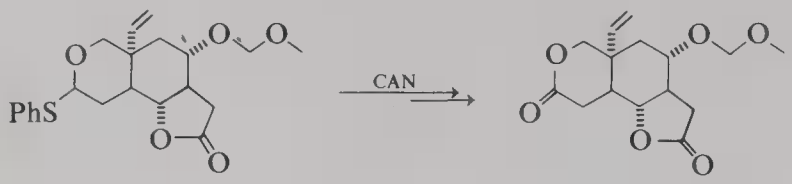


It is interesting to note that γ-thioacetalated phosphonium salts suffer oxidative desulfurization readily, except for the phosphonium nitrates.[137] The abnormal sulfoxide formation intervenes only when the anion is a nitrate *and* the phosphonium center is three carbon atoms away from the thioacetal carbon.

The production of an unsaturated aldehyde from CAN oxidation of 2-(1-phthalimidoethyl)-1,3-dithiolane[138] is due to a nucleophilic participation of the imidic oxygen atom which directs the generation of the ketene dithioacetal. Being more inert to hydrolysis the ketene dithioacetal undergoes allylic oxidation instead.



In a synthesis of the antitumor sesquiterpene vernolepin,[139] difficulties were encountered in converting a hemiacetal ether intermediate to the lactone. The problem was solved by means of exchange to the monothioether followed by a two-step oxidation: first with CAN, then with Jones' reagent.



Thiols are oxidized to the disulfides with a variety of Ce(IV) reagents[7–10] in excellent yields.

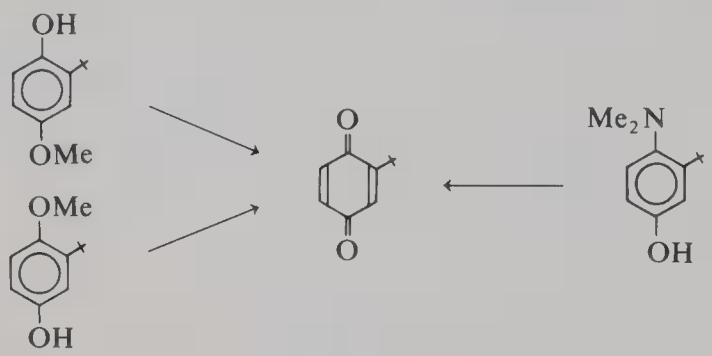
3.6. Aromatic Compounds

3.6.1. Quinones from Phenol Derivatives and Polycyclic Arenes

Electron-rich arenes such as oxygenated benzenes and polycyclic aromatic hydrocarbons are quite reactive toward Ce(IV) species. Exceptionally facile oxidation of hydroquinones to quinones has been reported.[140]

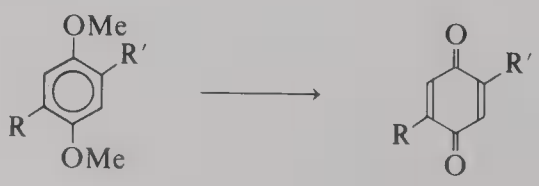
The hydroquinones oxidation is rather general, as it is applicable to the preparation of *p*, *o*-, and diquinones. The base sensitive fluorobenzoquinone has been obtained using this method.[141] The dual oxidant system CAN–$NaBrO_3$ is also useful.[133]

Hydroquinone monoalkyl ethers[142,143] are converted to the quinones; these include the condensed ring analogs such as 6-hydroxychromans and 5-hydroxycoumarans.[144,145] In a similar manner, 3-*t*-butyl-4-dimethylaminophenol is oxidatively deaminated.[146]

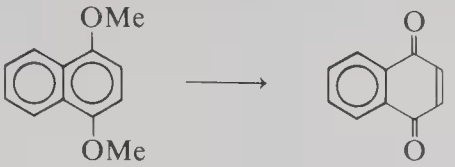


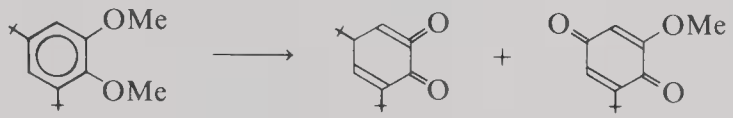
Some interesting results emerged from the Ce(IV) oxidation of 1,4-dimethoxybenzenes. Using excess cerium(IV) sulfate, dimeric quinones have been obtained.[147]

Simple oxidative demethylation occurs when 2,5-alkyl-1,4-dimethoxybenzenes[148,149] are treated with CAN in aqueous acetonitrile. Even benzylic hydroxyl and *t*-butoxy-carbonyl functions survive the oxidation.

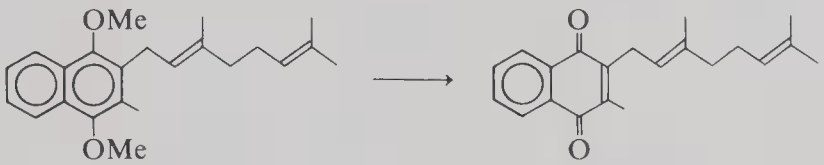


Similarly, 1,4-dimethoxynaphthalene and 1,2-dimethoxy-3,5-di-*t*-butylbenzene are oxidized to the quinones. De-*t*-butylation occurs to some extent.

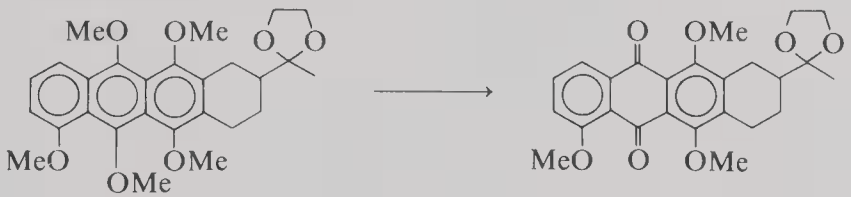




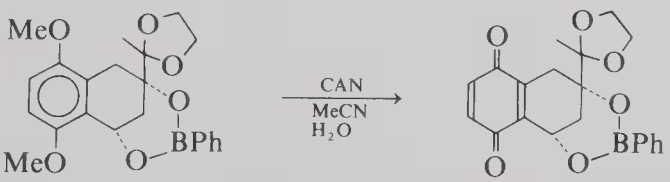
At least for *p*-quinone formation the oxidation is best performed in the presence of an azinecarboxylic acid derivative (e.g., pyridine-2,6-dicarboxylic acid *N*-oxide)[150] which complexes with the metal ion. Pyridine-2,4,6-tricarboxylic acid appears to be the best catalyst, and it has been used in the synthesis of ubiquinone-2, menaquinone-2, and their analogs.[151]



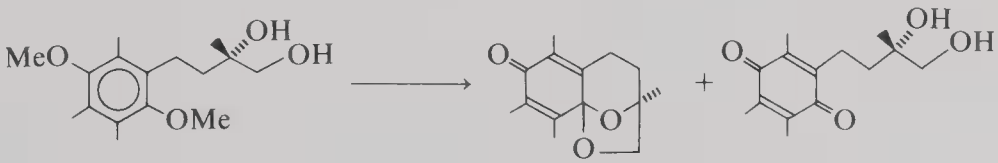
Regioselective oxidation of the C-ring in a tetracyclic intermediate by CAN helped clear the synthetic pathway leading to daunomycinone.[152]



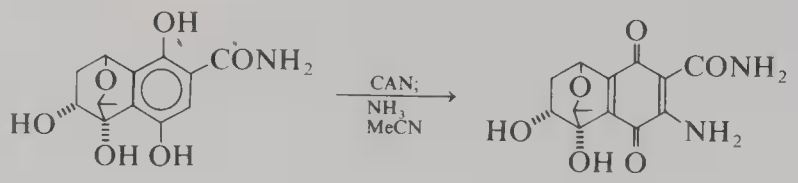
Alternatively, a highly functionalized dimethoxytetralin was oxidized to the quinone in 97% yield which was ultimately converted into 4-demethoxydaunomycin.[153]



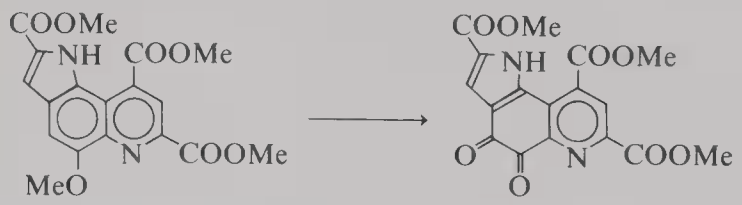
When the substituted *p*-dimethoxybenzene contains properly hydroxylated side-chain, a dioxaspiro system may result[154] from the Ce(IV) oxidation.



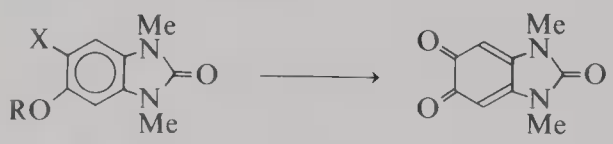
Controlled CAN oxidation with *in situ* amination completed a synthesis of the antibiotic sarubicin A.[155] The yield of 74% represents an extremely effective reaction in view of the presence of the many functional groups.



In a synthesis of the alcohol dehydrogenase coenzyme[156] from methylotrophic bacteria, the *o*-quinone unit was established by means of CAN oxidation.



o-Quinones are also produced in the Ce(IV) oxidation of alkoxybenzimidazoles.[157,158] Noteworthy is the accompanying dealkylation.



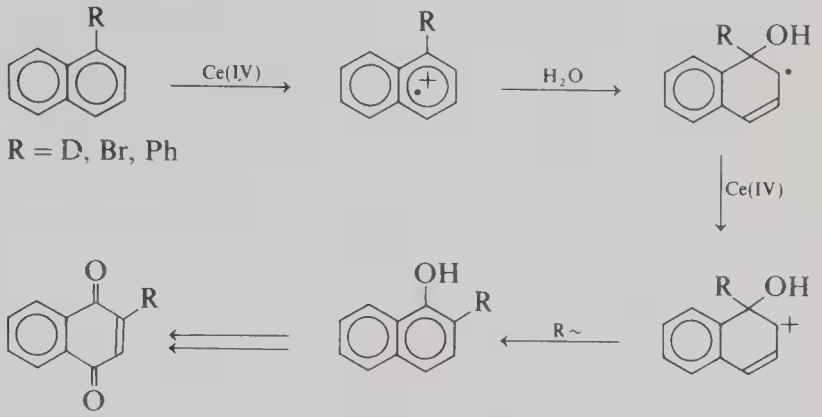
R = Me, X = Cl
R = Et, X = NHAc

Although the preparative value of the Ce(IV) oxidation of simple phenols is probably low, it is indicated that (2,3-, 2,5-, 3,5-) xylenols give the corresponding quinones as sole products[159] on the basis of thin layer chromatography.

In structural terms, furans may be considered as truncated 1,4-dialkoxybenzenes. The electron-richness of these heterocycles makes them susceptible to attack by Ce(IV) ions. Indeed, fair yields of enedicarbonyl products are obtained from such oxidations.[160]

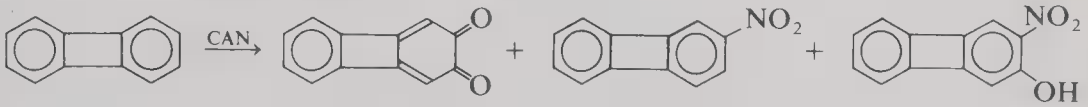
The major products from the CAN oxidation of polycyclic arenes in aqueous acetonitrile are quinones.[161] For example, 1,4-naphthoquinone (20%), 9,10-anthraquinone (61%), phenanthrenequinones (9,10-: 27%, 1,4-: 11%), and 2-(phenylethynyl)-1,4-naphthoquinone (87%)[149] have been obtained. Better yields of the quinones are claimed for the oxidation carried out with cerium(IV) ammonium sulfate.[162] A recently developed preparative system[65a] consists of CAN, $AgNO_3$, sodium dodecyl sulfate and ammonium persulfate.

It has been shown that 1,4-naphthoquinone formation is accompanied by a 1,2-shift of the α-substituent.[163] However, an arene oxide is not involved. By this evidence the mechanistic difference between Ce(IV) and Cr(VI) oxidation of arenes is further substantiated.



In a recent patent the preparation of benzene[164] from anthracene is described. The process involves Ce(IV)-catalyzed oxidation and thermal cracking of the resulting anthraquinone.

The most convenient method for the synthesis of biphenylene-2,3-dione appears to be that of CAN oxidation of the hydrocarbon.[165]

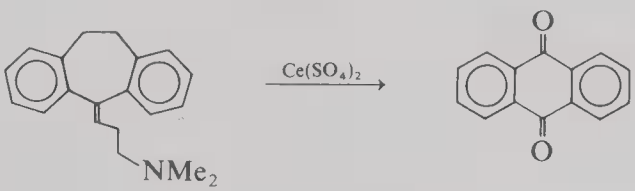


21% 6.7% 1.8%

Incorporation of solvent other than water into the substrate can be appreciated from examination of the CAN oxidation of anthracene.[166] In methanol, anthracene is converted into bianthrone (7%), anthraquinone (35%), and 10-methoxyanthrone (58%). It appears that the anthracene radical cation is intercepted to form anthrol nitrate. Hydrolysis of the latter compound and further oxidation then lead to the observed products. Under similar conditions, anthrone, xanthene, and thioxanthene are oxidized to anthraquinone (80%), xanthone (87%), and thioxanthone (75%), respectively.[167] Acridine yields acridone (66%) and small amounts (<5%) of 3-nitroacridone, 3,7-dinitroacridone, and biacridone.

In refluxing acetic acid 1,3,7-trinitroacridone and 1,3,7,9-tetranitroacridone are produced (16% and 67%, respectively). Phenazine gives mono-*N*-oxide (54%). Electron-rich benzene derivatives such as anisole undergo acetoxylation with CAN in acetic acid.[51] The *o*/*p* isomer distribution follows the odd-electron density at the various positions of the anisole radical cation. It is significantly different from that observed in the $Pb(OAc)_4$/HOAc reaction. On the other hand, polynitro benzene derivatives may be alkylated by degrading a carboxylic acid ($RCOOH \rightarrow R^{\cdot}$) with CAN in their presence.[168]

A rather unusual use of cerium(IV) is in the assessment of the amitriptylene level in plasma through extractive oxidation which yields anthraquinone.[169] The latter is then determined by electron-capture gas chromatography. The Ce(IV) oxidation is better than that of alkaline permanganate, chromic acid/acetic acid, and barium peroxide in sulfuric acid.



3.6.2. Miscellaneous

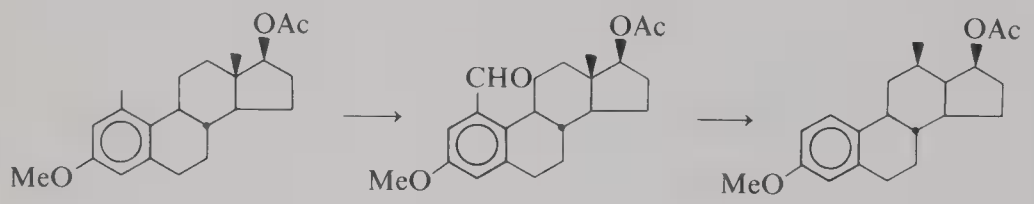
Benzylic methyl and methylene groups can be converted to carbonyl functions by treatment with cerium(IV) species in an acidic medium (acetic, nitric, or perchloric acid).[170,171]

The reaction normally stops at the mono-carbonyl stage, because the electron-withdrawing function thus introduced deactivates the ring such that further electron transfer becomes very difficult. However, a second methyl group may undergo oxidation under more drastic conditions.

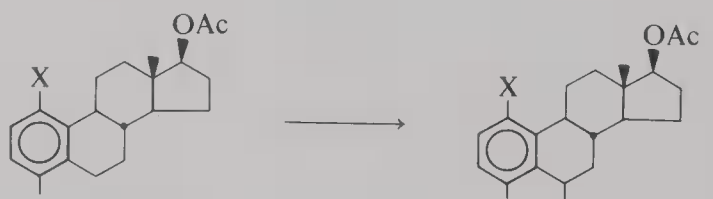
Continuous regeneration of the Ce(IV) species in an anode for the oxidation of alkylbenzenes[172,173] such as *p*-xylene, *t*-butyltoluene, and *p*-cresyl methyl ether to the corresponding aldehydes is a preparatively expedient process.

The effect of surfactants on CAN oxidation is the following.[174] Cationic (ammonium salts) and nonionic (polyethers) surfactants tend to inhibit the reaction, whereas the anionic surfactant sodium dodecyl acts as a promotor. Binding of the aromatic compounds and the Ce(IV) ions to the surface of the micelles is the basis of the catalytic action.

The Ce(IV) oxidation is a key step in the synthesis of 19-norsteroids[175] from 1-methylestradiol derivatives. The latter compounds are obtained from $\Delta^{1,4}$-androstadien-3-ones.



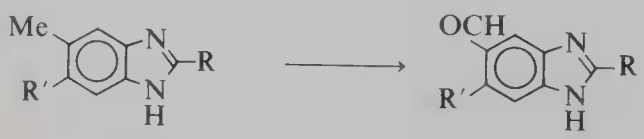
Interestingly, oxidation of 4-methylestra-1,3,5(10)-trienes gives the corresponding 6-acetates.[176]



X = OMe, OAc, Cl

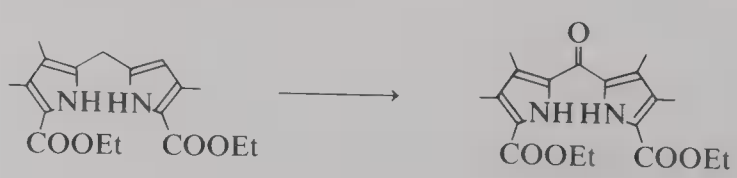
The methyl ether and acetate of estrone are rapidly oxidized at C-9 to furnish the $\Delta^{9,(11)}$-derivatives.[177] The styrenes are then transformed into the 9α,11β-diol 11-nitrates.

5-Methylbenzimidazoles are susceptible to CAN oxidation to provide aldehydes.[178] However, demethylative (at C-6) nitration occurs when 5,6-dimethylbenzimidazol-2-one is treated with CAN.



R H, Me
R' H, Me

The CAN oxidation of dipyrromethanes to dipyrroketones[179] is superior to previously known procedures using either lead(IV) or halogens.



57%

1-Methoxy-cyclohexano[1, 2-*b*]-9*H*-xanthen-9-one is oxidized by CAN at the benzylic position activated by two ethereal oxygen atoms.[180]

54%

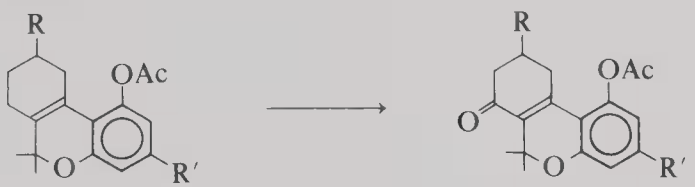
It should be emphasized that the nature of the benzylic oxidation product is a function of reaction conditions as well as stoichiometry. In oxygen-free acetic acid and with two equivalents of CAN, polymethylbenzenes give benzyl nitrates and acetates,[55] the ratio of which depends on the homogeneity of the reaction. In dilute nitric acid, benzyl nitrates are formed.[181]

Rather oddly, mesitylene undergoes nuclear acetoxylation in oxygen-free acetic acid in the presence of CAN, as previously mentioned. Dimesityl is produced when mesitylene is treated with cerium(IV) trifluoroacetate in trifluoroacetic acid.[58] The low nucleophilicity of the trifluoroacetate ion and acid accounts for their negligible participation in the product formation.

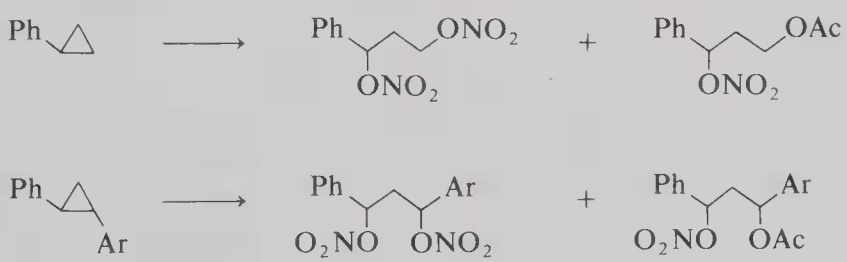
A free radical aromatic nitromethylation of benzene and toluene with nitromethane by Ce(IV) salts[182] indicates that best results are from reaction with cerium(IV) acetate generated by ozonation of Ce(III) species in acetic acid. With this reagent the side reaction leading to aldehyde is avoided. Cerium(III) nitrate is effective for that side reaction.

Polymethylbenzenes, polymethoxybenzenes, and naphthalene undergo nuclear iodination[183] with either alkali iodides and tetrabutylammonium iodide, or molecular iodine, and in the presence of CAN in acetonitrile. Stoichiometric and substoichiometric quantities of Ce(IV) salt are required in the case of iodide and iodine, respectively.

$\Delta^{6a(10a)}$-Tetrahydrocannabinyl acetates are oxidized by CAN to afford 7-oxo derivatives.[184] The allylic oxidation is expected on the ground that the free radical at C-7 is the only one which enjoys an extended conjugation with the aryl oxygen atoms.



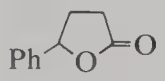
Ring opening has been observed when arylcyclopropanes are treated with ceric ammonium nitrate.[185] Similarly, 1,2-diarylethanes are converted only to cleavage products.[186]



$$ArCH_2CH_2Ar \xrightarrow{CAN} ArCHO + ArCH_2OH + ArCH_2ONO_2$$

Undoubtedly both reactions are initiated by electron removal from the aromatic rings. Cerium(IV) acetate promotes a radical-type addition of acetic acid to aromatic

hydrocarbons to give arylacetic acids (30%–40%).[187] The reaction with styrene proceeds in exactly the same manner as that effected by manganese(III) acetate.

$$PhCH=CH_2 \xrightarrow[MeCOOH]{Ce(OAc)_4}$$ 

However, the main product from a photochemical reaction is an ester.

$$PhCH=CHMe \xrightarrow[h\nu]{Ce(OAc)_4} PhCH(OAc)-CHMe_2$$

This ester arises from interception of the methyl radical generated from the decomposition of cerium(IV) acetate.

3.7. Organometallics

Organometallic complexes liberate π-lingands on treatment with cerium(IV) ion. Thus, the theoretically very interesting molecule cyclobutadiene was first shown to exist in the free state by its release from the iron tricarbonyl complex on treatment with cerium(IV).[188]

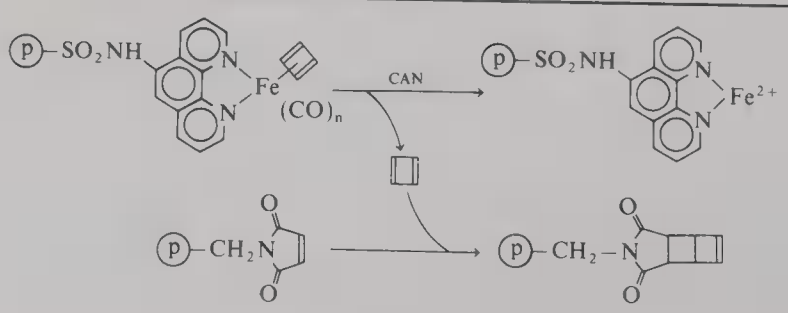
The triphase technique provides another stringent probe for the existence of free, singlet-state cyclobutadiene.[189] By attaching the cyclobutadienyliron carbonyl complex and a dienophile to polymeric supports, treating the polymer mixture with a cerium(IV) solution, the Diels–Alder adduct of cyclobutadiene with the dienophile has been obtained. The cyclobutadiene released from a solid phase moves through the solution and then anchors to another solid.

When an optically active, substituted cyclobutadieneiron tricarbonyl was subjected to CAN oxidation in the presence of dienophiles, only racemic Diels–Alder adducts were formed.[190,191] At 50% reaction, the recovered complex retained its optical activity, while the adduct was in racemic form.[191]

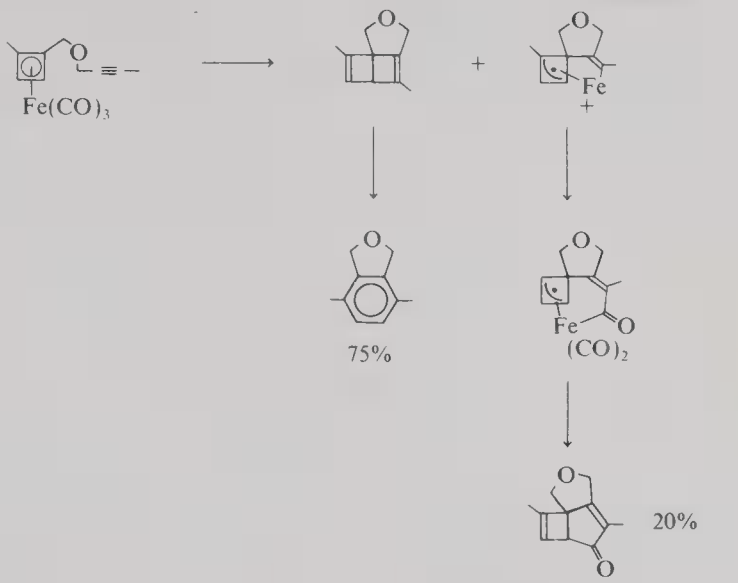
Ratio 2 : 1 : 1

When the complexes containing a dangling dienophilic side-chain are exposed to CAN, intramolecular Diels–Alder reaction could result. For compounds with short chains, a trapping process involving σ C–Fe bond formation becomes competitive to ligand release; this process leads to optically active products from optically active metal complexes.[192]

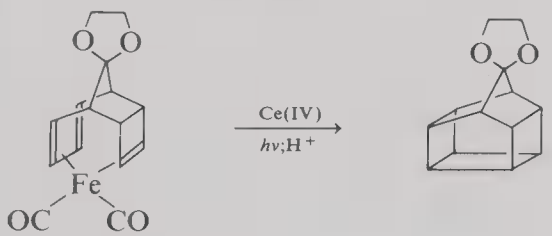
SCHEME 6



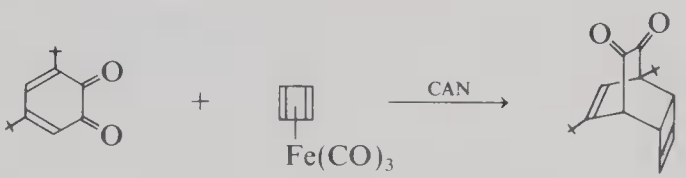
SCHEME 7



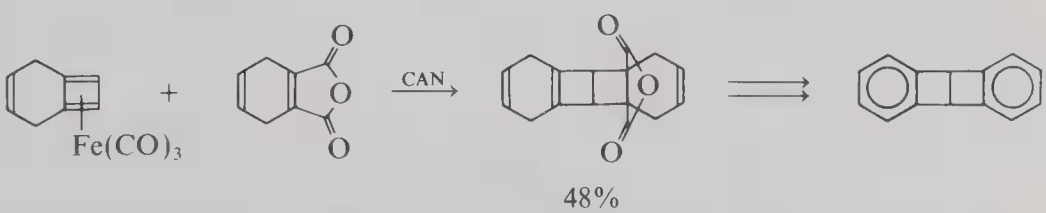
By virtue of this technique of nascent cyclobutadiene generation, many intriguing compounds become accessible. Examples include short routes to cubane[193] and hypostrophene.[194] A related application pertains to the homopentaprismanone synthesis.[195]



Cyclobutadiene has also been captured by 3,5-di-*t*-butyl-1,2-benzoquinone,[196] affording the adduct in 51% yield. As *o*-quinones are accessible in an instantaneous CAN oxidation of catechols, it is of interest to modify the technique (cooxidation) so that adducts from less stable, less highly substituted *o*-quinones may be formed.

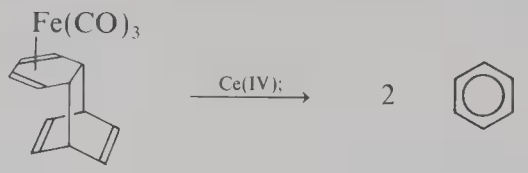


9,10-Dewar-anthracene has been synthesized from a fused cyclobutadiene tricarbonyliron.[197]

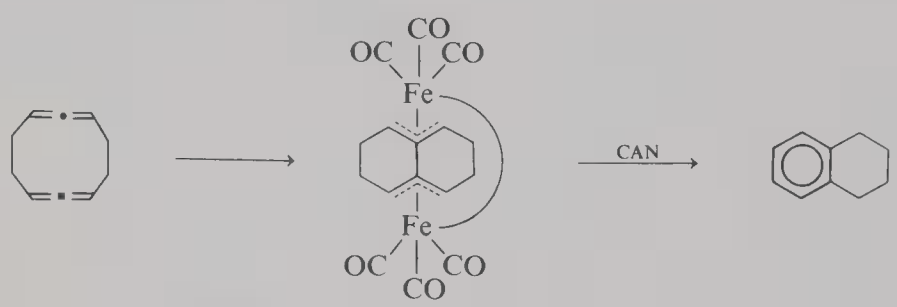


Release of the organic ligand from metal complexes often leads to products with totally different bonding characteristics, if the free ligand is thermodynamically unstable. For exam-

ple, the formal Diels–Alder adduct of two benzene molecules, when liberated from its tricarbonyliron complex[198] by Ce(IV) oxidation, immediately reverts to benzene. Electrocyclic isomerization of the olefin ligand is attended by the oxidation of the complex of tricyclo-[4.3.0.0^{7,9}]nona-2,4-diene,[199] if the educt is warmed above 30°C.

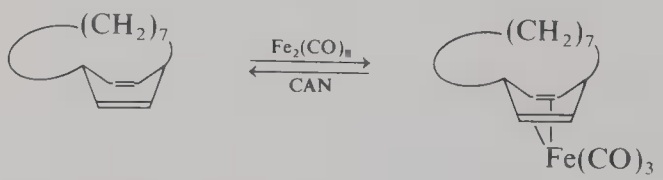


Carbonyliron complexation of allenes is accompanied by a C–C bond formation with the central atom. The free ligand of such complexes cannot exist as a stable entity; therefore hydrogen shifts within the molecular framework is inevitable. The formation of tetralin from 1,2,5,6-cyclodecatetraene[200] is illustrative.

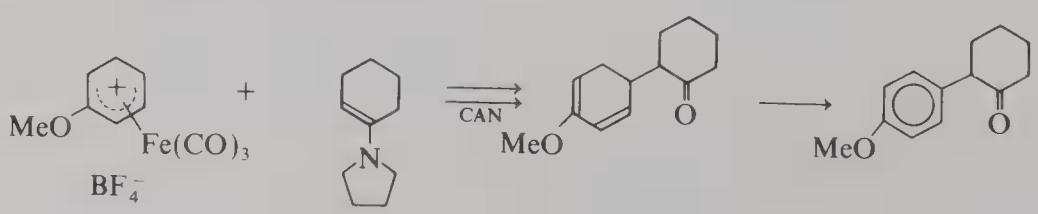


The cycloadditive reactivity of polyenes can be modified by complexation with transition metals. Metal-free adducts can then be generated by Ce(IV) oxidation.[201,202]

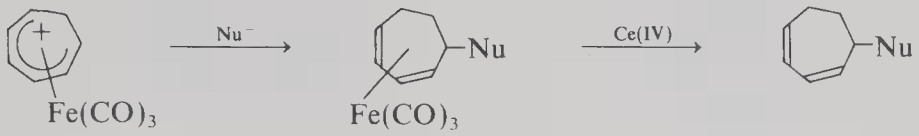
Metal complexation also provides a means of alkene purification (e.g., via the well-known Ag^+ complexes). Thus the highly strained inside–outside bicycloalkadiene derivatives have been isolated as $Fe(CO)_3$ complexes and then regenerated by CAN oxidation.[203]



A two-step reduction of cross-conjugated dienones has been achieved by consecutive reactions with an iron carbonyl and CAN.[204] Similar diene (2-methoxy vs. 2-hydroxyl) complexes are obtainable from alkylation involving the complexed methoxycyclohexadienyl cation. Upon removal of the metal moiety from the adduct, either a cyclohexenone[205] or a substituted anisole[206] may be formed.

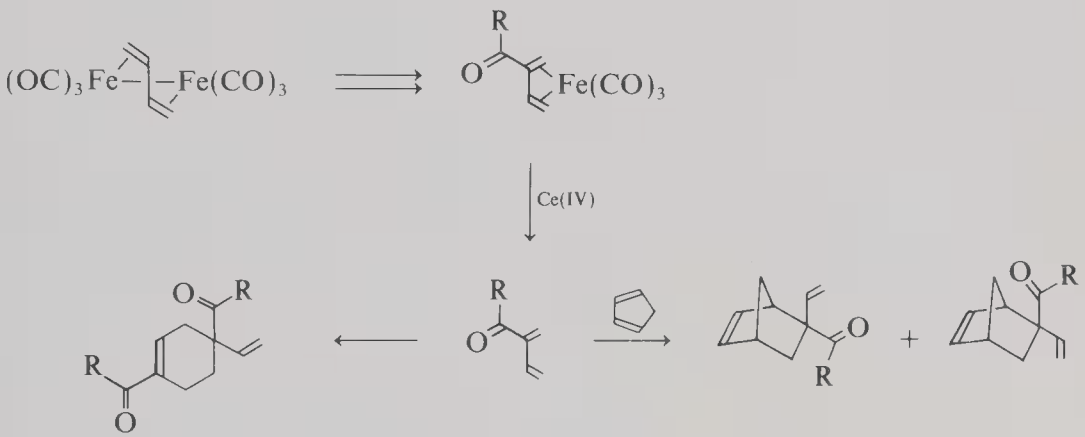


By a hydride abstraction the 1,3-cycloheptadienyl complex becomes susceptible to attack by nucleophiles.[207] Thus a net allylic substitution results after the decomplexation.



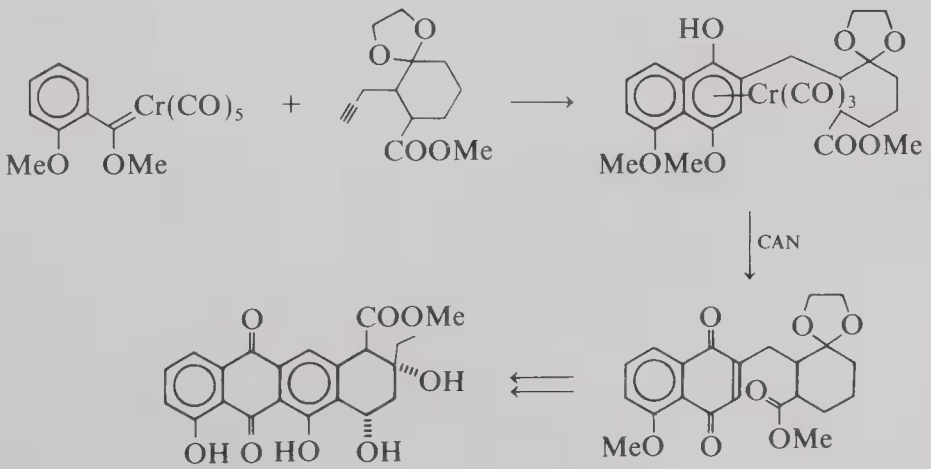
Simple olefins can also be activated in the form of the tetracarbonyliron complexes such that they react with sodiomalonic esters.[208] Iron-free alkylmalonates are released accordingly.

Friedel–Crafts acylation of butadiene (hexacarbonyl)diiron followed by protolysis and Ce(IV) oxidation furnishes 2-acylbutadienes.[209] These products are extremely reactive and they possess high potential for synthesis.



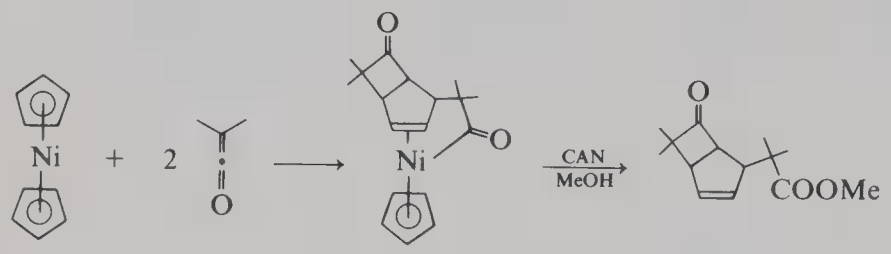
Mixtures of 2,5- and 2,6-disubstituted benzoquinones are produced from a two-step reaction[210]: photodimerization of alkynes in the presence of pentacarbonyliron and Ce(IV) oxidation in aqueous ethanol.

In an approach to aklavinone, a reaction of an alkyne with a carbene–chromium complex yielded a naphthol derivative. Oxidation of the latter compound with CAN led directly to a crucial naphthoquinone intermediate.[211]

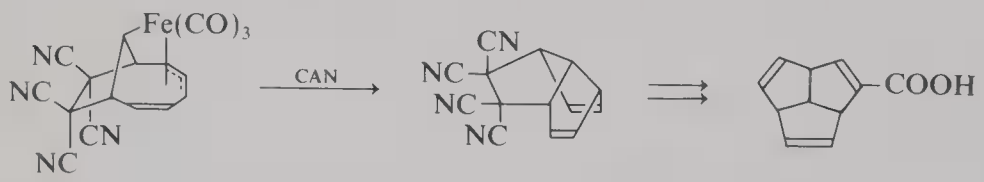


The tricarbonylchromium group activates an aromatic ring it complexes. As the benzylic hydrogen is also acidified, a process for specific deuteration at that carbon atom is realized[212] when decomplexation with Ce(IV) ion is taken into account.

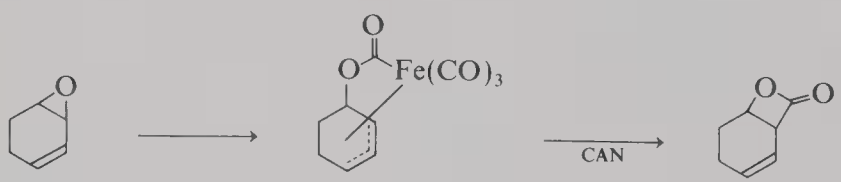
Organometallic sandwiches are rapidly destroyed by Ce(IV) ions. Kinetic studies[213] show the reaction of ferrocene involving initially a fast one-electron transfer. Nickelocene forms a 1:2 adduct with dimethylketene whose structure was revealed with the aid of CAN oxidation.[214]



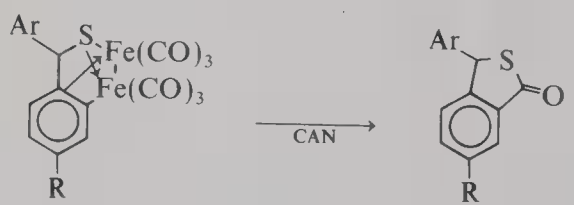
Oxidative degradation of alkene–metal complexes can result in C–C bond formation. This process holds great promise in the synthesis of many intriguing molecules. The exceptionally expedient synthesis of triquinacene-2-carboxylic acid[215] is instructive.



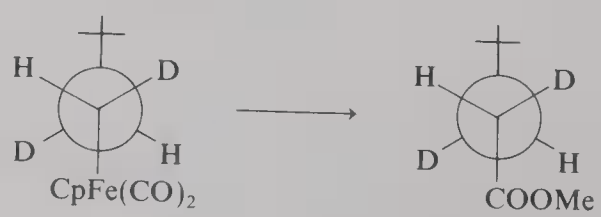
The monoepoxides of conjugated dienes react with pentacarbonyliron to afford complexes in which CO insertion into the oxirane had occurred. CAN oxidation leads to β-lactones.[216] Similarly accessible are the β-lactams.[217]



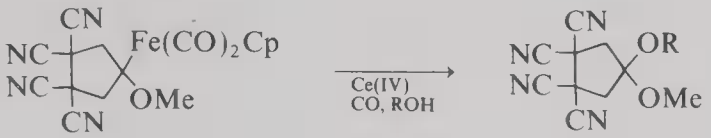
Somewhat related is the carbon monoxide insertion reaction that results in thiolactones[218] from the oxidative cleavage of the thiobenzophenone–hexacarbonyldiiron complexes.



When the acylmetal intermediate is intercepted by an external nucleophile, a carboxylic acid derivative (e.g., ester) is formed in the process.[219–221]



However, exceptions[222] are known.



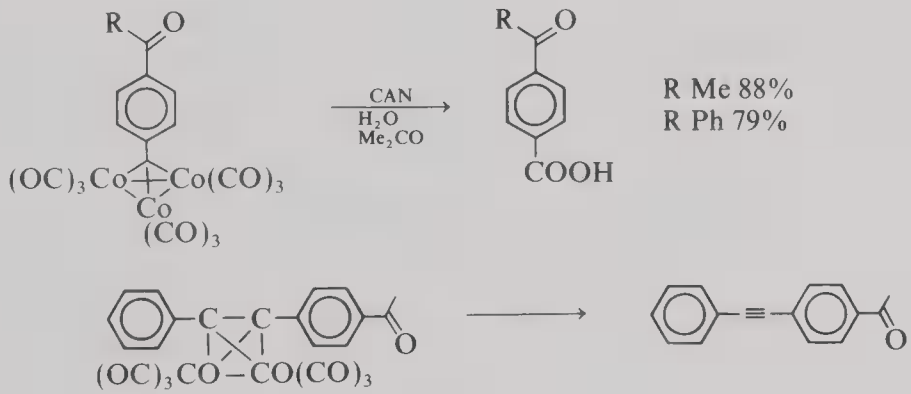
88%

Although Ce(IV) oxidation has been extensively applied to organoiron complexes, substances containing other transition metals also undergo facile demetallation; examples include coupling of diarylnickel (III)[223] and disengagement of manganese from its allene complexes.[224]

Transition metal–carbenoid complexes give carbonyl compounds on oxidation. Cerium (IV) salts, especially CAN, have been frequently used for this purpose.[225,226] The synthesis of α-methylene-γ-butyrolactone[227] demonstrates a unique approach to such reactive molecules.

76%

Metal clusters that contain carbon–metal bonds suffer oxidative degradation on exposure to Ce(IV) ion, as shown by the following examples.[228,229]



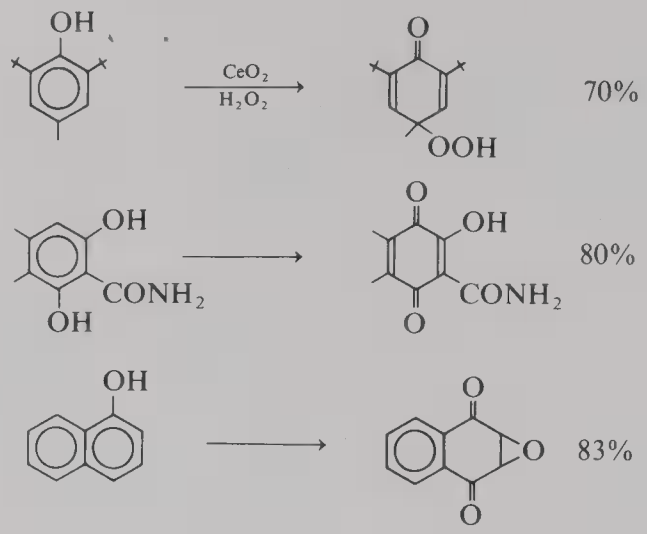
3.8. Miscellaneous Topics

Since cerium(IV) is a strong oxidant, it effects O–H bond rupture of hydroperoxides, as lead(IV) does. These reactions have been used for preparing high concentrations of alkylperoxy radicals for ESR investigations.[230] Since very small amounts of addition products are detected in the decomposition of hydroperoxides in the presence of olefins,[231] the reaction has little synthetic value.

$$\mathrm{ROOH + Ce(IV) \longrightarrow ROO^{\cdot} + H^{+} + Ce(III)}$$

An interesting observation is that singlet oxygen is generated (and intercepted by 9,10-diphenylanthracene) from the CAN oxidation of *sec*-butylhydroperoxide,[232] but not from *t*-butyl hydroperoxide or hydrogen peroxide.

A combination of aged (20 years) or thermally treated cerium(IV) oxide with hydrogen peroxide is capable of oxidizing a number of phenols and homonuclear conjugate dienes.[233] The reaction is attributed to singlet oxygen generated on the surface of cerium(IV) oxide. Comparison of this oxidizing system with trihydroxycerium (IV) hydroperoxide[9] should be interesting.



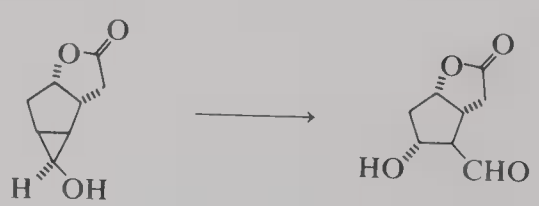
Cerium salts catalyze autoxidation of organic molecules, although only sporadic examples are found in the literature. Thus, cyclic ethers, such as tetrahydrofuran, are oxidized to lactones in moderate yields.[234] However, 2,6-dimethyl-tetrahydropyran-3-carboxaldehyde gives the corresponding acid without oxidation at the 2 or 6 position.[235]

Telomerization of butadiene to give 1,8-dibromooctadiene in 46% yield is observed[236] when the former is treated with ceric ions in the presence of bromide ions in an aqueous acid solution.

$$2H_2C=CH-CH=CH_2 \xrightarrow{Ce^{IV}/Br^-} BrCH_2-CH=CH-CH_2-CH=CH-CH_2Br$$

In the presence of olefins, the azido radical, generated by electron removal from the azide ion with CAN, is trapped, resulting in the formation of α-azido-β-nitroalkanes.[237]

A catalytic effect of cerium(IV) on oxidation with other reagents is often observed. In a prostaglandin synthesis,[238] a key intermediate is obtained by Ce(IV)-catalyzed chromic acid oxidation of a cyclopropanol. Other reagents, including Hg(II), Tl(III), Pb(IV) acetates, are either totally ineffective or inferior.



The Ce–Cr system effects complete oxidation of many organic molecules such as sugars to carbon dioxide and water under mild conditions,[239,240] while Ce(IV) alone brings about oxidation to formic acid.

A mechanistically obscure reaction of CAN with bromoalkanes in the presence of uranium(VI) fluoride[241] delivers mostly alkyl nitrates.

NOTE ADDED IN PROOF

Unsaturated carbonyl compounds are obtained via oxidative fragmentation of γ-hydroxy silanes.[252]

In constructing a CD-ring synthon for vitamin D_3, 9-bromocamphor was elaborated to

an isoborneol homolog. CAN cleavage of the latter compound afforded a cyclopentene containing three contiguous chiral centers which correspond to the configurations of C-13, 17, and 20 of the steroids.[253]

p-Hydroxyphenyl and *p*-dimethylaminophenyl esters are susceptible to cleavage by CAN in the presence of water.[254]

Polycyclic aromatic compounds undergo oxidative nitration on exposure to silica gel-supported CAN.[255]

4. EXPERIMENTAL CONDITIONS AND PROCEDURES

In general, cerium(IV) oxidation is conducted in acetic acid, acetone, acetonitrile, and their aqueous mixtures. These are the solvents which are quite resistant to destruction by the strong oxidant, while having compromising solvent power for both the oxidant and most organic compounds. Depending on the reactivities of the substrates, the oxidation may be accomplished at ambient temperature to 100°C, most conveniently in the range of 60–75°C. Oftentimes, the reaction can be monitored by noting color change of the reaction mixtures.

The most commonly used reagents are cerium(IV) sulfate, cerium(IV) perchlorate, and especially the double salt ceric ammonium nitrate (CAN, or diammonium hexanitratocerate). All these compounds are relatively nontoxic and are readily available in the U. S. and Western Europe (see Chem Sources).

Preparation of Dinitratocerium(IV) Chromate Dihydrate.[8] To a hot solution of potassium dichromate (3.2 g, 10 mmol) in distilled water (10 ml) is added a solution of CAN (5.48 g, 10 mmol) in water (20 ml) with stirring. On cooling, the orange–red precipitate is filtered and washed several times with distilled water and acetone and dried in the air to give the title compound (3.2 g, 79%).

Preparation of Trihydroxycerium Hydroperoxide.[9] To a stirred solution of cerium (III) chloride heptahydrate (7.4 g) in water (100 ml) is added concentrated ammonium hydroxide (15 ml) and then 30% hydrogen peroxide (20 ml). Stirring continues for 15 min and the orange-red precipitate is collected and washed thoroughly with water and then with acetone. Drying in the air affords the hydroperoxide (4.45 g, 95%).

Oxidation of Organic Compounds with Dinitratocerium(IV) Chromate Dinitrate or Trihydroxycerium Hydroperoxide.[8,9] A mixture of the cerium(IV) reagent (20–40 mmol) and the organic compound (10 mmol) in benzene (20–30 ml) is refluxed for 5–300 min. The cooled reaction mixture is filtered, and the filtrate evaporated. The product is isolated by silica gel chromatography.

General Procedure for the Oxidation of Benzyl and Related Alcohols by Ceric Ammonium Nitrate.[68] To a solution of the alcohol (19 mmol) in glacial acetic acid (40 ml) is added 1 *N* aqueous ceric ammonium nitrate (40 ml), and the whole is heated at a temperature up to 90°C to complete the reaction (fading of the deep red color to yellow or colorless). The mixture is cooled, diluted with water, and extracted thrice with ether or dichloromethane. The combined organic extracts are washed with water, base. and then dried. The solvent is removed and the product analyzed by NMR spectroscopy.

Ceric Ammonium Nitrate Oxidation of Adamantan-2-ol.[34] Adamantan-2-ol (475 mg, 3.2 mmol) in acetonitrile (10 ml) is treated with ceric ammonium nitrate (14.25 g, 26 mmol) in water (30 ml) for 3 h at 60°C. After cooling to room temperature. the reaction mixture is extracted with chloroform. Evaporation of the dried exact yields a yellowish waxy solid which is sublimed to give 2-oxahomoadamantan-3-one; yield: 250 mg (50%); m.p. 285–287°C.

Procedure for Regeneration of Carbonyl Compounds from Oximes and Semicarbazones.[92] The oxime or semicarbazone (5 mmol) is dissolved in ethanol (20 ml), cooled to the selected temperature (−20–0°C), and mixed with the oxidant prepared by adding aqueous ceric ammonium nitrate (0.3 *M* in 0.5 or 1.0 *N* nitric acid, 67 ml, 20 mmol) at 0°C to ethanol at −40°C, which is then adjusted to the desired reaction temperature. After being stirred for

5 min, the mixture is diluted with an equal volume of ice water and extracted with chloroform (3 × 50 ml). The extracts are processed in the usual manner to yield the carbonyl product.

CAN/$NaBrO_3$ Oxidation of Sulfides.[133] A mixture of sulfide (2 mmol), sodium bromate (378 mg, 2.5 mmol), and CAN (28 mg, 0.05 mmol) in aqueous acetonitrile (10 ml, 7:3 v/v) is stirred vigorously at room temperature. Extractive work-up with chloroform and recrystallization or distillation of the product gives the sulfoxide.

General Procedure for Dethioacetalization with Ceric Ammonium Nitrate.[134] Treatment of the dithioacetal (1.0 mmol) in 75% aqueous acetonitrile (12 ml) with ceric ammonium nitrate (4.0 mmol) at room temperature for 3 min, followed by quenching with water and extraction with ether, gives the parent carbonyl compound. The pure product is obtained by distillation, by filtration through a neutral alumina column and recrystallization, or as its 2,4-dinitrophenylhydrazone.

Hydrolysis of Carboxylic Acid Hydrazides by Ceric Ammonium Nitrate: General Procedure.[104] Addition of ceric ammonium nitrate (1.65 g, 3 mmol) to a stirred solution of the acid hydrazide (1 mmol) in 75% aqueous acetonitrile (8 ml) results in a brisk, exothermic reaction. Work-up of the colorless mixture by dilution with water, extraction with ether, drying, and concentration of the extract yields a crude acid which is purified by alkaline dissolution, reacidification, and recrystallization or sublimation.

Cerium(IV) Ammonium Sulfate Oxidation of Polycyclic Aromatic Hydrocarbons: General Procedure.[162] To a solution (or suspension) of the organic substrate (1 mmol) in acetonitrile and 4 *N* sulfuric acid (40 ml/10 ml), cerium(IV) ammonium sulfate (6 mmol) in 4 *N* sulfuric acid (50 ml) is added and the mixture is stirred. The cerium (IV) salt precipitates as the reaction proceeds. The solution is decanted into a separatory funnel, diluted with water, and extracted with ether. The solvent is removed under reduced pressure.

4-Hydroperoxy-4-methyl-2,6-di-t-butylcyclohexa-2,5-dienone.[233] 4-Methyl-2,6-di-*t*-butylphenol (220 mg) in ethanol (20 ml) is treated with technical cerium(IV) oxide (400 mg) and hydrogen peroxide (30%; 10 ml). The mixture is heated under reflux for 2 h, cooled, and filtered. The filtrate is diluted with water (200 ml) and extracted with ether (3 × 30 ml). Evaporation of the dried extracts ($MgSO_4$) gives the hydroperoxy-dienone (180 mg, 70%), m.p. 115–116°C.

5. TABULAR SURVEY OF OXIDATION REACTIONS

In the following tables, the reagent is identified by:

1. CAN/H_2O
2. CAN/ROH
3. CAN/HOAc
4. CAN/aq. CH_3CN
5. CAN-azinecarboxylic acids
6. CAN-$NaBrO_3$/aq. CH_3CN

6a. $Ce(SO_4)_2$-$NaBrO_3$/aq. CH_3CN

7. $Ce(ClO_4)_4/H_2O$ or $Ce(IV)/HClO_4$
8. CAS
9. $Ce(IV)/H_3O^+$
10. $(Et_3NH)_2\,Ce(NO_3)_6/CH_2Cl_2$
11. $[Ce(NO_3)_3]_2\,CrO_4/CH_2Cl_2$
12. $[Ce(NO_3)_3]_2\,CrO_4/C_6H_6$
13. $Ce(NO_3)_2\,CrO_4 2H_2O/C_6H_6$
14. $Ce(OH)_3\,OOH/C_6H_6$
15. $[Ce(NO_3)_3]\,H_2IO_6/C_6H_6$
16. Ce(IV)-Ag(I)-$(NH_4)_2S_2O_8$

TABLE II. Ce(IV) Oxidation of Alcohols

Alcohol	Reagent	Product (Yield, %)	Reference
C_2H_5OH	5	CH_3CHO (90)	66
c-$C_3H_5CH_2OH$	1	c-C_3H_5CHO (64)	68
$PhCH_2OH$	3	PhCHO (94)	70
	6	PhCHO (90)	65
	10	PhCHO (95)	6
	11	PhCHO (25–30)	7
	12	PhCHO (85–95)	7
	13	PhCHO (100)	8
	14	PhCHO (95)	9
	15	PhCHO (90–95)	10
4-$BrC_6H_4CH_2OH$	3	4-BrC_6H_4CHO (93)	70
4-$O_2NC_6H_4CH_2OH$	3	4-$O_2NC_6H_4CHO$ (92 ± 9)	70
	13	4-$O_2NC_6H_4CHO$ (20)	8
	14	4-$O_2NC_6H_4CHO$ (60)	9
4-$MeC_6H_4CH_2OH$	6	4-MeC_6H_4CHO (92)	65
4-$MeOC_6H_4CH_2OH$	3	4-$MeOC_6H_4CHO$ (94)	70
	10	4-$MeOC_6H_4CHO$ (97)	6
	14	4-$MeOC_6H_4CHO$ (95)	9
	15	4-$MeOC_6H_4CHO$ (90–95)	10
3,4-$OCH_2OC_6H_3CH_2OH$	12	3,4-$OCH_2OC_6H_3CHO$ (85)	7
	13	3,4-$OCH_2OC_6H_3CHO$ (75)	8
	14	3,4-$OCH_2OC_6H_3CHO$ (90)	9
9-Phenanthrene-CH_2OH	14	ArCHO (50–65)	9
1,2-$C_6H_4(CH_2OH)_2$	12	1,2-$C_6H_4(CHO)$ CH_2OH (40) 1,2-$C_6H_4(CHO)_2$ (40)	7
	13	1,2-$C_6H_4(CHO)_2$ (85)	8
	15	1,2-$C_6H_4(CHO)$ CH_2OH (40) 1,2-$C_6H_4(CHO)_2$ (55)	10
Furan, 2,5-Ph_2-3,4-$(CH_2OH)_2$	14 (1.5 equiv.)	Ar(CHO) CH_2OH (85)	6
	14 (4 equiv.)	$Ar(CHO)_2$ (95)	6
Thiophene, 2,5-Ph_2-3,4-$(CH_2OH)_2$	14 (1.5 equiv.)	Ar(CHO) CH_2OH (85)	6
	15 (2 equiv.)	Ar(CHO) CH_2OH (85), $Ar(CHO)_2$ (7), lactone (3)	10
	15 (4 equiv.)	Ar(CHO) CH_2OH (40), $Ar(CHO)_2$ (50), lactone (6)	10
$PhCH=CHCH_2OH$	10	$PhCH=CHCHO$ (10)	6
	12	$PhCH=CHCHO$ (10), PhCHO (5)	7
	13	$PhCH=CHCHO$ (20), PhCHO (10)	8
	14	$PhCH=CHCHO$ (15)	9
	15	$PhCH=CHCHO$ (70), PhCHO (30)	10
Ph_2CHOH	6	Ph_2CO (83)	65
	10	Ph_2CO (97)	6
	11	Ph_2CO (30–35)	7
	12	Ph_2CO (95)	7
	13	Ph_2CO (100)	8
	14	Ph_2CO (100)	9
	15	Ph_2CO (90–95)	10
4-Dodecanol	6	4-dodecanone (94)	80
11-Dodecen-2-ol	6	11-dodecen-2-one (3)	80
Cyclopentanol	9	cyclopentanone (57)	73
Cyclohexanol	9	cyclohexanone (72)	73
4-t-Butylcyclohexanol	6	4-t-butylcyclohexanone (86)	80
Cyclododecanol	6	cyclododecanone (98)	80

Table continued

TABLE II. *Continued*

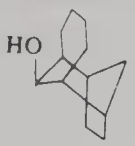
Alcohol	Reagent	Product (Yield, %)	Reference
Norborneol	6	norcamphor (82)	80
Borneol/isoborneol	6	camphor (77)	80
(-)Menthol	6	(-)-menthone (82)	80
Adamantanol	4	adamantanolactone (50)	34
	4	ketone (90)	79
3β-Cholestanol	6	3-cholestanone (97)	80
5α-Bromo-3β,17β-diacetoxy-androstan-6β-ol	4	6-ketosteroid (85)	74
1,2-Decanediol	6	1-hydroxy-2-decanone (50)	80
1,3-Undecanediol	6	1-hydroxy-3-undecanone (88)	80
1,10-Undecanediol	6	11-hydroxy-2-undecanone (86)	80
cis-3-(2-Hydroxyethyl)-cyclopentanol	6	3-(2-hydroxyethyl)-cyclopentanone (89)	80
4-Hydroxymethylcyclohexanols	6	4-hydroxymethylcyclohexanone (83)	80
4-(1-Hydroxyethyl)benzyl alcohol	6	4-hydroxymethylacetophenone (59) 4-(1-hydroxyethyl)benzaldehyde (19) 4-acetylbenzaldehyde (13)	80
endo-2,3-Bis(hydroxymethyl)-norbornane	6	lactone (87)	80

TABLE III. Cleavage of Aliphatic/Alicyclic Alcohols with Ce(IV)

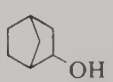
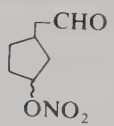
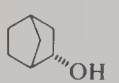
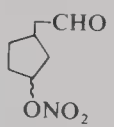
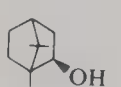
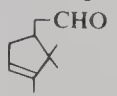
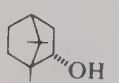
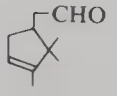
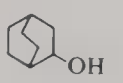
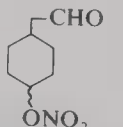
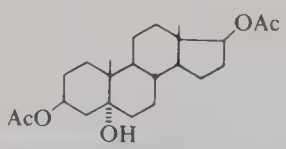
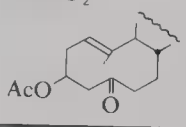
Alcohol	Reagent	Product (Yield, %)	Reference
	4	 (36),  (18),  (20)	23
	4	 (43),  (19),  (20)	23
	4	 (55)	23
	4	 (43)	23
	4	 (*cis* 29, *trans* 20),  (46)	23
	4	 (80)	74

Table continued

TABLE III. *Continued*

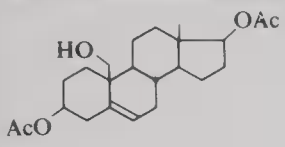
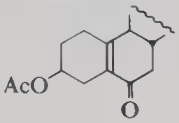
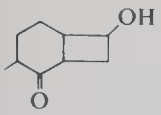
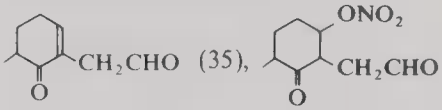
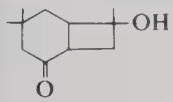
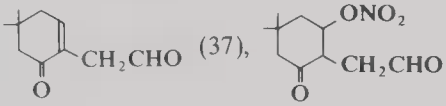
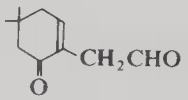
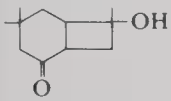
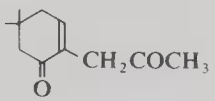
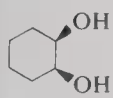
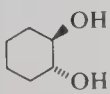
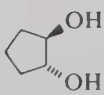
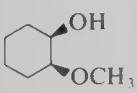
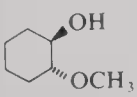
Alcohol	Reagent	Product (Yield, %)	Reference
	4	 (40–60)	74
Cyclobutanol	1	$OHC(CH_2)_6CHO$ (70) $CH_2{=}CHCH_2CHO$ (18) $HO(CH_2)_3CHO$ (5)	24
Cyclobutanol	7	$OHC(CH_2)_2CHO$ (3) $CH_2{=}CHCH_2CHO$ (59) $O_2NO(CH_2)_3CHO$ (11) $HO(CH_2)_3CHO$ (4)	24
Cyclobutanol	4	$O_2N(CH_2)_3CHO$ (20) $O_2NO(CH_2)_3CHO$ (61) $HO(CH_2)_3CHO$ (5)	24
Cyclobutanol	$4/O_2$	$OHC(CH_2)_2CHO$ (84)	24
1-Methylcyclobutanol	1	$CH_3CO(CH_2)_6COCH_3$ (48) $CH_3(CH_2)_2COCH_3$ (25)	24
	3		75
	3		75
	4	 (73)	75
	4	 (65–75)	75
	3	(86)	75
	7	$OCH(CH_2)_4CHO$ (98.5)	73
	7	$OCH(CH_2)_4CHO$ (91.3)	73
	9	$OCH(CH_2)_3CHO$ (103)	73
	9	$OCH(CH_2)_4CHO$ (24.9)	73
	7	$OCH(CH_2)_4CHO$ (54.8), HCHO (55.1)	73

Table continued

TABLE III. *Continued*

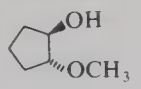
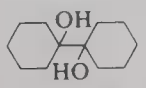
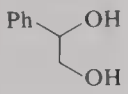
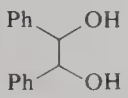
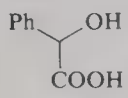
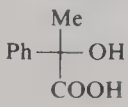
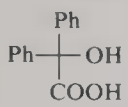
Alcohol	Reagent	Product (Yield, %)	Reference
	9	$OCH(CH_2)_3CHO$ (105)	73
	3	$(CH_2)_5C=O$ (94)	28
	13	PhCHO (85–90)	8
	15	PhCHO (95–100)	10
	15	PhCHO (90–95)	10
	13	PhCHO (100)	8
	14	PhCHO (95)	9
	15	PhCOMe (100)	10
	14	Ph_2CO (95)	9
	15	Ph_2CO (100)	10

TABLE IV. Ce(IV) Oxidation of Aryl Alkyl Carbinols

Alcohol	Reagent	Product (Yield, %)	Reference
MeCHOHPh	6	MeCOPh (86)	65
	4	MeCOPh (55.2), PhCHO (2.83)	17
$MeCHOHC_6H_4Me(p)$	13	$MeCOC_6H_4Me$ (95)	8
EtCHOHPh	12	EtCOPh (85)	7
	13	EtCOPh (90)	8
	14	EtCOPh (80)	9
	4	EtCOPh (18), PhCHO (60), $EtONO_2$ (36)	17
$PhCH_2CHOHPh$	12	$PhCH_2COPh$ (85–90)	7
	13	$PhCH_2COPh$ (95)	8
	14	$PhCH_2COPh$ (80)	9
i-PrCHOHPh	4	*i*-PrCOPh (0.51), PhCHO (91.9)	17
i-BuCHOHPh	4	*i*-BuCOPh (15), PhCHO (55.6)	20
t-BuCHOHPh	4	*t*-BuCOPh (0.49), PhCHO (94.9)	17
c-$PrCH_2CHOHPh$	4	*c*-$PrCH_2COPh$ (3.15), PhCHO (75.5)	20
c-BuCHOHPh	4	*c*-BuCOPh (4.79), PhCHO (6.14)	20
c-PnCHOHPh	4	*c*-PnCOPh (1.16), PhCHO (74.4)	20
c-HxCHOHPh	4	*c*-HxCOPh (0.75), PhCHO (89.6)	20
$CH_2=CH(CH_2)_4CHOHPh$	4	$CH_2=CH(CH_2)_4COPh$ (13.8), PhCHO (44)	20
$F(CH_2)_2CHOHPh$	4	$F(CH_2)_2COPh$ (45), PhCHO (10)	20
$Cl(CH_2)_2CHOHPh$	4	$Cl(CH_2)_2COPh$ (46), PhCHO (22)	20
$Br(CH_2)_2CHOHPh$	4	$Br(CH_2)_2COPh$ (62), PhCHO (6.4)	20
$Br(CH_2)_4CHOHPh$	4	$Br(CH_2)_4COPh$ (44), PhCHO (25)	20
$MeO(CH_2)_2CHOHPh$	4	$MeO(CH_2)_2COPh$ (39.8), PhCHO (19.4)	20
$MeO(CH_2)_3CHOHPh$	4	$MeO(CH_2)_2COPh$ (24.7), PhCHO (26.9)	20
$MeO(CH_2)_4CHOHPh$	4	$MeO(CH_2)_4COPh$ (21.8), PhCHO (47)	20
$MeO(CH_2)_2CEt(OH)Ph$	4	$MeO(CH_2)_2COPh$ (60.3), EtCOPh (7.8)	20

TABLE V. Oxidative Cyclization of Alcohols

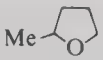
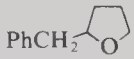
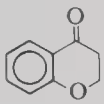
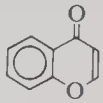
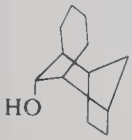
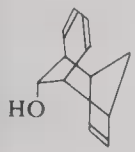
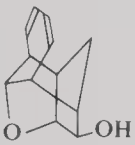
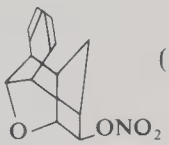
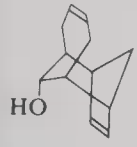
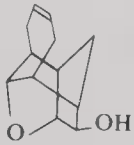
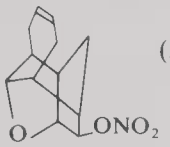
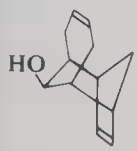
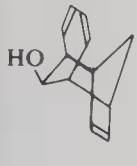
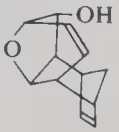
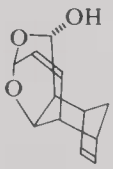
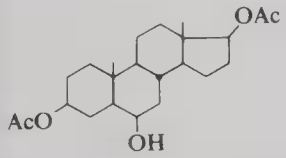
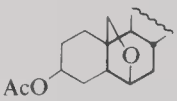
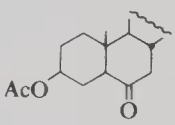
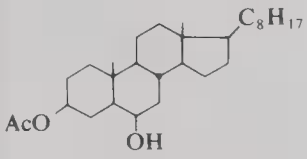
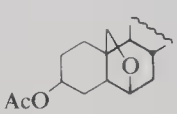
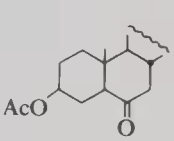
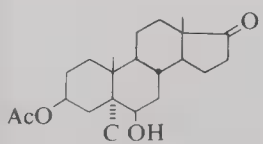
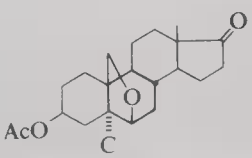
Substrate	Product (Yield, %)		Reference
$Me(CH_2)_4OH$	 (20)		44
$Ph(CH_2)_4OH$	 (24),	$Ph(CH_2)_4ONO_2$ (12)	45
$Ph(CH_2)_5OH$	 (40)		45
$Ph(CH_2)_3OH$	 (30),	 (17)	45
	 (85)		79
	 (28),	 (38)	79
	 (36),	 (33)	79
	 (39)		79
	 (30),	 (26)	79
	 (63),	 (22)	74
	 (60),	 (30)	74
	 (25)		74

TABLE VI. Oxidation of Benzoins

Benzoin	Reagent	Product (Yield, %)	Reference
Benzoin	6	PhCOCOPh (66)	80
	10	PhCOCOPh (85)	6
	12	PhCOCOPh (85–90)	7
	13	PhCOCOPh (45)	8
	14	PhCOCOPh (90)	9
	15	PhCOCOPh (100)	10
	4	PhCHO (80), PhCOOH (86)	31
p-Toluoin	4	MeC_6H_4CHO (87), MeC_6H_4COOH (86)	31
p-Anisoin	4	$MeOC_6H_4CHO$ (87), $MeOC_6H_4COOH$ (88)	31
4,4′-Diphenylbenzoin	4	PhC_6H_4CHO (78), PhC_6H_4COOH (81)	31
α-Naphthoin	4	α-$C_{10}H_7CHO$ (82), α-$C_{10}H_7COOH$ (84)	31
α-Furoin	10	FuCOCOFu (90)	6
	12	FuCOCOFu (75–80)	7
	13	FuCOCOFu (30)	8
	14	FuCOCOFu (95)	9
	15	FuCOCOFu (100)	10
	4	FuCOOH (83), FuCOCOFu (5)	31

TABLE VII. Oxidative Cleavage of Ethers[a,b]

Substrate	Product	(Yield, %)
$C_6H_{11}OCH_3$	Cyclohexanone	(81)
$C_6H_{11}OC_2H_5$	Cyclohexanone	(92)
$C_6H_{11}OSi(CH_3)_3$	Cyclohexanone	(75)
$C_6H_{11}OSi(CH_3)_2C_4H_9{}^t$	Cyclohexanone	(65)[c]
n-$C_3H_7CH(n$-$C_4H_9)OCH_3$	n-$C_3H_7COC_4H_9{}^n$	(88)
n-$C_3H_7CH(n$-$C_4H_9)OC_2H_5$	n-$C_3H_7COC_4H_9{}^n$	(95)
n-$C_8H_{17}CHOCH_3$	n-$C_8H_{17}CHO$	(60)
n-$C_7H_{15}CH(CH_3)OSi(CH_3)_3$	n-$C_7H_{15}COCH_3$	(77)
$C_6H_5CHOCH_2C_6H_5$	C_6H_5CHO	(95)
$C_6H_5CH(i$-$C_3H_7)OSi(CH_3)_3$	$C_6H_5COC_3H_7{}^i$	(84)

[a] Reference 81.
[b] CAN/$NaBrO_3$, aq. CH_3CN, 80°C, 12 h.
[c] 2,4-DNP.

TABLE VIII. Ce(IV) Oxidation of Carbonyl Compounds

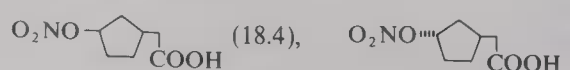
Substrate	Product (Yield, %)	Reference
Ph_3CCHO	Ph_3COH (75)	35
Cyclopentanone	$O_2NO(CH_2)_4COOH$ (6.96)	34
	$CH_3CH(ONO_2)(CH_2)_2COOH$ (4.64)	
	$O_2NO(CH_2)_3COOH$ (9.86)	
	$CH_3CH(ONO_2)CH_2COOH$ (7.54)	
Cyclohexanone	$O_2NO(CH_2)_5COOH$	
	$CH_3CH(ONO_2)(CH_2)_3COOH$ (33 combined)	34
Norcamphor	 (18.4), (27.6)	34

TABLE VIII. *Continued*

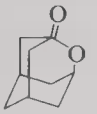
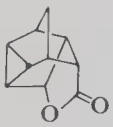
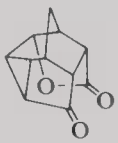
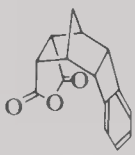
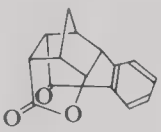
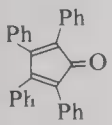
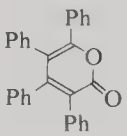
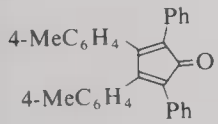
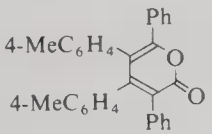
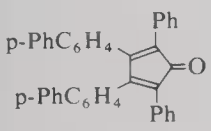
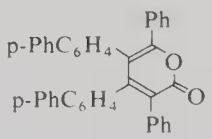
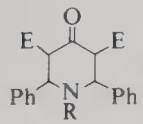
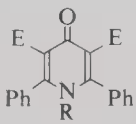
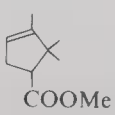
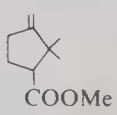
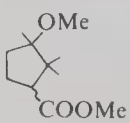
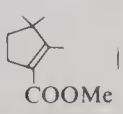
Substrate	Product (Yield, %)	Reference
Adamantanone	 (73.4)	34
	 (80)	84
	 (78)	85, 86
	 (82)	84
	 (30),  (40)	87
	 (77.5)	88
	 (40)	88
	 (61)	88
 (E = COOEt)	 R = H (35) R = Me (81) R = CH_2Ph (75) R = $CH_2CH=CH_2$ (60)	89
	 (62),  (21)  (12),  (4)	36

TABLE IX. Oxidative Hydrolysis of Oximes and Semicarbazones with Ce(IV) Reagents

Substrate	Reagent	Product (Yield, %)	Reference
n-Heptaldoxime	2	*n*-Heptanal (72)	92
Piperonaldoxime	12	Piperonal (30)	7
Salicylaldoxime	12	Salicylaldehyde (25)	7
Cinnamaldoxime	—	$(PhCH=CHCH=N-)_2$ ↓ O	95
Cyclopentanone oxime	2	Cyclopentanone (83)	92
Cyclohexanone oxime	2	Cyclohexanone (88)	92
Cycloheptanone oxime	2	Cycloheptanone (82)	92
Camphor oxime	2	Camphor (27)	92
Carvoxime	2	Carvone (71)	92
Acetophenone oxime	2	Acetophenone (90)	92
Benzophenone oxime	2	Benzophenone (79)	92
11-Oximino-9β-estrone methyl ether	2	11-Ketone (37)	93
2-Methyl-2-(2-oximinohept-6-enyl)-cyclopentanone	2	Diketone (45)	94
Cyclohexanone semicarbazone	2	Cyclohexanone (78)	92
Cycloheptanone semicarbazone	2	Cycloheptanone (81)	92

TABLE X. CAN Oxidation of Nitroalkanes in the Presence of Triethylamine

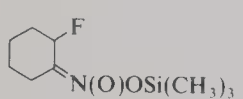
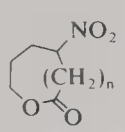
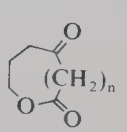
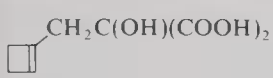
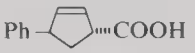
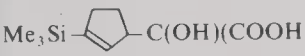
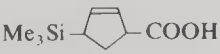
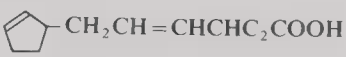
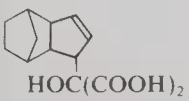
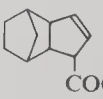
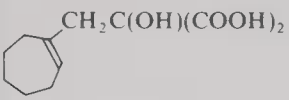
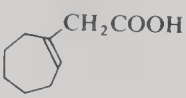
Substrate	Product (Yield, %)	Reference
nitrocyclohexane	cyclohexanone (80)	96
c-$C_6H_{11}CH_2NO_2$	c-$C_6H_{11}CHO$ (75)	96
n-$C_6H_{13}CH_2NO_2$	n-$C_6H_{13}CHO$ (67)	96
2-fluoronitrocyclohexane	2-fluorocyclohexanone (80)	96
4-$MeC_6H_4CH_2NO_2$	4-MeC_6H_4CHO (85)	96
$PhCH=CHCH_2NO_2$	$PhCH=CHCHO$ (78)	96
$(CH_2)_5C=N(O)OSi(CH_3)_3$	cyclohexanone (92)	96
	2-fluorocyclohexanone (90)	96
	 ($n=4$, 78; $n=5$, 76; $n=6$, 81; $n=10$, 75)	97

TABLE XI. CAN Degradation of α-Hydroxymalonic Acids[a]

Substrate	Product	Yield (%)
$PhCH=CHCH_2C(OH)(COOH)_2$	$PhCH=CHCH_2COOH$	(83)
$PhC(=CH_2)CH_2C(OH)(COOH)_2$	$PhC(=CH_2)CH_2COOH$	(64)
$CH_2=CH(CH_2)_3CH=CHCH_2C(OH)(COOH)_2$	$CH_2=CH(CH_2)_3CH=CHCH_2COOH$	(87)
$HOOC(CH_2)_7CH=CH-CH_2C(OH)(COOH)_2$	$HOOC(CH_2)_7CH=CHCH_2COOH$	(82)
$HO(CH_2)_8CH=CHCH_2C(OH)(COOH)_2$	$HO(CH_2)_8CH=CHCH_2COOH$	(60)
		(98)
		(81)
		(84)
		(68)
		(33)
		(45)

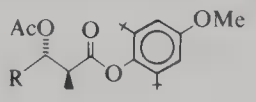
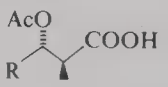
[a] Reference 103.

TABLE XII. CAN Oxidation of Carboxylic Acid Hydrazides[a,b]

Substrate	Product	(Yield, %)
$PhCONHNH_2$	$PhCOOH$	(83)
p-$CH_3C_6H_4CONHNH_2$	p-$CH_3C_6H_4COOH$	(65)
p-$CH_3OC_6H_4CONHNH_2$	p-$CH_3OC_6H_4COOH$	(76)
p-$ClC_6H_4CONHNH_2$	p-ClC_6H_4COOH	(80)
m-$ClC_6H_4CONHNH_2$	m-ClC_6H_4COOH	(78)
β-$C_{10}H_7CONHNH_2$	β-$C_{10}H_7COOH$	(85)
n-$C_6H_{13}CONHNH_2$	n-$C_6H_{13}COOH$	(90)
$PhCH=CHCONHNH_2$	$PhCH=CHCOOH$	(70)
$Ph_2C(OH)CONHNH_2$	Ph_2CO	(67)

[a] Reference 104.
[b] 3 equiv. CAN, 75% aq. CH_3CN, r.t.

TABLE XIII. Oxidative Hydrolysis of 2,6-Di-*t*-butyl-4-methoxyphenyl Esters[a]

Ester	Acid (Yield, %)
	 R = Et (46) R = *i*-Pr (81) R = *t*-Bu (79)

[a] Reference 108.

TABLE XIV. CAN Reaction with Dialkylaminoarenes[a]

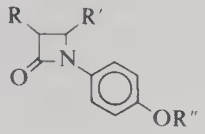
Substrate	Medium	Product (Yield, %)
Me_2NPh	CH_3CN	$2,4\text{-}(O_2N)_2C_6H_3NHMe$ (11)
	CH_3COOH	$2,4\text{-}(O_2N)_2C_6H_3NHMe$ (47)
	CH_3OH	$Me_2NC_6H_4C_6H_4NMe_2$ (40)
$4\text{-}Me_2NC_6H_4OMe$	CH_3CN	*p*-methoxy-*N*,2,6-trinitro-*N*-methylaniline (52)
	CH_3COOH	*p*-methoxy-*N*,2,6-trinitro-*N*-methylaniline (77)
$4\text{-}Me_2NC_6H_4Cl$	CH_3CN	4-chloro*N*,2,6-trinitro-*N*-methylaniline (22)
		4-chloro-2,6-dinitro-*N*-methyl-aniline (6)
	CH_3COOH	4-chloro-*N*,2,6-trinitro-*N*-methylaniline (25)
		4-chloro-2,6-dinitro-*N*-methylaniline (17)
$4\text{-}Me_2NC_6H_4NO_2$	CH_3OH	$4\text{-}MeNHC_6H_4NO_2$ (89)
	CH_3CN	$4\text{-}MeNHC_6H_4NO_2$ (60)
	CH_3COOH	$4\text{-}MeNHC_6H_4NO_2$ (23)

[a] Reference 113.

TABLE XV. Oxidative Hydrolysis and Transamidation of *N*-Acyl-5,6-Dihydrophenanthridines

Amide	Nucleophile	Product (%)	Reference
11-Bromoundecanoyl	H_2O	RCOOH (95)	106
	$Ph(CH_2)_2NH_2$	$RCONH(CH_2)_2Ph$ (85)	107
Phenylacetyl	H_2O	RCOOH (96)	106
2-Phenylbutyryl	H_2O	RCOOH (94)	106
	$Ph(CH_2)_2NH_2$	$RCONH(CH_2)_2Ph$ (79)	107
	$PhCH(Me)NH_2$	RCONHCH(Me)Ph (70)	107
4-Phenylbutyryl	H_2O	RCOOH (97)	106
	$Ph(CH_2)_2NH_2$	$RCONH(CH_2)_2Ph$ (82)	107
	$PhCH(Me)NH_2$	RCONHCH(Me)Ph (85)	107
5-Benzoylvaleryl	H_2O	RCOOH (79)	106
Benzoyl	L-Leu-OEt	RCO-Leu-OEt (94)	107
Terephthalaldehydyl	$Ph(CH_2)_2NH_2$	$RCONH(CH_2)_2Ph$ (76)	107
3-Oxo-5β-cholan-24-oyl	H_2O	RCOOH (98)	106
	$Ph(CH_2)_2NH_2$	$RCONH(CH_2)_2Ph$ (84)	107

TABLE XVI. Selective Deblocking of *N*-Aryl-β-lactams



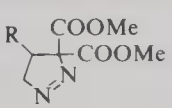
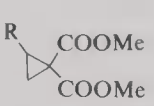
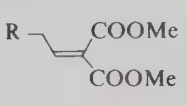
R	R′	R″	Dearyl product (%)	Reference
NHCOO-*t*-Bu	CH=CHPh	Me	(48)	125
NHCOO-*t*-Bu	COOMe	Me	(55)	125
NHCOO-CH_2Ph	COOMe	Me	(83)	125
NHCOO-CH_2Ph	CH_2N_3	Me	(67)	125
N_3	$CH=CHCH_2CH(OMe)_2$	CH_2OMe	(>74)	124

TABLE XVII. Decomposition of Aryldiazomethanes with CAN[a]

Substrate	Product (Yield, %)
$PhCHN_2$	*Z*-PhCH=CHPh (84.5), *E*-PhCH=CHPh (15.4)
4-$CH_3C_6H_4CHN_2$	*Z*-(4-$CH_3C_6H_4CH=CHC_6H_4CH_3$) (76), *E*-(4-$CH_3C_6H_4CH=CHC_6H_4$-4-$CH_3$) (23.5)
4-$ClC_6H_4CHN_2$	*Z*-(4-$ClC_6H_4CH=CHC_6H_4$-4-Cl) (70), *E*-(4-$ClC_6H_4CH=CHC_6H_4$-4-Cl) (30)

[a] Reference 128.

TABLE XVIII. Quantitative Decomposition of Pyrazolinediesters by Catalytic Ce(IV)[a]

		
R = COOMe	100	0
R = COMe	100	0
R = Et	100	0
R = MeCHBr	100	0
R = 4-$MeOC_6H_4CH_2$	100	0
R = 4-$O_2NC_6H_4$	100	0
R = Ph	56	44
R = 4-$MeOC_6H_4$	10	90
R = Ch=CHPh	50	50

[a] Reference 129.

TABLE XIX. Oxidation of Sulfides to Sulfoxides

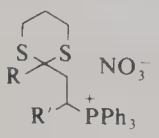
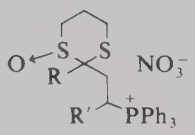
Sulfide	Reagent	Product (Yield, %)	Reference
n-Bu_2S	6	*n*-Bu_2SO (83)	133
PhSMe	4	PhS(O)Me (78)	131
	6	PhS(O)Me (83)	133
Ph_2S	4	Ph_2SO (82)	131
	6	Ph_2SO (92)	133
$(4\text{-}ClC_6H_4)_2S$	4	$(4\text{-}ClC_6H_4)_2SO$ (92)	131
$(4\text{-}BrC_6H_4)_2S$	4	$(4\text{-}BrC_6H_4)_2SO$ (94)	131
$(2\text{-}O_2NC_6H_4)_2S$	4	$(2\text{-}O_2NC_6H_4)_2SO$ (95)	131
Dibenzothiophene	4	Dibenzothiophene oxide (100)	131
	6	Dibenzothiophene oxide (95)	133
Thiaxanthone	4	Thiaxanthone oxide (97)	131
	4	 R = Me, R′ = H (75) R = R′ = H (63) R, R′ = $(CH_2)_3$ (68)	137

TABLE XX. Regeneration of Carbonyl Compounds from Thioacetals

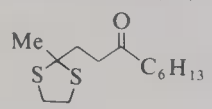
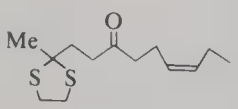
Thioacetal	Product (Yield, %)	Reference
$PhCHS(CH_2)_2S$	PhCHO (73.4)	134
$PhC(Me)(CH_2)_2S$	PhCOMe (80)	134
$Ph_2CS(CH_2)_2S$	Ph_2CO (85.7)	134
$(CH_2)_5CS(CH_2)_2S$	Cyclohexanone (87)	134
$(CH_2)_6CS(CH_2)_3S$	Cycloheptanone (70)	134
$PhCH_2C(Me)S(CH_2)_3S$	$PhCH_2COMe$ (85)	134
	$MeCO(CH_2)_2COC_6H_{13}$ (80)	134
	$MeCO(CH_2)_2COCH_2CH_2CH{=}CHEt$ (77.8)	134
$Ph_2P(O)CH_2CH_2C(Me)S(CH_2)_3S$	$Ph_2P(O)CH_2CH_2COMe$ (79)	137
$Ph_3\overset{+}{P}(CH_2)_3C(Me)S(CH_2)_3S\ NO_3^-$	$Ph_3\overset{+}{P}(CH_2)_3COMe\ NO_3^-$ (85)	137

TABLE XX. *Continued*

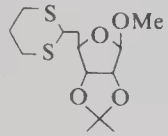
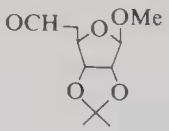
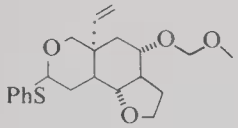
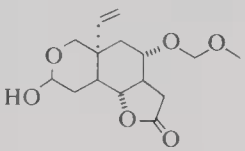
Thioacetal	Product (Yield, %)	Reference
$Ph_3\overset{+}{P}CHR'CH_2\overset{\frown}{C(R)S(CH_2)_3S}\ X^-$	$Ph_3\overset{+}{P}CHR'CH_2COR\ X^-$	137
	R = Me, R′ = H, X = BF_4 (83)	
	R = Me, R′ = H, X = ClO_4 (80)	
	R = R′ = Me, X = BF_4 (87)	
	R = R′ = Me, X = ClO_4 (75)	
	R = H, R′ = Me, X = BF_4 (68)	
	R = H, R′ = Me, X = ClO_4 (74)	
	R = H, R′ = Ph, X = BF_4 (75)	
	R = H, R′ = Ph, X = ClO_4 (82)	
	R,R′ = $(CH_2)_3$, X = BF_4 (58)	
	R,R′ = $(CH_2)_3$, X = ClO_4 (67)	
	 (78)	136
	 (>88)	139

TABLE XXI. Conversion of Thiols to Disulfides

Thiol	Reagent	Disulfide (Yield, %)	Reference
n-BuSH	12	(*n*-BuS)$_2$ (80–85)	7
s-BuSH	12	(*s*-BuS)$_2$ (80)	7
i-BuSH	12	(*i*-BuS)$_2$ (65–70)	7
t-BuSH	12	(*t*-BuS)$_2$ (75–80)	7
c-$C_6H_{11}SH$	12	(*c*-$C_6H_{11}S)_2$ (75–80)	7
	15	(*c*-$C_6H_{11}S)_2$ (100 conv.)	10
$PhCH_2SH$	12	$(PhCH_2S)_2$ (70–80)	7
	13	$(PhCH_2S)_2$ (85–90)	8
	15	$(PhCH_2S)_2$ (90–100)	10
PhSH	12	$(PhS)_2$ (80–90)	7
	14	$(PhS)_2$ (97)	9
	15	$(PhS)_2$ (90–100)	10
3-MeC_6H_4SH	12	(3-$MeC_6H_4S)_2$ (55–60)	7
	13	(3-$MeC_6H_4S)_2$ (75–80)	8
	14	(3-$MeC_6H_4S)_2$ (90)	9
	15	(3-$MeC_6H_4S)_2$ (90–100)	10
2-Mercaptobenzothiazol	12	Disulfide (80–90)	7
	13	Disulfide (75)	8
	14	Disulfide (95)	9
	15	Disulfide (90–100)	10

TABLE XXII. Ce(IV) Oxidation of Quinols and Derivatives

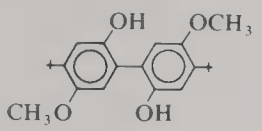
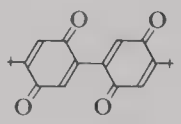
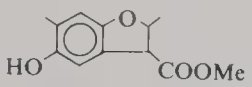
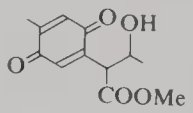
Substrate	Reagent	Quinone (Yield, %)	Reference
Catechol	12, 14	*o*-Benzoquinone (100 conv.)	7, 9
Hydroquinone	4	Benzoquinone (83.3)	140
	6	Benzoquinone (96)	133
	12	Benzoquinone (90)	7
	13, 14	Benzoquinone (100)	8, 9
2-Fluorohydroquinone	4	Fluorobenzoquinone (78)	141
t-Butylhydroquinone	4	*t*-Butylbenzoquinone (98)	140
2,5-Di-*t*-Butylhydroquinone	4	2,5-Di-*t*-butylbenzoquinone (98)	140
2,3,5,6-Tetrabromohydroquinone	6	2,3,5,6-Tetrabromobenzoquinone (92)	133
4-*t*-Butylcatechol	4	4-*t*-Butyl-*o*-benzoquinone (86.2)	140
1,4-Naphthalenediol	4	1,4-Naphthoquinone (89.7)	140
	6	1,4-Naphthoquinone (90)	133
Quinizarin	4	1,4,9,10-Anthradiquinone (90)	140
2-*t*-Butyl-4-methoxyphenol	8	2-*t*-Butylbenzoquinone (75)	142
3-*t*-Butyl-4-methoxyphenol	8	2-*t*-Butylbenzoquinone (75)	142
3-*t*-Butyl-4-dimethylaminophenol	8	2-*t*-Butylbenzoquinone (75)	146
	8	 (75)	143
	4	 (60)	145
1,4-Dimethoxybenzene	4	*p*-Benzoquinone (57)	148
2,5-Dimethyl-1,4-dimethoxybenzene	4	2,4-Dimethylbenzoquinone (95)	148
2,5-Dimethyl-4-methylbenzyl alcohol	4	2-Hydroxymethyl-5-methyl-benzoquinone (73)	148
2,5-Dimethoxy-4-(2-nitropropenyl)-toluene	4	2-Methyl-5-(2-nitropropenyl)-benzoquinone (65)	148
2,5-Dimethoxy-4-(2-acetamino-propyl)toluene	4	2-Methyl-5-(2-acetamino-propyl)benzoquinone (64)	148
2,5-Dimethoxy-4-(2-(*N*-*t*-butoxy-carbonylamino)propyl)toluene	4	2-Methyl-5-(2-(*N*-*t*-butoxy-carbonylamino)propyl) benzoquinone (61)	148
2,4,5-Trimethoxy-1-(2-benzamino-propyl)benzene	4	2-Methoxy-5-(2-benzamino-propyl)benzoquinone (35)	148
3,5-Di-*t*-butyl-1,2-dimethoxybenzene	4	3,5-Di-*t*-butyl-*o*-benzoquinone (3), 2-*t*-butyl-6-methoxybenzoquinone (26)	148
1,2-Dimethoxy-3,5-di-*t*-butylbenzene	4	3,5-Di-*t*-butyl-*o*-benzoquinone (3.8), 2-*t*-Butyl-6-methoxybenzoquinone (33)	148
1,4-Dimethoxybenzene	8	2,2′-Di(benzoquinone) (20)	147
2,5-Dimethoxytoluene	8	2,2′-Di(5,5′-dimethyl)benzoquinone (65)	147
2,5-Dimethoxy-*p*-xylene	8	2,2′-Di(3,6,3′,6′-tetramethyl)-benzoquinone (20)	147
	5	2,5-Dimethylbenzoquinone (99)	150
2,5-Dimethoxy-*m*-xylene	5	2,6-Dimethylbenzoquinone (63)	150

TABLE XXII. *Continued*

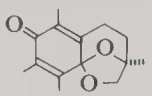
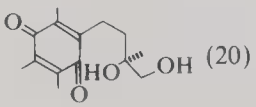
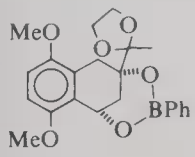
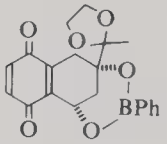
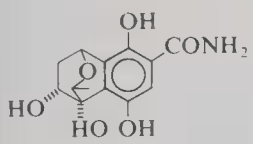
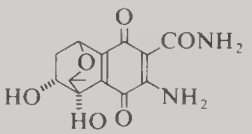
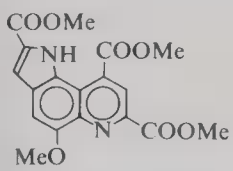
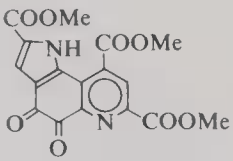
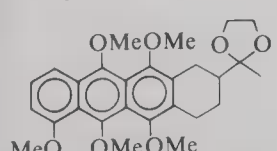
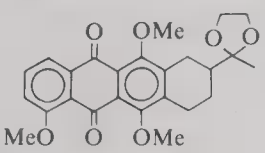
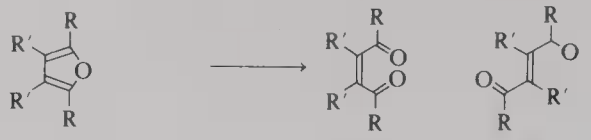
Substrate	Reagent	Quinone (Yield, %)	Reference
2,6-Diisopropyl-1,4-dimethoxybenzene	5	2,6-Diisopropylbenzoquinone (92)	150
2,3,5,6-Tetramethyl-1,4-dimethoxybenzene	5	Duroquinone (96)	150
2,3,4,5-Tetramethoxy-6-allyltoluene	5	2-Allyl-3-methyl-5,6-dimethoxybenzoquinone (70)	150
		2-Allyl-3-methyl-5,6-dimethoxybenzoquinone (89)	151
2,3,4,5-Tetramethoxy-6-geranyltoluene	5	2-Geranyl-3-methyl-5,6-dimethoxybenzoquinone (85)	150
		2-Geranyl-3-methyl-5,6-dimethoxybenzoquinone (87)	151
1,4-Dimethoxy-2,5-(3-hydroxybut-1-ynyl)benzene		2,5-Di(3-hydroxybut-1-ynyl)benzoquinone (40)	149
1,4-Dimethoxy-2,3,5-trimethyl-(3*S*-3,4-dihydroxy-3-methylbutyl)benzene		 (64),  (20)	154
	4	 (97)	153
	CAN/CH_3CN; NH_3	 (>74)	155
	4	 (60)	156
1,4-Dimethoxynaphthalene	8	1,4-Naphthoquinone (94)	147
1,4-Dimethoxy-2-methylnaphthalene	5	2-Methyl-1,4-naphthoquinone (99)	150
1,4-Dimethoxy-2-allyl-3-methylnaphthalene	5	2-Allyl-3-methyl-1,4-naphthoquinone (94)	150
1,4-Dimethoxy-2-prenyl-3-methylnaphthalene	5	2-Prenyl-3-methyl-1,4-naphthoquinone (84)	150
1,4-Dimethoxy-2-geranyl-3-methylnaphthalene	5	2-Geranyl-3-methyl-1,4-naphthaquinone (58)	150
		 (96)	152

TABLE XXIII. Enediones from Furans via CAN Oxidation[a]



(Z) (E)

R = Ph, R′ = H (Z, 77)
R = Ph, R′ = COOEt (Z, 70)
R = Ph, R′ = COPh (Z, 70)
R = Me, R′ = H (E, 18)
R = R′ = H (E, 48)

R = H, X = CH (70)
R = Ph, X = CH (90)
R = OMe, X = CH (70)
R = H, X = CCHO (50)
R = H, X = N (57)
R = Ph, X = N (85)

[a] Reference 160.

TABLE XXIV. Ce(IV) Oxidation of Arenes to Quinones

Arene	Reagent	Quinone (Yield, %)	Reference
Naphthalene	1/THF	1,4-naphthoquinone (NQ, 20)	161
	8	1,4-naphthoquinone (90–95)	162
	16	1,4-naphthoquinone (81)	65a
1-Bromonaphthalene	8	NQ (18), 2-Br-NQ (10), 5-Br-NQ (15), 4-Br-1,2-NQ (30)	162
1-Phenylnaphthalene	8	2-Ph-NQ (24), 5-Ph-NQ (28)	163
2-Methylnaphthalene	16	2-Me-NQ (60), 6-Me-NQ (20)	65a
2-Methoxymethylnaphthalene	16	2-$MeOCH_2$-NQ (26.5), 6-$MeOCH_2$-NQ (28.5)	65a
2-Acetoxymethylnaphthalene	16	2-$AcOCH_2$-NQ (28), 6-$AcOCH_2$-NQ (31)	65a
2-Chloromethylnaphthalene	16	2-$ClCH_2$-NQ (27.5), 6-$ClCH_2$-NQ (47)	65a
2-*t*-butylnaphthalene	8	2-*t*-Bu-NQ (26), 6-*t*-Bu-NQ (45)	162
2-Phenylethynylnaphthalene		2-PhC≡C-NQ (87)	149
1,5-Dibromonaphthalene	8	2,5-Br_2-NQ (66)	163
2,3-Dimethylnaphthalene	16	2,3-Me_2-NQ (55), 6,7-Me_2-NQ (25)	65a
2,6-Dimethylnaphthalene	16	2,6-Me_2-NQ (78)	65a
2,7-Dimethylnaphthalene	16	2,7-Me_2-NQ (89)	65a
1,2,4-Trimethoxynaphthalene	16	2-MeO-NQ (27.5)	65a

TABLE XXIV. *Continued*

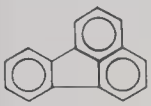
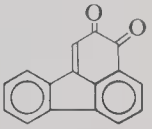
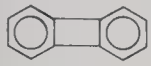
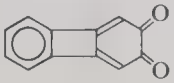
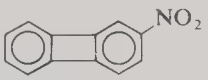
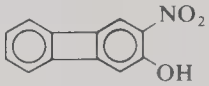
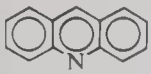
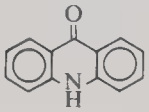
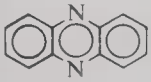
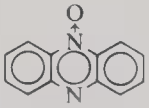
Arene	Reagent	Quinone (Yield, %)	Reference
Anthracene	1/THF	Anthraquinone (61)	161
	16	Anthraquinone (52)	65a
		Anthraquinone (80)	167
Phenanthrene	16	9,10-PQ (58)	65a
	1/THF	9,10-PQ (27.4), 1,4-PQ (11.5)	161
	8	9,10-PQ (60), 1,4-PQ (15)	162
		 (73)	162
		 (21)	165
		 (6.7)	
		 (1.8)	
		 (66)	167
		 (54)	167

TABLE XXV. CAN Oxidation of Alkylarenes

Substrate	Product (Yield, %)	Reference
PhMe	PhCHO (92)	170
	PhCHO (36)	171
1,2-$Me_2C_6H_4$	2-MeC_6H_4CHO (100)	170
1,3-$Me_2C_6H_4$	3-MeC_6H_4CHO (100)	170
1,4-$Me_2C_6H_4$	4-MeC_6H_4CHO (100)	170
	4-MeC_6H_4CHO (73)	171
1,3,5-$Me_3C_6H_3$	3,5-$Me_2C_6H_3CHO$ (100)	170
2-MeC_6H_4Cl	2-ClC_6H_4CHO (74)	170
3-MeC_6H_4Cl	3-ClC_6H_4CHO (60)	170
4-MeC_6H_4Cl	4-ClC_6H_4CHO (54) 4-$ClC_6H_4CH_2OH$ (19) 4-$ClC_6H_4CH_2OAc$ (8)	171
4-MeC_6H_4Br	4-BrC_6H_4CHO (51)	171
2-$MeC_6H_4NO_2$	2-$O_2NC_6H_4CHO$ (43)	170
3-$MeC_6H_4NO_2$	3-$O_2NC_6H_4CHO$ (50)	170
4-$MeC_6H_4NO_2$	4-$O_2NC_6H_4CHO$ (47)	170

Table continued

TABLE XXV. *Continued*

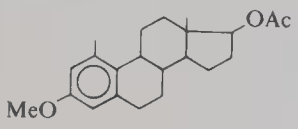
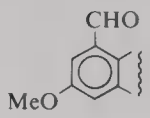
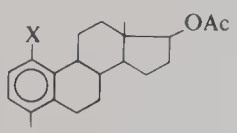
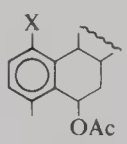
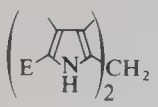
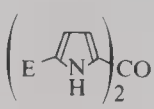
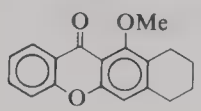
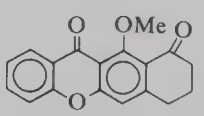
Substrate	Product (Yield, %)	Reference
$2\text{-}MeC_6H_4NHAc$	$2\text{-}AcNHC_6H_4CHO$ (93)	170
$4\text{-}MeC_6H_4NHAc$	$4\text{-}AcNHC_6H_4CHO$ (94)	170
$2\text{-}MeC_6H_4OMe$	$2\text{-}MeOC_6H_4CHO$ (63)	170
$4\text{-}MeC_6H_4OMe$	$4\text{-}MeOC_6H_4CHO$ (100)	170
$3\text{-}MeC_6H_4OSO_2Ph$	$3\text{-}PhSO_3C_6H_4CHO$ (100)	170
$4\text{-}PhSO_3C_6H_4Me$	$4\text{-}PhSO_3C_6H_4CHO$ (100)	170
PhEt	PhCOMe (77)	170
Ph_2CH_2	Ph_2CO (76)	170
Indane	1-Indanone (78)	170
Tetralin	α-Tetralone (76)	170
	 (68)	175
	 (25–65)	176
	 (57)	179
E = COOEt		
Xanthene	Xanthone (87)	170
Thiaxanthene	Thiaxanthone (75)	170
	 (54)	180

TABLE XXVI. CAN Cleavage of Arylcyclopropanes[a] and Bibenzyls[b]

Substrate	Medium	Product (Yield, %)
Phenylcyclopropane	CH_3CN	phenylpropane-1,3-diol dinitrate (44)
	CH_3COOH	phenylpropane-1,3-diol dinitrate (61), 1-nitrato-3-acetoxyphenylpropane (15)
1,2-Diphenylcyclopropane	CH_3CN	1,3-diphenylpropane-1,3-diol dinitrate (80)
	CH_3COOH	1,3-diphenylpropane-1,3-diol dinitrate (53)
Bibenzyl	CH_3CN	C_6H_5CHO (62), $C_6H_5CH_2ONO_2$ (40), $C_6H_5CH_2OH$ (4)
4,4′-Dimethoxybibenzyl	CH_3CN	$4\text{-}CH_3OC_6H_4CHO$ (117), $4\text{-}CH_3OC_6H_4CH_2OH$ (24)
4,4′-Dimethylbibenzyl	CH_3CN	$4\text{-}CH_3C_6H_4CHO$ (100), $4\text{-}CH_3C_6H_4CH_2OH$ (23), $4\text{-}CH_3C_6H_4CH_2ONO_2$ (12)

[a] Reference 185.
[b] Reference 186.

TABLE XXVII. Ligand Dissociation of Organometallics with Ce(IV)

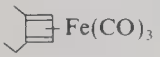
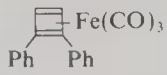
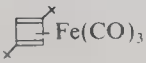
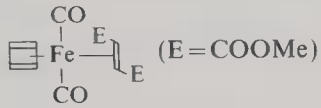
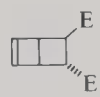
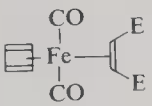
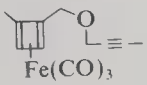
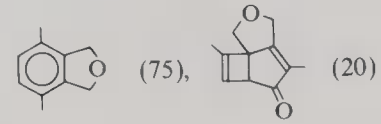
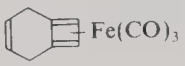
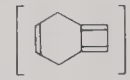
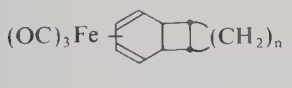
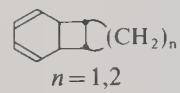
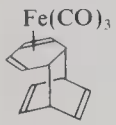
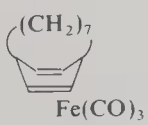
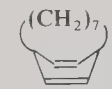
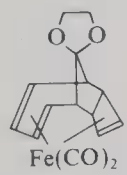
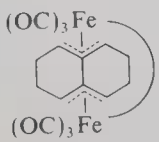
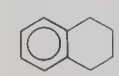
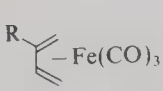
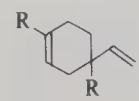
Substrate	Product (Yield, %)	Reference
		188, 196, 242, 243, 244
		191
		245
		246
		246
		246
		192
		197
		199
		198
		203
		195
		200
	 R = COOEt (90), R = CHO (50)	209

Table continued

TABLE XXVII. *Continued*

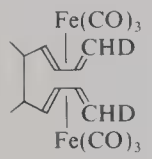
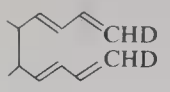
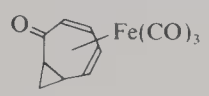
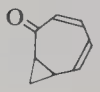
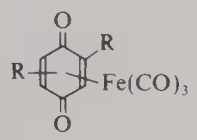
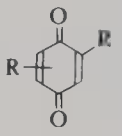
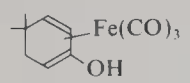
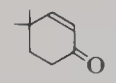
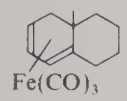
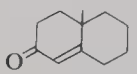
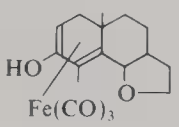
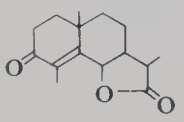
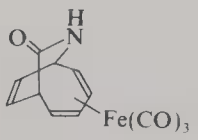
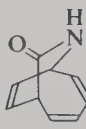
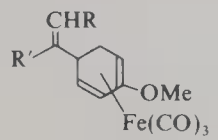
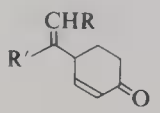
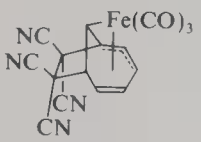
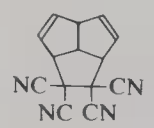
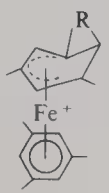
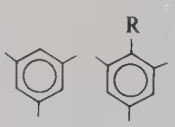
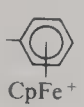
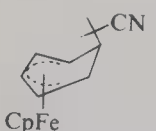
Substrate	Product (Yield, %)	Reference
		248
		247
		210
	 (80)	204
	 (80)	204
	 (80)	204
		215
	 (70)	205
	 (98)	215
	 R = CN (53) R = CH_2NO_2 (45) R = CH_2COOBu^t (50)	249
	PhMe	250
	PhH, 	250

TABLE XXVII. *Continued*

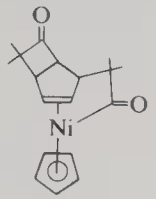
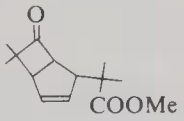
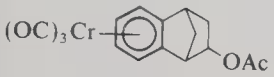
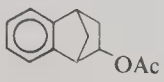
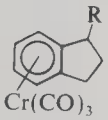
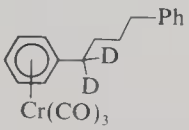
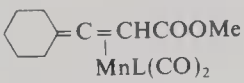
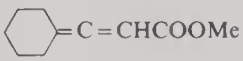
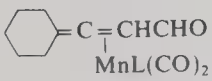
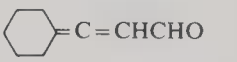
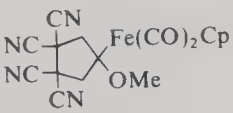
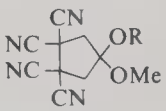
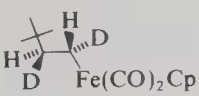
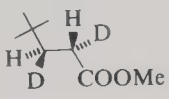
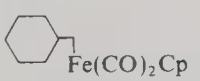
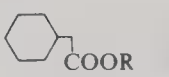
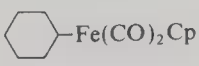
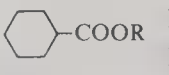
Substrate	Product (Yield, %)	Reference
		214
		251
		212
	$PhCD_2CH_2CH_2Ph$	212
$CH_2=C=CHCOOEt$ $\vert$ $MnL(CO)_2$	$CH_2=C=CHCOOEt$ (81)	224
n-$BuCH=C=CHCOOMe$ $\vert$ $MnL(CO)_2$	n-$BuCH=C=CHCOOMe$ (95)	224
	 (72)	224
	 (71)	224
	 (88)	222
	 (38)	221
	 R = Et (85) R = *i*-Pr (60) R = *t*-Bu (5)	219
	 R = Me (64) R = Et (48)	219
$Ph(CH_2)_2Fe(CO)_2Cp$	$Ph(CH_2)_2COOEt$ (70)	219
4-$FC_6H_4CH_2Fe(CO)_2Cp$	4-$FC_6H_4CH_2COOMe$ (100)	220
4-$FC_6H_4CH_2CH_2Fe(CO)_2Cp$	4-$FC_6H_4CH_2CH_2COOMe$ (100)	220
4-$FC_6H_4CH_2W(CO)_3Cp$	4-$FC_6H_4CH_2COOMe$ (100)	220

Table continued

TABLE XXVII. *Continued*

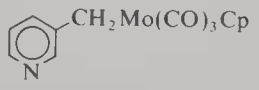
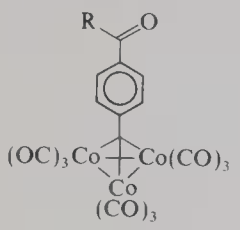
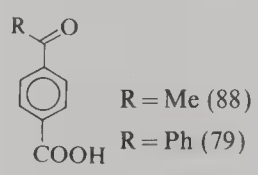
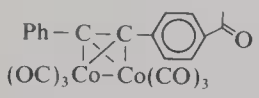
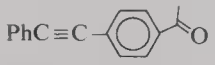
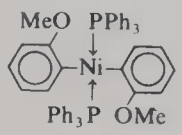
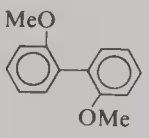
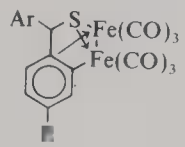
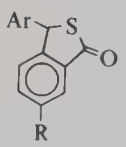
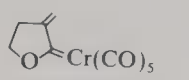
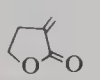
Substrate	Product (Yield, %)	Reference
$4\text{-}FC_6H_4CH_2Mo(CO)_3Cp$	$4\text{-}FC_6H_4CH_2COOMe$ (100)	220
	 (100)	220
$PhCOFe(CO)_2Cp$	PhCOOMe (100)	220
$4\text{-}FC_6H_4CH_2COCo(CO)_3PPh_3$	$4\text{-}FC_6H_4CH_2COOMe$ (100)	220
	 R = Me (88) R = Ph (79)	228
		228
	 (90)	223
	 (58–81)	218
	 (76)	227

TABLE XXVIII. Lactones[216] and Lactams[217] from Acyliron Complexes

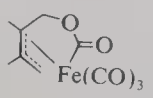
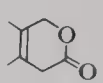
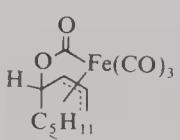
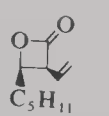
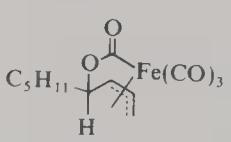
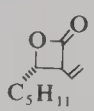
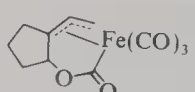
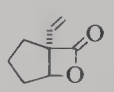
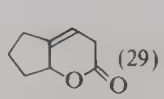
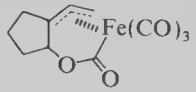
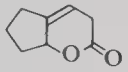
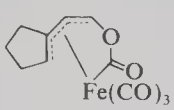
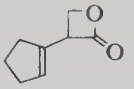
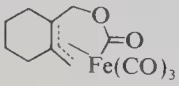
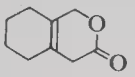
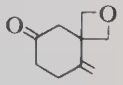
	 (16),  (42)	
	 (38)	
	 (64)	
	 (68)	
	 (51),  (29)	

Table continued

TABLE XXVIII. *Continued*



(75)



(100)



(55), 
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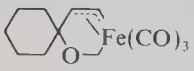
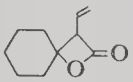
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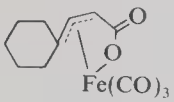
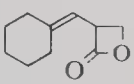
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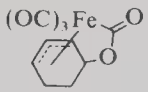
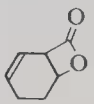
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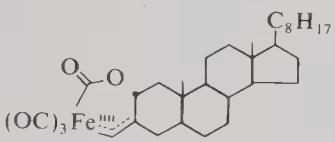
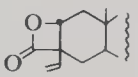
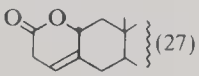


(12), 
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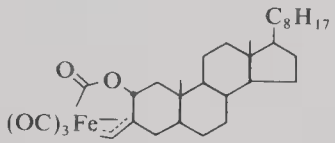
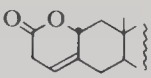
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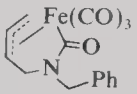
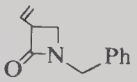
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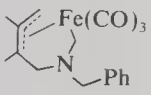
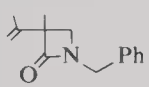
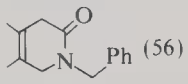


(34), 
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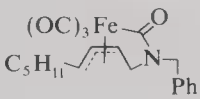
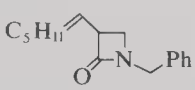
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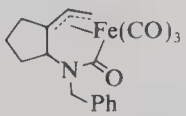
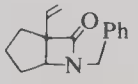
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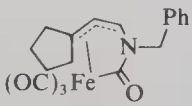
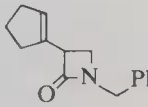
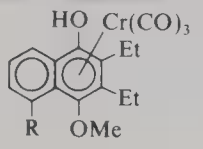
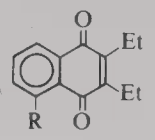
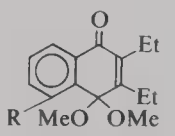
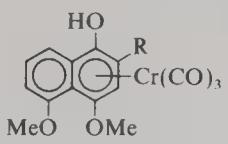
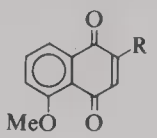
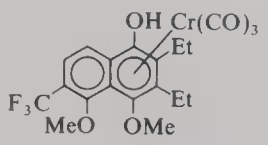
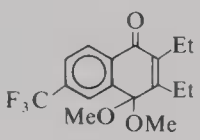
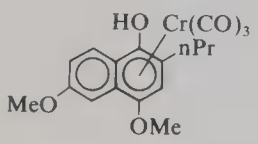
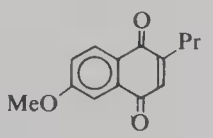
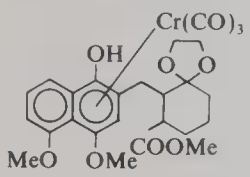
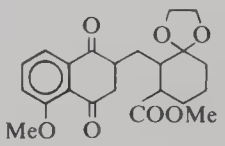


(88)

TABLE XXIX. Demetallation/Oxidation of Naphthol Complexes[a]

	9		R = H (96) R = OMe (70)
	2		R = OMe (72)
	9		R = Pr (74) R = $(CH_2)_3COO^tBu$ (66) R = $(CH_2)_3CONH\text{-}^tBu$ (70)
	2		(55)
	9		(76)
	9		(48)

[a] Reference 211.

TABLE XXX. Oxidation of Phenols and Dienes with CeO_2-H_2O_2[a]

Substrate	Product (Yield, %)
p-Cresol	4-Hydroperoxy-4-methylcyclohexa-2,5-dienone (77)
2,4-Xylenol	4-Hydroperoxy-2,4-dimethylcyclohexa-2,5-dienone (46)
Mesitol	4-Hydroperoxy-2,4,6-trimethylcyclohexa-2,5-dienone (70)
4-Methyl-2,6-di-*t*-butyl-phenol	4-Hydroperoxy-4-methyl-2,6-di-*t*-butyl-cyclohexa-2,5-dienone (70)
2,6-Dihydroxy-3,4-dimethylbenzamide	2-Hydroxy-4,5-dimethyl-3,6-dioxocyclohexa-1,4-dienecarboxamide (80)
1-Naphthol	2,3-Epoxy-2,3-Dihydro-1,4-naphthoquinone (83)
1,5-Naphthalenediol	5-Hydroxy-1,4-naphthoquinone (18)
Ergosteryl acetate	5α,8α-Epidioxy-5,8-dihydroergosteryl acetate (38)
Lumisteryl acetate	5β,8β-Epidioxy-5,8-dihydrolumisteryl acetate (45)

[a] Reference 233.

TABLE XXXI. Synthesis of α-Azido-β-nitratoalkanes[a,b]

Substrate	Product(Yield, %)
Indene	1-Nitrato-2-azidoindane (70)
β-Methylstyrene	1-Nitrato-2-azidopropylbenzene (76)
Styrene	1-Nitrato-2-azidoethylbenzene (73)
1-Hexene	2-Nitrato-1-azidohexane (56±7)
2-Methyl-1-pentene	2-Methyl-2-nitrato-1-azidopentane (49±3)
Acenaphthylene	Acenaphthylene nitratoazide (—)

[a] Reference 237.
[b] Olefin + CAN + NaN_3.

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12

Oxidations of Organic Compounds with Osmium Tetroxide

Hari Shankar Singh

1. INTRODUCTION

Metal compounds like potassium permanganate, hexacyanoferrate(III), ruthenium tetroxide, and osmium tetroxide are widely employed as oxidants in an alkaline medium. Apart from synthetic applications in the laboratory these oxidants are also important in industrial syntheses. Osmium tetroxide is the oldest compound and has been generally used for hydroxylation of olefins. Ruthenium tetroxide reacts in the same way as a vigorous oxidant even under mild conditions.

The oxidation states of osmium vary from (0) to (VIII). Good π donor ligands such as fluoride, oxide, or nitride form complexes with higher oxidation states (V–VIII) of osmium, whereas good π acceptor ligands like CN^-, NO^+, CO, arsines, phosphines, 2-2′ bipyridyl, and stilbenes stabilize the low (0) to (II) states. Good σ donor but poor π acceptor or donor ligands such as Cl^-, Br^-, I^-, NH_3, ethylenediamine, etc., stabilize the intermediate (III) and (IV) states of osmium.

1.1. Chemical Nature of Osmium Tetroxide

Osmium tetroxide is the most common osmium compound. It is manufactured either by the oxidation of the metal or by the action of nitric acid on any of its compounds. In the vapor phase it exists in monomeric form. The tetrahedral structure of the molecule has been established by x-ray,[1] infrared, and Raman[2] spectroscopy and by electron diffraction[3] measurements.

It is a powerful oxidizing agent. In alkaline medium it forms unstable octahedral[4,5] osmium(VIII) complexes of the form *trans*-$OsO_4(OH)_2^{2-}$ and $OsO_4(OH)(H_2O)^{1-}$.

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Therefore, osmium tetroxide has been extensively used in organic chemistry as an oxidizing agent or as a catalyst. It is most reactive to attack the π-cloud of aromatic hydrocarbons[6] in the presence of bases such as pyridine, whereas in an inert organic solvent it reacts smoothly at room temperature with olefinic double bonds yielding *cis*-diols. In these reactions OsO_4 competes with, e.g., ruthenium oxide. However, with the latter more vigorous oxidant sometimes C–C bond cleavage is observed. Osmium tetroxide in catalytic amounts has a wide range of applications in organic hydroxylations by barium and silver chlorate or Milas's reagent (a solution of hydrogen peroxide in *t*-butyl alcohol). In addition, it is also used as a staining and fixative reagent for biological tissues[7] in electron microscopy. It is believed that the staining of biological membranes with osmium tetroxide proceeds via attack on unsaturated entities of the tissues.[8–10] Recently it has again been used as a universal catalyst in the oxidation of organic substrates using co-oxidants in aqueous medium. The following sections will deal largely with the synthetic use based on mechanistic aspects of OsO_4 oxidation reactions.

In the following sections we will also outline the mechanism of Os oxidations and give a more detailed account of their scope and limitations. Finally, experimental procedures are provided for the synthetic organic chemist.

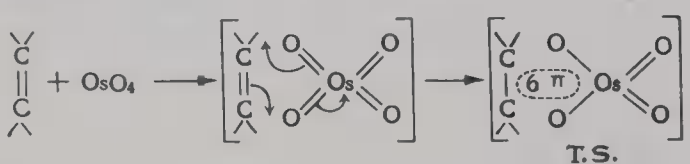
2. GENERAL MECHANISM OF OSMIUM TETROXIDE OXIDATION REACTIONS

Osmium tetroxide can be used (i) in stoichiometric amounts either in its original form or in the form of some trioxo–osmium(VIII) complex, and (ii) in catalytic amounts in the presence of a suitable co-oxidant, e.g., hydrogenperoxide, metalchlorates, *tert*-butyl hydroperoxide, sodium periodate, oxygen, hexacyanoferrate(III), chloramine-T, etc.

In most of the reactions (catalytic or noncatalytic) osmium tetroxide has a tendency to form inner-sphere complexes with the organic substrates, which in turn disproportionate into organic products and osmium(VI) species. In reactions where a stoichiometric amount of osmium tetroxide is used the reaction ceases after reductive hydrolysis, whereas in catalytic reactions the osmium(VIII) species are regenerated with the help of the co-oxidant used.

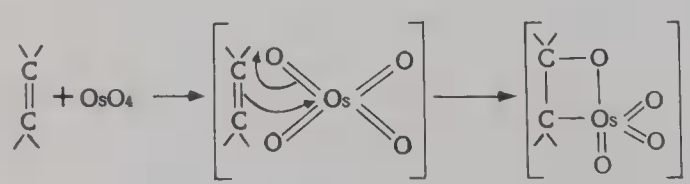
The mechanism of osmium tetroxide in hydroxylation reactions (stoichiometric or catalytic) can be explained by taking alkenes as a suitable example.

There is a general consensus of opinion that the oxidation of alkenes by osmium tetroxide proceeds via direct oxygen attack at the unsaturated center,[11–13] giving rise to a six-electron transition state (**2**) leading to the *cis*-product.



1 **2**

More recently, Sharpless *et al.*[14] have suggested indirect attack of alkenes by osmium tetroxide based on the fact that nucleophilic attack on carbonyl compounds occurs exclusively at C and not at O. Similarly, a carbon–carbon double bond, although a weak nucleophile, would attack at Os (electropositive) and not at 0, thus forming an organometallic intermediate (**4**).

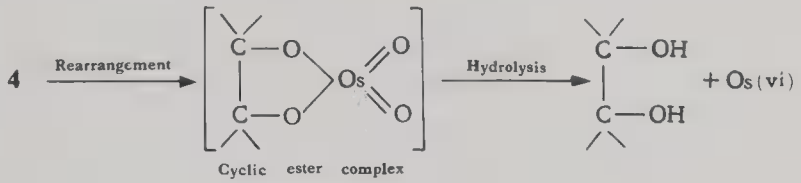


3 **4**

This intermediate **4** then undergoes rearrangement during the rate-determining step to a five-membered cyclic ester complex (**5**), which, on subsequent rapid hydrolysis[15] (reductive or oxidative) yields the product.

According to Crieges,[16,17] on the other hand, the *cis*-hydroxylation of alkenes by osmium tetroxide proceeds 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 tetroxide resulting in vicinal *cis*-diols in good yields. Criegee[17] has noticed that the rate of osmium(VI)–ester complex formation could be highly increased by the addition of excess of tertiary amines such as pyridine to the solution of osmium tetroxide and alkene mixture. The reaction stages in the absence and presence of amines are as follows:

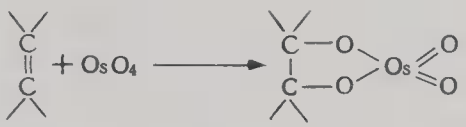
(i) Formation of Osmium(VI)–Ester Complex in Absence of Tertiary Amines. During *cis*-hydroxylation of olefins, osmium tetroxide forms an intermediate osmium(VI)–ester complex, usually written as a tetrahedral species.[18,19]



5

It might be a transient species in solution but unlikely to exist in the solid state, because third-row transition metals have no tetrahedral d^2 stereochemistry. In addition to this, the O(ester)–Os–O(ester) angle strain in the tetrahedral configuration is unfavorable.

In nonreducing[16,20–22] organic solvents like ether, benzene, and cyclohexane, dark green to black complexes **5** and **6** are formed from OsO_4 and alkenes.



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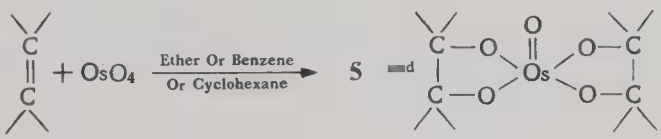
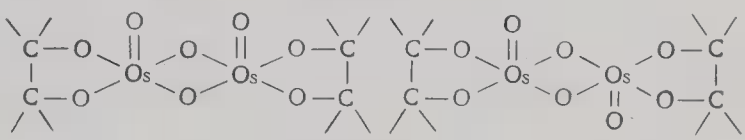
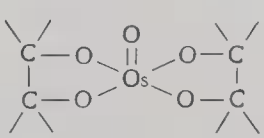


6

However, the structures of these intermediate osmium(VI)–ester complexes were reviewed relatively recently and formulated as dimeric monoester complexes (*syn*-[23] and *anti*-[24]) **7a** and **7b** and monomeric diester complexes (**6**).



7a **7b**

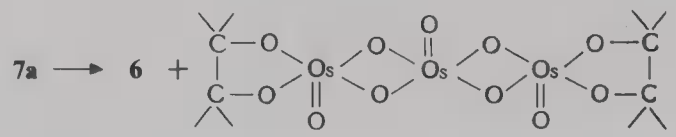


6

Structure confirmation was obtained by ir and x-ray crystallographic studies.

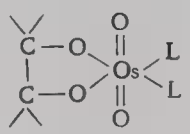
Alkenes like cyclohexene, ethylene, etc. generally form dimeric monoester complexes,

whereas less active alkenes, i.e., tetra substituted alkenes or those having electron-withdrawing groups, form diester monomeric complexes. The dimeric monoester complexes (**7a**) after standing in solution for some time change into monomeric diester complexes (**6**) along with a black highly insoluble trimer (**8**).



8

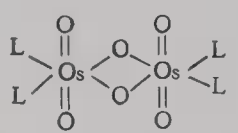
(ii) Formation of Osmium(VI)–Ester Complex in Presence of Tertiary Amine. A diamagnetic brown colored product has been isolated and characterized as diolatodioxobis (amine) osmium(VI)–ester complexes **9**.



9

(where L = pyridine,[17,21,24,25] isoquinoline,[24] quinoline,[17] bipyridyl,[27–30] 3-picoline,[30,31] 4-picoline,[30] (3-pyridyl) mercuric acetate,[31] and 3-chloropyridine[30,31]).

Similarly, osmium tetroxide can be reduced by an alcohol,[34] in the presence of an excess of tertiary amine (L) to produce the dimeric (amine) osmium(VI) complexes **10**.



10

(where L = pyridine,[26,35] 3-picoline,[35], 3-chloropyridine,[35] bipyridyl,[36] imidazole,[37] etc.).

A bis (amine) osmium(VI) complex analogous to **9** has also been observed by the reaction of osmium tetroxide with nucleic acid components such as uridine,[28,29,40] cytidine,[28,29,40,44] adenosine,[28,29] guianosine,[28,29] uracil,[40–42] thymine,[41,42,25] and thymidine[27–29,31,40,42,43] in the presence of tertiary amines.

In addition to the aforementioned reactions, osmium tetroxide can oxidize various other classes of organic molecules (i.e., alcohols,[45–50] diols,[51,52] digole,[53,54]*; aldehydes,[55] ketones,[56] acids,[57–64] etc.) in the presence of secondary oxidants like hexacyanoferrate(III), periodates, etc. From the abundant literature on these oxidations it appears that in most cases osmium tetroxide forms a 1:1 complex with the organic substrate or anion derived from it, which disproportionates slowly in the rate-determining step. Specific examples of this are given in the next section (Sections 3.6–3.11, alcohols, aldehyles, and acids). The osmium(VI), thus produced, is quantitatively oxidized by the secondary oxidants:

$$OsO_4(OH)_2^{2-} + S \rightleftharpoons \text{complex}$$

$$\text{Complex} \xrightarrow{\text{slow}} \text{osmium(VI)} + \text{products}$$

$$\text{Osmium(VI)} + \text{Ox} \xrightarrow{\text{fast}} \text{osmium(VIII)} + \text{redox}$$

* The chemical name of digol is diethylene glycol. Similarly methyl digol, ethyl digol, and butyldigol are also named as diethylene glycol monomethyl ether, diethylene glycol mono ethyl ether, and diethylene glycol monobutyl ether, respectively.

where S is the organic substrate, Ox is the secondary oxidant, and redox is the reduced oxidant. In some cases a 1:2 complex of osmium(VIII) and the organic compound is reported which is resistant to disproportionation.

3. SCOPE AND LIMITATIONS

Some of the OsO_4 reactions are carried out in the presence of stoichiometric amounts of osmium tetroxide as such, and some in the presence of imido-osmium(VIII) reagents. In recent years catalytic amounts of osmium tetroxide have been most frequently used in the presence of suitable co-oxidants like hydrogen peroxide, metal chlorates, periodate, oxygen, hexacyanoferrate(III) ion, chloramine-T, etc. The substrates that are oxidized by osmium tetroxide include representatives of the following classes of compounds: hydrocarbons (aliphatic, aromatic, and alicyclic), alcohols, aldehydes, ketones, acids. Depending on the reaction conditions, several other reaction media employed are ether, benzene, cyclohexane, pyridine, quinoline, isoquinoline, bi-pyridyl mercuric acetate, silver nitrate, acetonitrile, bisulfite, alkaline mannitol, hydrogen sulfide, lithium aluminium hydride, etc. Under normal conditions, the reactions with nitriles and imines are not generally observed. Alcohols are, however, oxidized more slowly than alkenes with osmium tetroxide.

Survey of the literature shows that hydroxylation of alkenes by stoichiometric amounts of OsO_4 is the superior method for *cis* diol synthesis.[16,17] This holds notwithstanding the high cost and toxicity of OsO_4. Systems containing catalytic amounts of OsO_4 and co-oxidants have their limitations in this respect, notably further oxidation to aldehydes, ketones, or acids. This is most noticeable with, e.g., oxygen or sodium periodate as cooxidant, but it is minimized by using *t*-butyl hydroperoxide or *N*-methyl morpholine *N*-oxide.

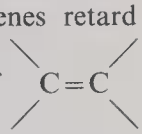
The stoichiometric method is the only one applicable for the hydroxylation of tri- and tetrasubstituted alkenes.

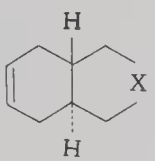
3.1. Oxidation of Alkenes and Related Compounds

3.1.1. Noncatalytic cis-Hydroxylation of Alkenes

Hydrolysis of Ester Complexes Resulting in cis-diol. In the preceding section we have described the formation of Os(VI)–ester complexes as a first step in *cis*-diol formation from alkenes. The hydrolysis of osmium(VI)–ester complexes is performed oxidatively or reductively to produce *cis*-diol. Reductive hydrolysis is performed using sodium or potassium sulfite or bisulfite,[16,17] lithium aluminium hydride,[65,66] or hydrogen sulfide.[67] The lower forms of osmium, thus produced, are removed by filtration. Recently ethylene diamine tetraacetic acid[68] has been used for reduction and possible hydrolysis of osmium(VI)–ester complexes.

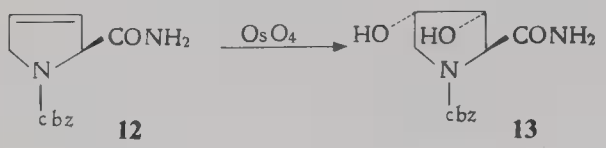
Tables I and II give data on noncatalytic *cis*-hydroxylation of some representative alkenes in the absence and presence of tertiary amines (pyridine), respectively. A good review has been made by Schröder[91] on the *cis*-hydroxylation of alkenes.

It is interesting to note that electron attracting groups attached to alkenes retard the reaction with osmium tetroxide[70,82,92] owing to decrease in nucleophilicity of  bond. For example, the relative rates of the reaction of **11** with osmium tetroxide decreases from 1 to 0.35 and from 1 to 0.28 if $X = CH_2$, O, and $C(OCH_3)_2$, respectively.[70]

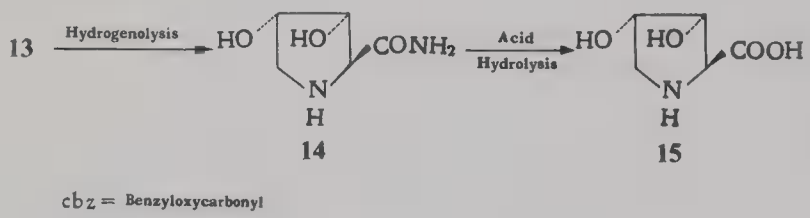


11

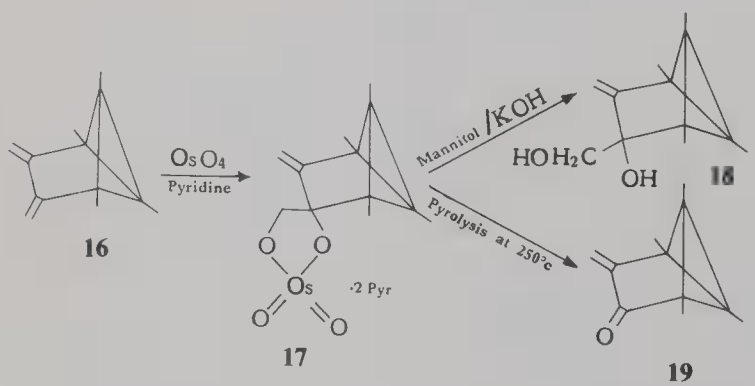
In an attempt to use osmium tetroxide in organic synthesis of several other series of compounds containing carbon–carbon double bonds, Hudson *et al.*[93] tried to prepare different isomers of 3,4-dihydroxy proline. Mauger *et al.*[94] have stressed the importance of proline and its analogs for use in metabolic studies.



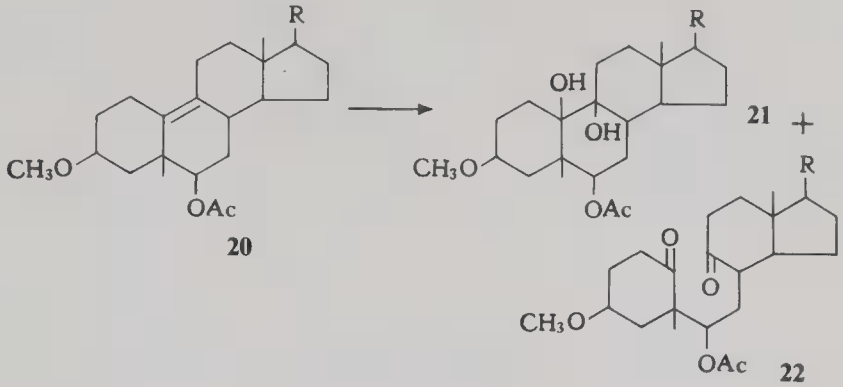
The action of osmium tetroxide on *N*-cbz-3, 4 dihydroprolinamide[95] (**12**) gave a crystalline α-glycol (**13**) in good yield. Hydrogenolysis of **13** to the amide **14** followed by acid hydrolysis gave 2,3-*trans*–3,4*cis*-amino acid (**15**).



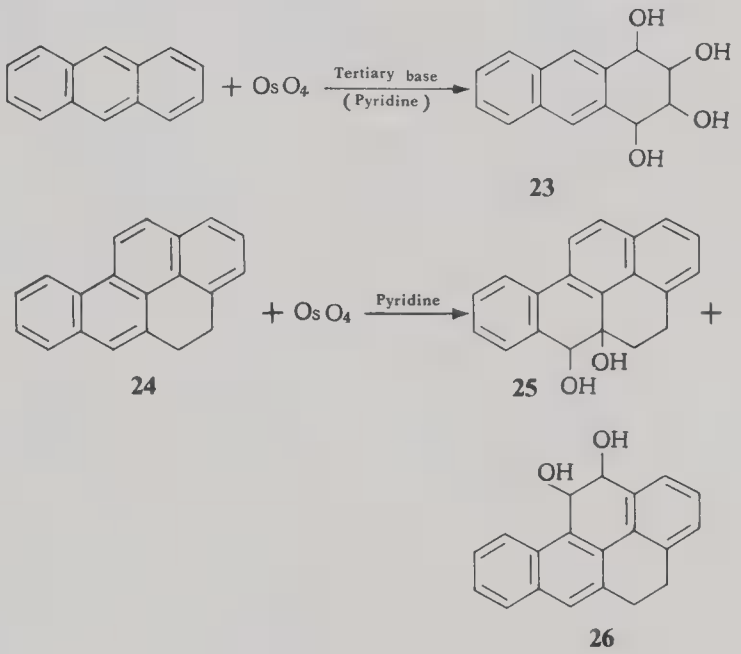
In many cases the OsO_4 adducts are sufficiently stable to permit their isolation.[17,96] For example, the addition of osmium tetroxide at room temperature to diene[97] (**16**) in ether containing pyridine (10:1) immediately resulted in a brown precipitate **17**. The reductive cleavage of **17** by mannitol in alkaline solution gives a glycol (**18**) and pyrolysis at 250°C results in an α,β-unsaturated ketone (**19**).



Osmium tetroxide differs from ruthenium tetroxide in the reaction course with olefins. The former attacks the double bond to give only *cis*-diol, whereas the latter cleaves the bond to produce predominantly ketones or acids with diols as minor products. This provides the basis for selective use of the two oxides according to the product one desires. Osmium tetroxide is preferable above ruthenium tetroxide if one aims to synthesize selectively a diol from an olefin. This is illustrated by the reaction of osmium tetroxide[98,99] with **20**, which yields only the diol **21**, whereas ruthenium tetroxide gives 67% diketone **22** and 12% diol **21**.



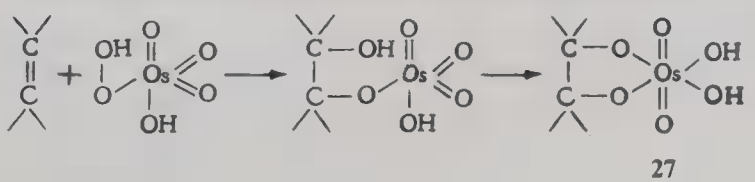
In the presence of tertiary bases like pyridine, osmium tetroxide is very reactive, attacking the π-system of aromatic hydrocarbons.[6] For example, a tetrol **23** is formed from anthracene and products **25** and **26** from 4,5 dihydrobenzo α pyrene[84,101] (**24**).



3.1.2. Catalytic cis-Hydroxylation of Alkenes

Catalytic use of osmium tetroxide can be more convenient owing to its high cost and toxicity. Although the oxidation of alkenes with a stoichiometric amount of osmium tetroxide gives good yields of *cis*-diols, a large number of secondary oxidants have been used in conjunction with osmium tetroxide (catalytic amount): hydrogen peroxide, metal chlorates, tertiary butyl hydroperoxide, *N*-methyl morpholine-*N*-oxide, oxygen, sodium periodate and sodium hypochlorite, etc. In these cases the secondary oxidants are capable of hydrolyzing the intermediate osmium(VI)–ester complex oxidatively to regenerate osmium(VIII), which in turn undergoes further reduction by the alkene.

3.1.2a. With Hydrogen Peroxide. The addition[100,102–104] of a solution of osmium tetroxide in *tert*-butyl-alcohol to hydrogen peroxide forms peroxyosmic acid, H_2OsO_6,[105–108] which rapidly reacts with alkenes to form the osmium(VIII)–ester complex[109] **27**. The hydrolysis of **27** gives osmium tetroxide and the corresponding *cis*-diol.[108]



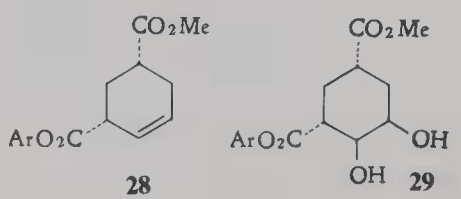
The main disadvantage of this method is further oxidation to produce carbonyl compounds, thus lowering the final yield of *cis*-diol. The reaction is carried out either under anhydrous conditions or in 8% water–benzene, ether and acetone as solvent, but the use of benzene is limited because of its slow oxidation to phenol and acidic products over a long period of time (a few days).

Table III represents the *cis*-hydroxylation of some important alkenes in the presence of hydrogen peroxide.

3.1.2b. With Metal Chlorates. A variety of alkenes (e.g., ethylene, propylene, amylene, indene, pinene, and dichloroethylene) with osmium tetroxide form osmium(VI)–ester complexes which are hydrolyzed by the chlorate ion to regenerate osmium tetroxide producing the corresponding *cis*-diols.

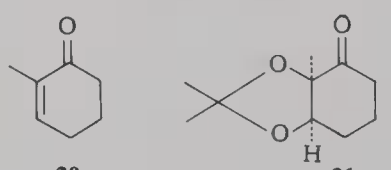
During the course of this oxidation, additional chlorohydroxy products[119] were reported, e.g., crotonic acid gave chlorohydroxy-crotonic acid by using osmium tetroxide catalytically in the presence of barium chlorate.[120] Braun[120,121] suggested the use of silver chlorate instead of potassium chlorate as a source of chlorate ions. In general, barium and silver chlorates give better yields of *cis*-diols and are more easily removed from the solution than sodium or potassium chlorate.

Despite the disadvantage of the formation of chlorohydroxy products, osmium tetroxide (catalytic amount) with sodium chlorate (Hofmann's reagent) is widely used as a *cis*-hydroxylating agent. Trost *et al.*[122] have utilized the reagent in an enantioconvergent synthesis of prostanoids. This involves oxidation of **28** from the less hindered side to give 84%–88% yield of **29**.



28 **29**

Very recently osmium tetroxide in conjunction with barium chlorate was used by Grieco *et al.*[123] in their total synthesis of the Prelog–Djerassi lactone to oxidize **30** to the corresponding *cis*-diol, isolated as its cyclic acetal derivative **31** in 65% yield.



30 **31**

In Table IV data on the oxidations using metal chlorates and osmium tetroxide are collected.

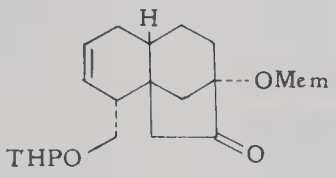
3.1.2c. With tert-Butyl Hydroperoxide. In most cases hydrogen peroxide is also a successful co-oxidant with osmium tetroxide (catalytic amount), but in a few cases further oxidation leading to high yields of ketols or other aldehydic products is a disadvantage. In addition to this, tri- and tetrasubstituted alkenes are difficult to oxidize because their osmium(VI)–ester complexes are inert towards oxidative hydrolysis.[132,133] This led to the development of *tert*-butyl hydroperoxide and *N*-methyl morpholine *N*-oxide as secondary oxidants in catalytic osmium tetroxide oxidations.

Byers *et al.*[134] were the first to use catalytic amounts of osmium tetroxide in the presence of *tert*-butyl hydroperoxide. The oxidation of 2,4,4-trimethylpent-1-ene yielded 2,4,4-trimethylpentane-1,2-diol together with formaldehyde and 2,2-dimethylpentane-4-one.

Sharpless *et al.*[132,133] have developed a new oxidant system involving osmium tetroxide as a catalyst with *tert*-butyl hydroperoxide in the presence of tetraethylammonium hydroxide[132] or tetraethyl ammonium acetate[133] in *tert*-butyl alcohol or acetone, respectively. It has been observed that the latter gives a better yield of *cis*-diol than the former with base sensitive alkenes.[133]

Table V represents data on oxidations using *tert*-butyl hydroperoxide and osmium tetroxide.

3.1.2d. With N-Methylmorpholine N-Oxide. Higher yields of *cis*-diol were obtained by using amine *N*-oxide such as *N*-methylmorpholine *N*-oxide[136] as secondary oxidants (prepared in an aqueous acetone/*t*-butyl alcohol solvent system) than with hydrogen peroxide and metal chlorates. Osmium tetroxide catalyzed oxidations of pregnadiene steroids[137] were studied with triethyl amine *N*-oxide as secondary oxidant. Corey *et al.*[138] have used the above reagent in the synthesis of gibberillic acid, **32** being oxidized to **33** in 89% yield.



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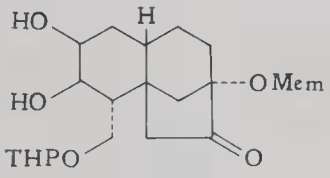
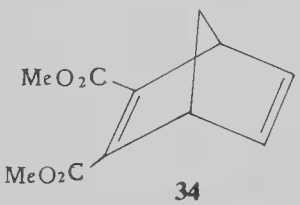


33

Similarly, in the synthesis of di-pentalenolacetone, Danishefsky *et al.*[139] oxidized **34** to **35**. Attack in both cases occurred to the less hindered side of the substrate.



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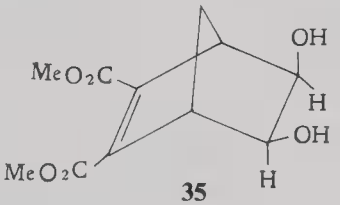
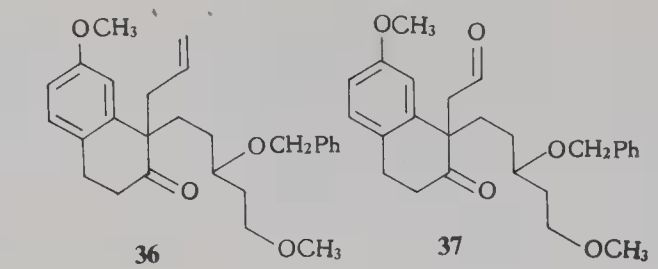


35

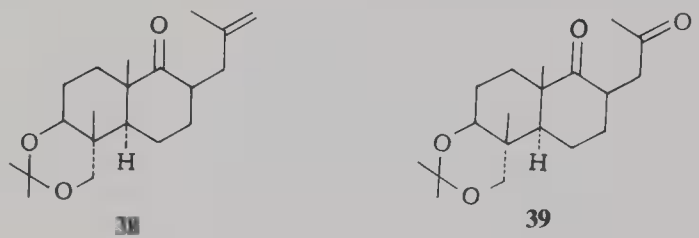
The results obtained with this oxidation system are listed in Table VI.

Similar to the *tert*-butyl hydroperoxide system the OsO_4/amine-oxide reagent is not efficient for *cis*-hydroxylation of tetra-substituted alkenes. Akasi *et al.*[133] have reported that *N*-methyl morpholine *N*-oxide as a co-oxidant failed to oxidize 2,3-dimethyl-2-octene. The high cost of *N*-methyl morpholine *N*-oxide may generally favor the use of *tert*-butyl hydroperoxide. Of all the methods for the *cis*-hydroxylation of tetra-substituted alkenes the most suitable process is to use stoichiometric amounts of osmium tetroxide as described by Criegee.[16,17,20–22]

3.1.2e. With Sodium Periodate. Periodates, being vigorous oxidants, can cleave the carbon–carbon bonds during oxidation reactions. Owing to this ability the *cis*-diols formed in the catalytic oxidation of alkenes by osmium tetroxide are effectively cleaved to such higher oxidation products as aldehydes or ketones. Thus, the oxidation of **36**[140] and **38**[141] results in **37** and **39** in 97% and 86% yield, respectively, as the corresponding ketone products in place of *cis*-diols.



36 37



38 39

Therefore, if the oxidation of alkenes is to be carried out by this method, alcohol protecting groups should be applied to prevent the formation of aldehydic or acidic products.

Table VII summarizes the data on the oxidations of alkenes by osmium tetroxide and sodium periodate.

In addition to the aforesaid studies, osmium tetroxide can also be used catalytically to oxidize other substrates[212–221] with secondary oxidants such as periodate.

3.1.2f. With Oxygen. With oxygen the osmium metal gets oxidized to osmium(VIII), and hence oxidation of alkenes[146] occurs. Similarly an aqueous solution of osmium(VI) is oxidized[147] to osmium(VIII) by air.[6] It has been reported that these oxidations are highly pH dependent. They are fast at pH 11, but quite slow above pH 12.5 and below pH 8. Disproportionation of the Os–ester complex occurs below pH 8.

Cairns *et al.*[148] have investigated the oxidation of alkenes in the presence of trisodium-phosphate and disodium-hydrogen phosphate (alkaline buffer)[148] by osmium tetroxide and oxygen. These oxidations are temperature dependent, being slower at 25°C and faster at 80°C. In such oxidations, although *cis*-diols are obtained, the major products are oxalic acid along with carbon dioxide.

3.1.2g. With Sodium Hypochlorite. The use of sodium hypochlorite as a co-oxidant with a catalytic amount of OsO_4 in the oxidation of alkenes is a recent development. It has been observed that in the reaction between osmium tetroxide and metal chlorates, hypochlorous acid is formed in the later stages of the reaction leading to the formation of appreciable amounts of chlorinated products. *Cis*-hydroxylation of allyl-alcohol to glycerol in about 98% yield by using osmium tetroxide (catalytic amount) in the presence of sodium hypochlorite[149] has been reported. Also propene, cyclohexene, cyclo-octene, 1-octene, 1-decene, 3-chloroprene, acrylic acid, acrylamide, and methyl acrylate were successfully oxidized[149] to give *cis*-products. The oxidations of potassium oleate and sodium 10-undecanoate to give erythro-9,10-dihydroxy-stearic acid, and 10,11-dihydroxyundecanoic acid in 95% and 50%–60% yields, respectively, have also been reported.[150] Terminal alkenes, however, were found to be further oxidized leading to C–C bond cleavage.[99]

3.1.3. Oxidation of Alkenes and Related Compounds by Alkylimidoosmium Compounds

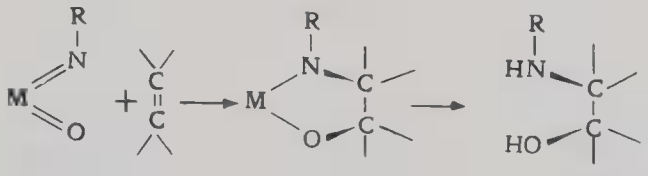
New synthetic opportunities are offered by alkylimidoosmium reagents to afford vicinal tertiary alkyl-amino alcohols in good yield with a variety of olefins via reductive cleavage of osmate esters. In addition to a large number of methods already available for β-amino alcohol[151–168] synthesis, this new procedure permits direct *cis*-addition of oxygen and nitrogen moieties to the olefinic double bonds.

Recently Sharpless *et al.*[169] have reported nitrogen (**40**) and carbon (**41**) atom transfer

processes analogous to oxygen-atom transfer of transition metal oxo-compounds (**42**) with olefins.

40 **41** **42**

This is illustrated in the formation of **43** from metal-aza compounds and olefins, anologous to the formation of **44** with metal oxo compounds.



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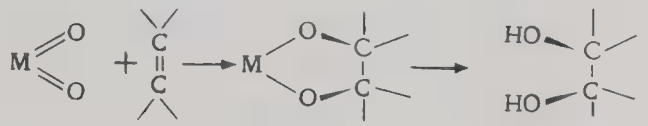
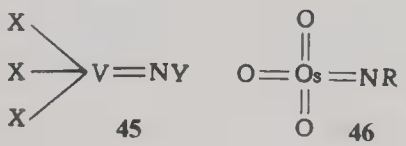


44

The two transition metals, vanadium[171,172] and osmium,[173–177] have a similar configuration and form similar types of alkylimido compounds **45** and **46**.



45 **46**

R = *tert*-butyl **46a**

R = 1-adamantyl **46b**

R = *tert*-amyl **46c**

This alkylimidoosmium reagent (**46**) forms a complex with alkenes which after reductive cleavage of osmate ester results in an excellent yield of vicinal tertiary alkyl amino alcohols. Table VIII represents comparative yields of amino-alcohols to diols for typical olefins.

The synthetic utility and limitation of this new reagent depends on solvent, temperature, olefin substitution pattern, and functional groups.

Correct choice of solvent[70] gives better yields of amino-alcohols. For example, if the oxyamination reaction is carried out in solvents like CH_2Cl_2, THF, *tert*-butyl alcohol, *tert*-butyl amine, and pyridine, the highest yield of amino-alcohol and the lowest of diol is obtained in pyridine. This might be due to the higher coordinating ability of pyridine compared to the other solvents.

The oxyamination reactions are highly temperature dependent. For example, oxyamination of (z)-5-decene in pyridine at room temperature results in 42% diol and 25% amino-alcohol, whereas at 0°C 65% amino-alcohol and 25% diol are produced in six days.

The substitution pattern[92,178] of the olefins has a pronounced effect on the reaction rate. For example, monosubstituted olefins react faster with the amido-reagent whereas di- and trisubstituted olefins are slow.

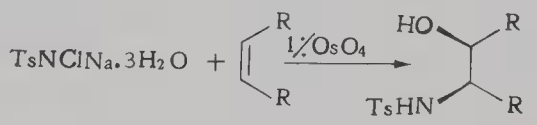
Substituents present in olefins also affect the reaction pattern. For example, 1-phenylbut-3-ene-1-ol and *N*-allyl aniline gave a large number of uncharacterized products in addition to the expected amino-alcohol.

Recently in order to improve the amino-alcohol/diol ratio Sharpless *et al.*[179] have studied the reaction of olefins with **46a** (*tert*-$BuNOsO_3$) in a noncoordinating solvent in the presence of certain tertiary alkyl bridge head amines such as quinuclidine, 3-quinucledione, 3-quinuclidinyl acetate, 1,4-diaza-bicyclo-2.2.2-octane, and hexamethylene tetramine. All these bases are much better than pyridine in promoting amino alcohol formation, quinuclidine being the most efficient.

The imidoosmium process has two main limitations: (i) a stoichiometric amount of the imidoosmium reagent **46** is required for the synthesis of amino-alcohols, and (ii) it is difficult to remove the *tert*-alkyl group from the product.

3.1.4. Oxidation of Alkenes by Chloramine-T (Osmium Catalyzed)

A new catalytic process for oxyamination reactions by chloramine-T (**47**) in the presence of 1% osmium tetroxide results in vicinal-hydroxy *p*-toluenesulphonamides[180–183] (**48**) from olefins.



47 **48**

It is a definite improvement considering the limitations of the imido reagent mentioned in Section 3.1.3. In the presence of silver nitrate monosubstituted and sym-disubstituted olefins gave faster reactions, giving better yields of oxyaminated products with this method.

The only limitation is with unsym-disubstituted and tri-substituted olefins, where oxyamination is less efficient.

Later on Harranz *et al.*[183] developed a new phase transfer catalyst (PTC) method[183] which was an improvement over the previous method for oxyamination of mono- and sym-disubstituted olefins on account of economy, better yields, and somewhat greater scope. The phase transfer catalyst used in the process is benzyltriethyl ammonium chloride.

Similarly, for unsym-disubstituted and tri-substituted olefins an alternative method has been suggested to get better yields. In this procedure the olefins are dissolved in *tert*-butyl alcohol followed by the addition of chloramine-T and osmium tetroxide at 55–60°C. These procedures are still not suitable for the oxyamination reaction of tetramethylethylene, cholesterol, diethylfumarate, or 2-cyclohexene-1-one. Some representative results have been summarized in Table IX.

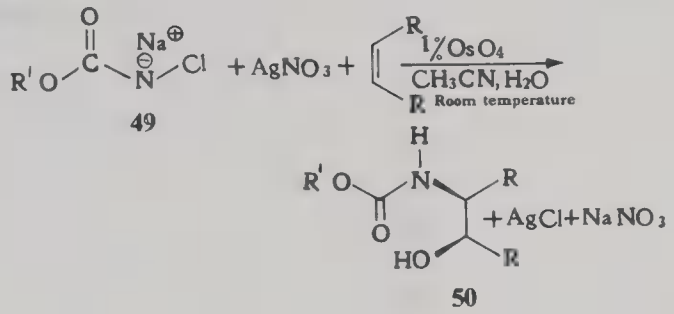
Recently the synthetic utility of vicinal hydroxy-*p*-toluenesulfonamides has again been explored in oxyamination procedures[184] to synthesize a variety of compounds, including some *N*-tosylaziridines. The various compounds synthesized are tabulated in Table X.

In addition to the aforesaid studies osmium tetroxide can be used to catalyze the oxidation of other substrates with chloramine-T.[217]

3.1.5. Oxidation of Alkenes by N-chloro-N-argentocarbamates (Osmium Catalyzed)

Sharpless *et al.*[181] have developed another new reagent, i.e., *N*-chloro-*N*-argentocarbamate with a catalytic amount of osmium tetroxide to overcome the difficulties of the

previous procedures.[169,170,180,186] The reagent[181,187] is formed *in situ* by the action of *N*-chloro-sodio-carbamates (**49**) with silver nitrate in acetonitrile. Vicinal hydroxycarbamate (**50**) is obtained in good yield from olefins using 1% osmium tetroxide (catalytic amount).



49 **50**

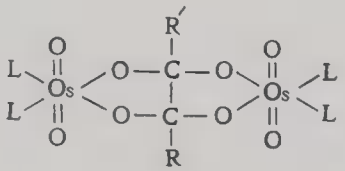
R′ = *tert*-butyl, *iso*-propyl, ethyl, benzyl

This procedure has a different scope of reactivity compared to the previous methods. It is more effective with electron deficient olefins such as di-methylfumarate. On the other hand, with this method trisubstituted olefins are less readily oxyaminated.

In addition to the argentocarbamates, Sharpless *et al.*[182] have developed a number of metallocarbamates in order to effect a more effective osmium-catalyzed oxidation of alkenes. The results obtained with various metals on styrene are given in Table XI. Mercury(II) salts give the most powerful oxyamination reagents.

3.2. Oxidation of Alkynes (Acetylenes)

Recently Griffith *et al.*[81] have studied the oxidation of alkynes with osmium tetroxide in the presence of tertiary bases. They have reported that osmium tetroxide reacts with alkynes (acetylene, diphenyl acetylene, phenylacetylene, and methyl-phenyl acetylene) in the presence of tertiary amines (pyridine or isoquinoline) affording *trans*-dioxo-osmium(VI) complexes $Os_2O_4(O_4C_2RR')L_4$ with structure **51**.



51

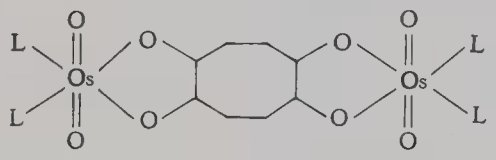
Here L = pyridine or isoquinoline, which on hydrolysis yields the corresponding alkyne derived products. Some of the hydrolysis products are listed in Table XII.

Catalytic amounts of OsO_4 with cooxidants like potassium chlorate in a *tert*-butyl alcohol–acetone–water solvent system react with diphenylacetylene to give benzil in 79% yield. On the other hand, the use of hydrogen peroxide as co-oxidant results in conversion of alkynes to the corresponding hydroxy aldehydes and hydroxy[188] acids.

3.3. Oxidation of Dienes

Osmium tetroxide (stoichiometric amount) reacts with a number of dienes,[71,103,111,189,190] resulting in tetrols or unsaturated diols. There have been few investigations on the reactions of osmium tetroxide with dienes in the presence of amines.[17,191] Generally the products have

been isolated, but no structure could be assigned. However, recently Grieffith *et al.*[81] have studied the reaction of osmium tetroxide with dienes, viz., cyclo-octa-1,5-diene, 2,3-dimethylbuta-1,3-diene, and 4-vinylcyclohexene in the presence of tertiary amines (pyridine or isoquinoline) giving products of the general formula $[Os_2O_4(O_4R)L_4]$ and $[OsO_2(O_2R)L_2]$, where R = Cyclo-octa-1,5-diene, 2,3-dimethylbuta-1,3-diene, and 4-vinylcyclohexene, having the structure of the type **52** and **53**.



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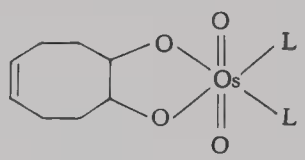
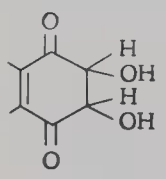


53

Tanaka[80] has obtained 14% yield of the product *cis*-cyclo-octan-5,6-diol upon hydrolysis of **52** with hydrogen sulfide, whereas with sodium sulfite 76% yield of diol was obtained.

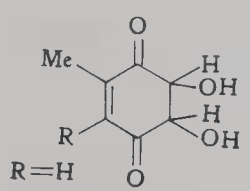
3.4. Oxidation of Quinones

Savoie *et al.*[114] have reported the osmic acid catalyzed oxidation of quinones in fairly good yields of the isomers of some *cis*-5,6-dihydroxycyclohex-2-ene-1,4 diones (**54**).



54

For example, toluquinone and *o*-xyloquinone give mixtures of two possible isomers **55** and **56**, whereas α-naphthaquinone gives product **57**.



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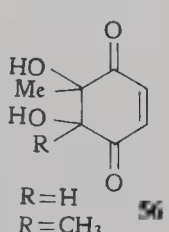

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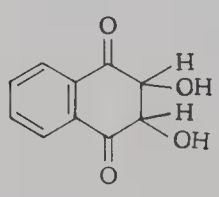

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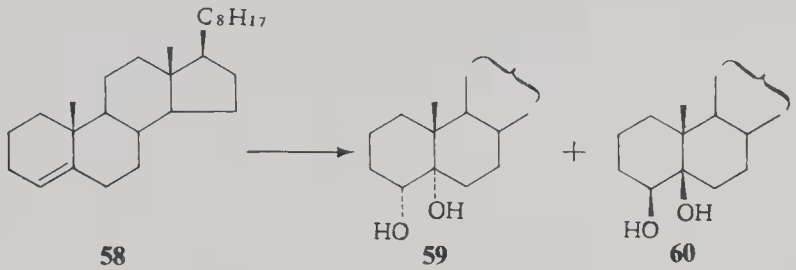
3.5. Oxidation of Steroids

The reaction[89,90,192–201] of osmium tetroxide either in stoichiometric amounts or in catalytic amounts in the presence of hydrogen peroxide with Δ^4-steroids results in *cis*-

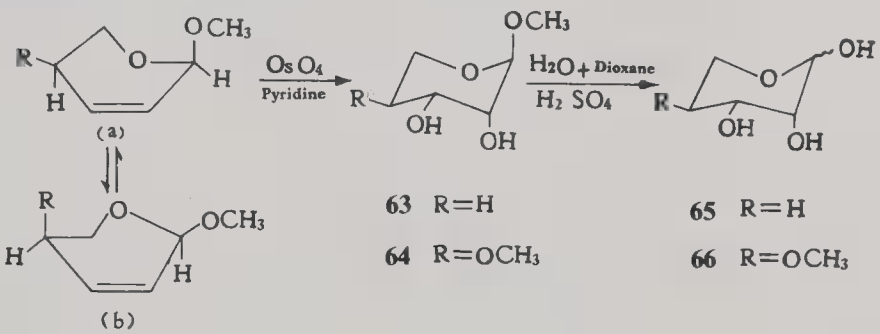
4,5 diols. Osmium tetroxide reacts with cholest-4-ene (**58**) to a mixture[196,197] of 4α,5α-diol (**59**) and 4β,5β-diol (**60**) in the ratio 5:1. Bathurst *et al.*[199] claimed the 4β,4β-diol (60) structure as the major product without comment. This has recently been confirmed by Bull *et al.*,[202,203] who have treated **58** with osmium tetroxide in the presence of pyridine at 25°C for about 48 h, resulting in a 1:3 ratio of **59** and **60**.



58 **59** **60**

3.6. Oxidation of Pyrans

Srivastava *et al.*[41] have synthesized 4-O-methyl-α-DL-lyxopyranoside (**64**) and methyl-4-deoxy-β-DL-erythro-pento-pyranoside (**63**) by the reaction of osmic acid in pyridine with *cis*-2,5-dimethoxy-5,6-dihydro-2H-pyran (**62**) and 2-methoxy-5,6-dihydro-2H-pyran (**61**), respectively. Hydrolysis of **64** and **63** gave 4-O-methyl-DL-lyxose (**66**) and 4-deoxy-DL-ribose (**65**), respectively. The total synthesis is outlined as follows:



61 R=H

62 R=OCH3

63 R=H

64 R=OCH3

65 R=H

66 R=OCH3

3.7. Oxidation of Alcohols and Related Compounds

Singh *et al.*[45–60,63,208] were the first to examine the kinetics of osmium tetroxide oxidations of various organic substrates,[204,205] e.g., alcohols, aldehydes, ketones, acids. It is suggested that the oxidation of alcohols[45–49] (primary and secondary) proceeds via the activated complex formation between alcohol and osmium tetroxide, which slowly decomposes to the osmium(VI) species and the corresponding intermediate product (Fig. 1 shows the effect of OH^- on the reaction rate). Osmium(VI) is rapidly regenerated to osmium(VIII) with the hexacyanoferrate(III) ion. The course of reaction is outlined as follows:

$$OsO_4(H_2O)(OH)^{1-} + OH^- \rightleftharpoons OsO_4(OH)_2^{2-} + H_2O$$

$$OsO_4(OH)_2^{2-} + \begin{matrix} R \\ \diagdown \\ CHOH \\ \diagup \\ H \end{matrix} \rightleftharpoons \left[\begin{matrix} R \\ \diagdown \\ CHO-OsO_3(OH)_3^{2-} \\ \diagup \\ H \end{matrix} \right]$$

Complex

$$[\text{Complex}] \xrightarrow[\text{slow}]{} \begin{matrix} R \\ \diagdown \\ C=O \\ \diagup \\ H \end{matrix} + OsO_2(OH)_4^{2-}$$

Intermediate product

$$OsO_2(OH)_4^{2-} + 2OH^- + 2Fe(CN)_6^{3-} \xrightarrow{\text{fast}} OsO_4(OH)_2^{2-} + 2H_2O + 2Fe(CN)_6^{4-}$$

Intermediate product $\xrightarrow{\text{fast}}$ Acids

Later Kalavoda *et al.*[206,207] confirmed the results of Singh *et al.*[45–49] by regenerating the osmium(VIII) species by polarography.

In addition to the above results, the oxidation of methyl digol, ethyl digol,[53] methoxyethanol, and ethoxyethanol[54] shows that the reaction proceeds in two ways: (i) acivated complex formation between osmium tetroxide and the organic substrate; (ii) activated complex formation between osmium tetroxide and an anion (derived from the alcohol molecule). In these cases the final oxidation products were the corresponding organic acids.

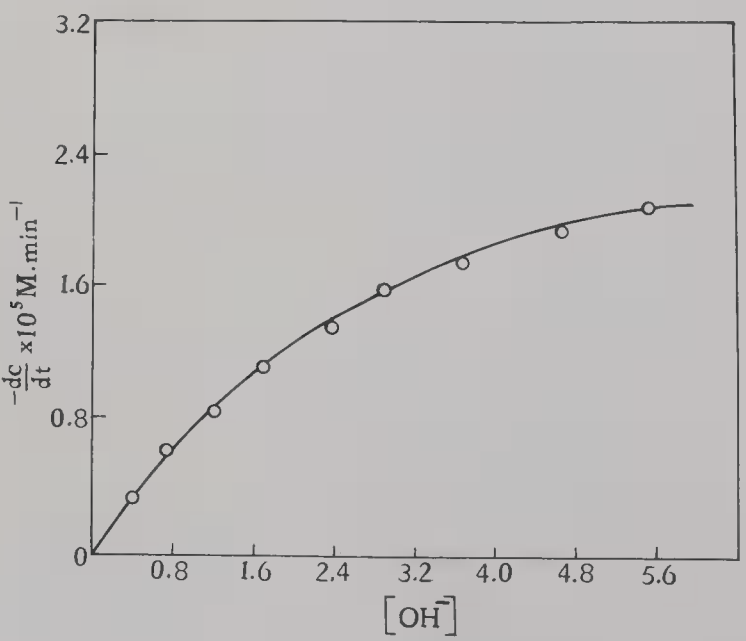


FIGURE 1. Osmium tetroxide catalyzed hexacyanoferrate(III) ion oxidation of ethanol, $K_3Fe(CN)_6 = 2.000 \times 10^{-3}$ *M*, ethanol = 0.10 *M*, $OsO_4 = 1.94 \times 10^{-5}$ *M*, $\mu = 0.5$ *M*, temperature = 30°C.

3.8. Oxidation of Diols and Related Compounds

The oxidation of diols[51,52] is of great interest because of the unusual oxidation pattern. Diols can react as alkoxide ions or as such. This peculiar behavior of diols was inferred from kinetic observations. Manifold variations of diol concentration show that the reaction velocity initially increases with diol concentration, reaches a maximum, and then decreases at still higher concentrations. This decrease in reaction velocity is attributed to the formation of a 1:2, osmium–diol complex (Fig. 2).

Plots of reaction rates versus hydroxide ion concentration (Figs. 3A and 3B) showed that the reaction is first order in hydroxide ion at lower OH^- concentration, but tends towards zero order at higher OH^- concentrations (Figs. 3C, 3D, and 3E).

The variation of osmium tetroxide and hexacyanoferrate(III) shows first-order and zero-order kinetics, respectively, for the entire course of the reaction. In order to explain the actual path of the reaction, two reaction schemes have been proposed (Schemes 1 and 2).

The final oxidation products have been identified by chromatography. In ethane-1,2-diol, oxalic acid has been confirmed as the final oxidation product. Oxalic acid and acetic acid were obtained as the final oxidation product in propane-1,2-diol, whereas formic acid, acetic acid, and oxalic acid were obtained in butane-2,3-diol.

Similar results have also been observed in the osmium tetroxide-catalyzed oxidation of sorbitol and mannitol.[208]

3.9. Oxidation of Aldehydes and Ketones

The exact role of osmium tetroxide has been examined in the oxidation of acetaldehyde,[55] acetone, and methyl-ethyl ketone[56] by aqueous alkaline hexacyanoferrate(III) ion. The kinetic data suggest that the oxidation of these organic substrates proceeds via the formation of an activated complex between enolate (derived from the

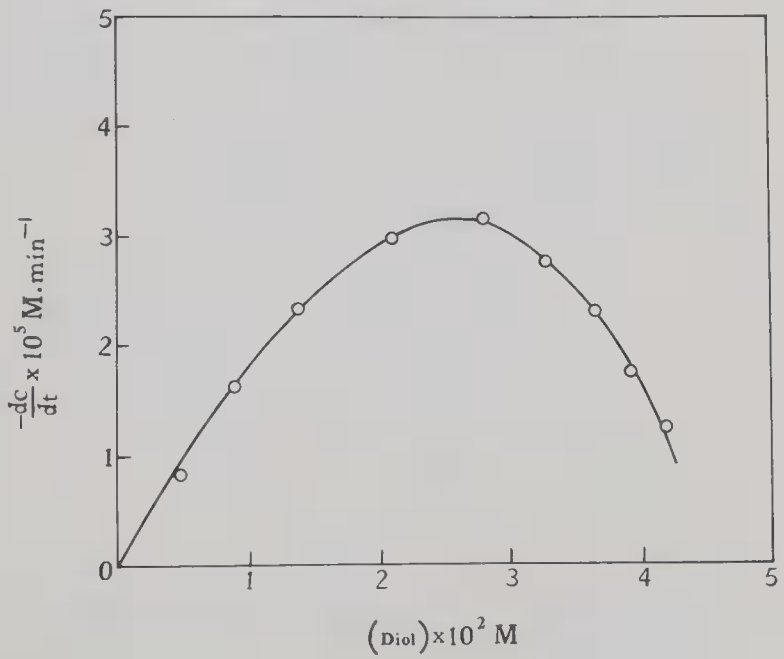


FIGURE 2. Osmium tetroxide catalyzed hexacyanoferrate(III) ion oxidation of diols. $K_3Fe(CN)_6 = 2.0 \times 10^{-3}$ *M*, $NaOH = 1.0 \times 10^{-2}$ *M* $OsO_4 = 1.95 \times 10^{-5}$ *M* (for ethane-1,2 diol), temperature = 30°C.

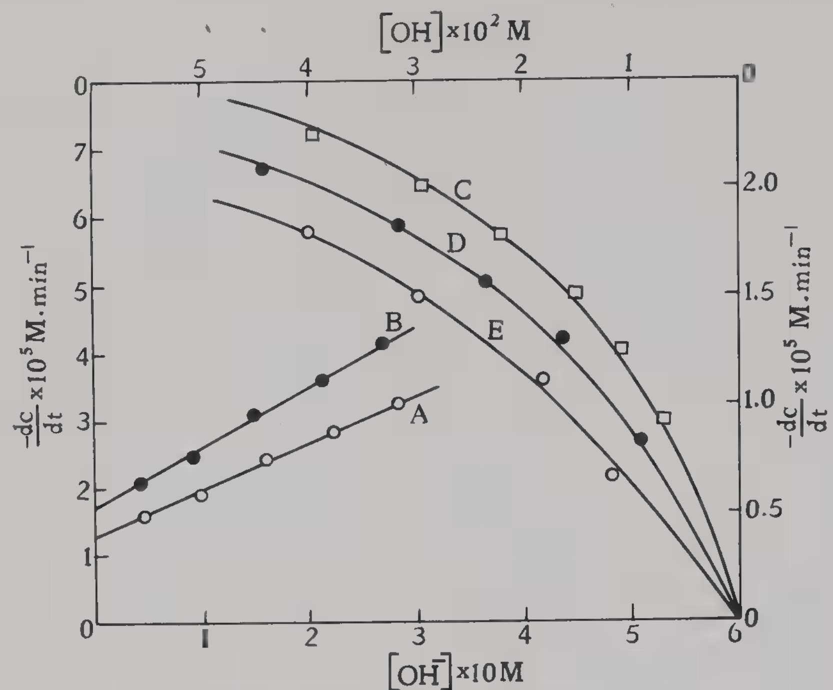


FIGURE 3. Osmium tetroxide catalyzed hexacyanoferrate(III) ion oxidation of diols. $K_3Fe(CN)_6 = 2.0 \times 10^{-3}$ *M*, $OsO_4 = 1.95 \times 10^{-5}$ *M* and temperature = 30°C. A, Ethane-diol = 4.0×10^{-2} *M*; B, propane-1,2-diol = 0.5×10^{-2} *M*; C, ethane-diol = 10.0×10^{-2} *M*; D, propane-1,2-diol = 1.0×10^{-2} *M*; E, butane-2,3-diol = 1.0×10^{-2} *M* and $OsO_4 = 3.90 \times 10^{-5}$ *M*.

organic substrate) and osmium tetroxide which rapidly decomposes followed by a fast reaction between reduced osmium(VI) species and hexacyanoferrate(III) ion. The reaction scheme is proposed as follows:

$$CH_3-\overset{\overset{\displaystyle R}{|}}{C}=O + OH^- \rightleftharpoons CH_2=\overset{\overset{\displaystyle R}{|}}{C}-\bar{O} + H_2O$$

$$CH_2=\overset{\overset{\displaystyle R}{|}}{C}-\bar{O} + OsO_4(OH)_2^{2-} \longrightarrow [\text{Complex}]$$

$$[\text{Complex}] \xrightarrow[\text{fast}]{OH^-} \begin{array}{l} CHO \\ | \\ CH_2OH \end{array} + OsO_4(OH)_2^{4-}$$

$$\begin{array}{l} CHO \\ | \\ CH_2OH \end{array} \xrightarrow{O} \begin{array}{l} CHO \\ | \\ CHO \end{array} \xrightarrow{O} \begin{array}{l} COO^- \\ | \\ COO^- \end{array}$$

R = H, for acetaldehyde; R = C_2H_5 for methyl-ethyl ketone; R = CH_3 for acetone.

$$OsO_4(OH)_2^{4-} + 2H_2O \xrightarrow{\text{fast}} OsO_2(OH)_4^{2-} + 2OH^-$$

$$OsO_2(OH)_4^{2-} + 2OH^- + 2Fe(CN)_6^{3-} \xrightarrow{\text{fast}} OsO_4(OH)_2^{2-} + 2H_2O + 2Fe(CN)_6^{4-}$$

SCHEME 1

$$G + OH^- \rightleftharpoons \bar{G}_- + H_2O$$

$$OsO_4(OH)(H_2O)^{1-} + OH^- \rightleftharpoons OsO_4(OH)_2^{2-} + H_2O$$

$$(C) \qquad (C_1)$$

$$C_1 + G^- \rightleftharpoons \text{Complex } (C_2)$$

$$C_1 + 2G^- \rightleftharpoons \text{Complex } (C_3)$$

$$C_2 \xrightarrow[\text{slow}]{} Os(VI) + \text{other reaction products}$$

$$Os(VI) + 2Fe(CN)_6^{2-} \xrightarrow{\text{fast}} Os(VIII) + 2Fe(CN)_6^{4-}$$

3.10. Oxidation of Hydroxy Acids

In order to explain the catalytic activity of osmium tetroxide in the oxidation of hydroxy acids, a considerable amount of kinetic data have been collected with a variety of acids.

3.10.1. Oxidation of Glycolic and Lactic Acids

With osmium tetroxide-catalyzed oxidation of glycolic and lactic acid[58] with hexacyanoferrate(III) ion, the oxidation product study suggests that the oxidation involves C–H bond fission via acid–osmium(VIII) activated complex formation. The complete course of the reaction may be represented as follows:

$$\begin{array}{l} \text{COO}^- \\ | \\ \text{H}-\text{C}-\text{OH} \\ | \\ \text{R} \end{array} + OsO_4(OH)_2^{2-} \rightleftharpoons \left[\begin{array}{l} \text{COO}^- \\ | \\ \text{H}-\text{C}-\text{O}-OsO_3(OH)_3^{2-} \\ | \\ \text{R} \end{array} \right]$$

$$\left[\begin{array}{l} \text{COO}^- \\ | \\ \text{H}-\text{C}-\text{O}-OsO_3(OH)_3^{2-} \\ | \\ \text{R} \end{array} \right] + OH^- \longrightarrow \begin{array}{l} \text{COO}^- \\ | \\ \text{C}=\text{O} + OsO_4(OH)_2^{4-} \\ | \\ \text{R} \qquad + H_2O + H^+ \end{array}$$

$$\begin{array}{l} \text{COO}^- \\ | \\ \text{C}=\text{O} \\ | \\ \text{R} \end{array} + O \xrightarrow{\text{fast}} \begin{array}{l} \text{COO}^- \\ | \\ \text{COO}^- \end{array}$$

R = H for glycolic acid; $R = CH_3$ for lactic acid.

The keto acids formed are further oxidized to oxalic acid as the final product.

SCHEME 2

$$OsO_4(OH)(H_2O)^{1-} + OH^- \rightleftharpoons OsO_4(OH)_2^{2-} + H_2O$$

$$(C) \qquad (C_1)$$

$$C_1 + G \rightleftharpoons \text{Complex } (C_4)$$

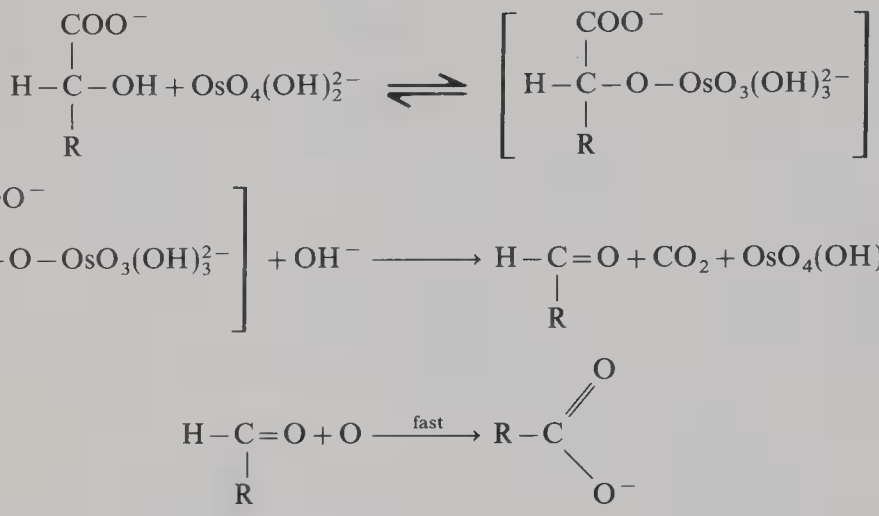
$$C_1 + 2G \rightleftharpoons \text{Complex } (C_5)$$

$$C_4 \xrightarrow[\text{slow}]{} Os(VI) + \text{other reaction products}$$

$$Os(VI) + 2Fe(CN)_6^{3-} \xrightarrow{\text{fast}} Os(VIII) + 2Fe(CN)_6^{4-}$$

3.10.2. Oxidation of Malic and Mandelic Acids

Kinetic data along with the product analysis led Singh *et al.*[57,63,209] to propose similar steps for the oxidation of malic and mandelic acid. It has been concluded that the oxidation of these molecules takes place by fission of the C–C bond rather than the C–H bond. Hence the probable steps might be represented as follows:

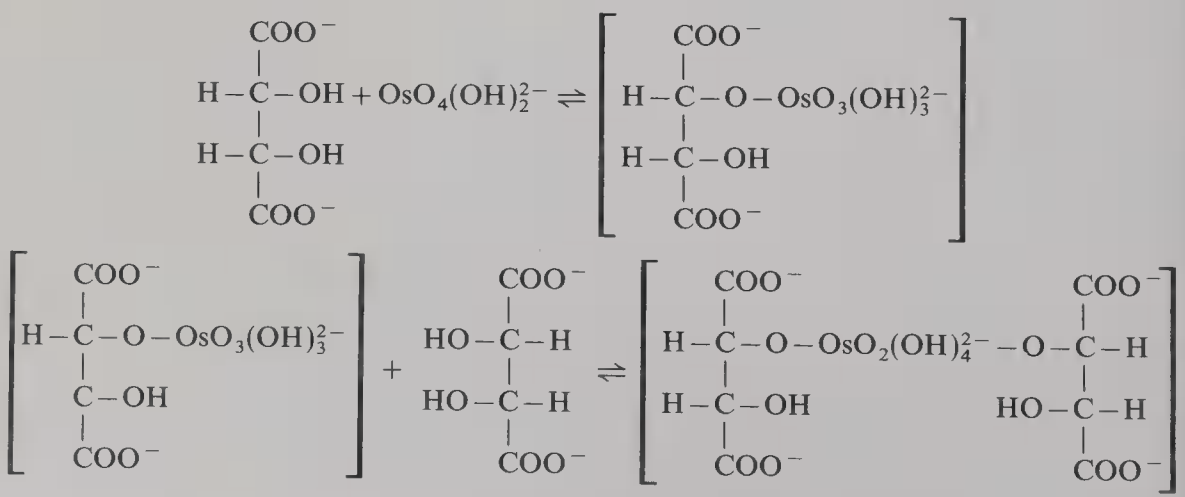


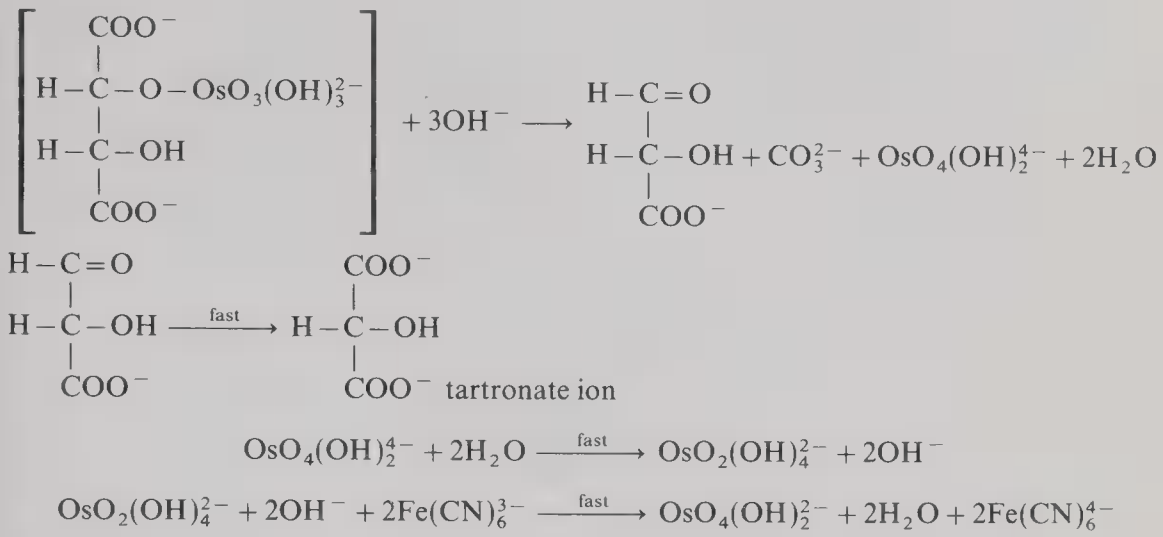
$R = -CH_2COOH$ for malic acid; $R = C_6H_5$ for mandelic acid.

The osmium(VI) is converted to osmium(VIII) in this reaction as described before.

3.10.3. Oxidation of Tartaric Acid

In the OsO_4-alkaline hexacyanoferrate(III) ion oxidation of the tartrate[57] ion the rate is consistent with a mechanism involving, as the first step, the formation of a 1:1 complex of osmium(VIII) and the anion of the organic acid followed by decomposition to the intermediate products and the osmium(VI) species by the hydroxide ion. Osmium(VI) is rapidly oxidized to osmium(VIII) by alkaline hexacyanoferrate(III) ion. The kinetic data obtained at higher tartrate concentrations indicate the formation of an osmium(VIII)–$(tartrate)_2$ complex which is resistent to decomposition. The possibility of the formation of osmium(VI)–organic anion complexes, causing a retarding effect on the reaction velocity during the kinetic run, has also been observed. The following reaction path has been proposed:





$$\begin{array}{l} H-C=O \\ | \\ H-C-OH \\ | \\ COO^- \end{array} \xrightarrow{\text{fast}} \begin{array}{l} COO^- \\ | \\ H-C-OH \\ | \\ COO^- \end{array} \quad \text{tartronate ion}$$

$$OsO_4(OH)_2^{4-} + 2H_2O \xrightarrow{\text{fast}} OsO_2(OH)_4^{2-} + 2OH^-$$

$$OsO_2(OH)_4^{2-} + 2OH^- + 2Fe(CN)_6^{3-} \xrightarrow{\text{fast}} OsO_4(OH)_2^{2-} + 2H_2O + 2Fe(CN)_6^{4-}$$

3.11. Oxidation of Dicarboxylic Acids

3.11.1. Maleic and Fumaric Acid

Maleic and fumaric acid are both oxidized to the corresponding diols. With the alkaline hexacyanoferrate(III)–OsO_4 system,[60,210,211] maleic acid gives the mesodiol and fumaric acid yields the Dl-diol. There is a little difference in mechanism and reaction rate, the oxidation being more facile with maleic acid. The data in the maleic acid case are consistent with a mechanism involving the formation of an Os(VIII)–maleate complex in the first equilibrium step followed by its disproportionation in the subsequent steps yielding the Os(VI) species and the tartrate ion.

The oxidation mechanism for the fumarate ion, on the other hand, is in consonance with the formation of an Os(VIII)–fumarate complex with a possible exchange of OH^- ion coordinated with Os(VIII) as in the species $OsO_4(OH)_2^{2-}$. The complex then undergoes a similar disproportionation, yielding Os(VI) and tartrate ion.

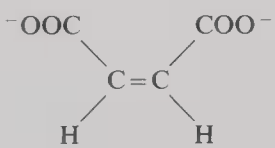
The Schemes 3 and 4 substantially account for the experimental data.

3.11.2. Oxidation of Malonic Acid

The active methylene group plays an important role in the oxidation of malonic acid[59] by hexacyanoferrate(III) ion in the presence of osmium tetroxide used as a homogeneous catalyst. The inner-sphere mechanism involves the formation of two types of complexes: one between osmium tetroxide and malonate ion and the other between osmium tetroxide and

SCHEME 3

(i) $\underset{C}{OsO_4(OH)(H_2O)^{1-}} + OH^- \rightleftharpoons \underset{C_1}{OsO_4(OH)_2^{2-}} + H_2O$

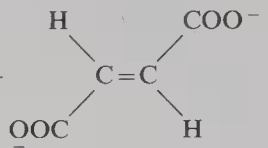
(ii) $OsO_4(OH)_2^{2-} +$  $\rightleftharpoons \underset{C_2}{[\text{Complex}]}$

(iii) $\underset{C_2}{[\text{Complex}]} \xrightarrow[H_2O]{} Os(VI) + \bar{O}OC-CH(OH)-CH(OH)-COO^-$

(iv) $Os(VI) + 2Fe(CN)_6^{3-} \xrightarrow{\text{fast}} Os(VIII) + 2Fe(CN)_6^{4-}$

SCHEME 4

(i) $OsO_4(OH)(H_2O)^{1-} + OH^- \rightleftharpoons OsO_4(OH)_2^{2-} + H_2O$
C C_1

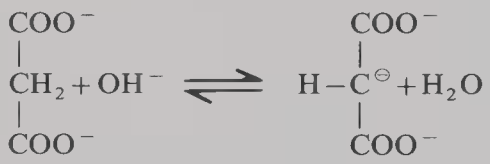
(ii) $OsO_4(OH)_2^{2-} +$  $\rightleftharpoons$ [Complex] + OH^-
C_3

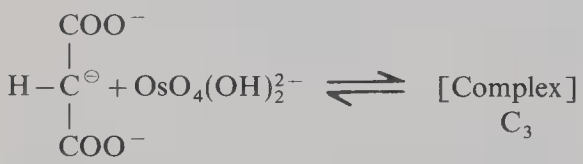
(iii) [Complex] $\longrightarrow$ Os(VI) + $\bar{O}OC\,CH(OH)-CH(OH)COO^-$
C_3

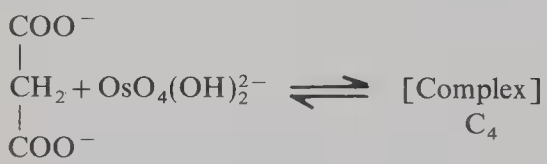
(iv) $Os(VI) + 2Fe(CN)_6^{3-} \xrightarrow{\text{fast}} Os(VIII) + 2Fe(CN)_6^{4-}$

malonate carban ion formed via the reaction between malonate ion and hydroxide ion. The malonate carban ion disproportionates slowly resulting in osmium(VI) species and other products.

(i) $OsO_4(OH)(H_2O)^{1-} + OH^- \rightleftharpoons OsO_4(OH)_2^{2-} + H_2O$
C_1 C_2

(ii) 

(iii) 
C_3

(iv) 
C_4

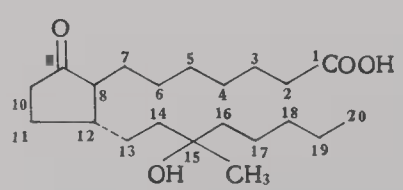
(v) $C_3 \xrightarrow{\text{slow}}$ Os(VI) + other reaction products

(vi) $Os(VI) + 2Fe(CN)_6^{3-} \xrightarrow{\text{fast}} Os(VIII) + 2Fe(CN)_6^{4-}$

3.12. Osmium Tetroxide in Biochemistry

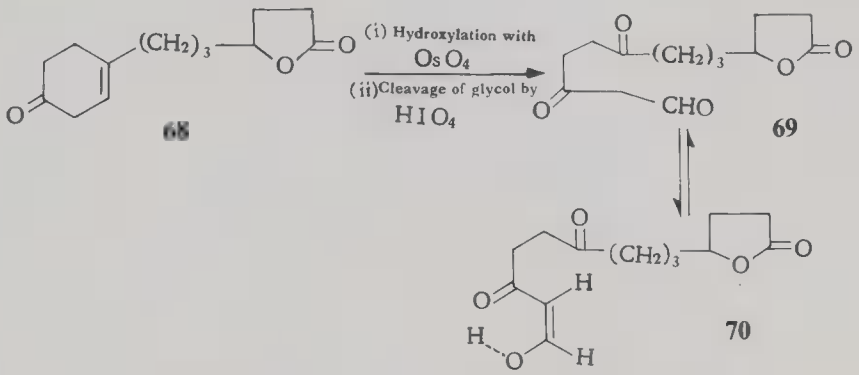
Osmium tetroxide has also been proved to be a versatile reagent in bioorganic synthesis. Below some important miscellaneous examples are given.

(i) Several 9-oxygenated 15-hydroxyprostanoic acids have been synthesized by Bagli *et al.*[223-225] without an oxygen function at C−11.

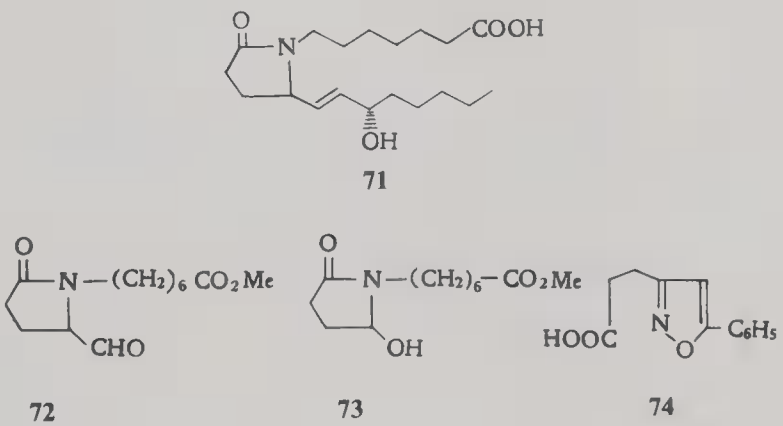


67

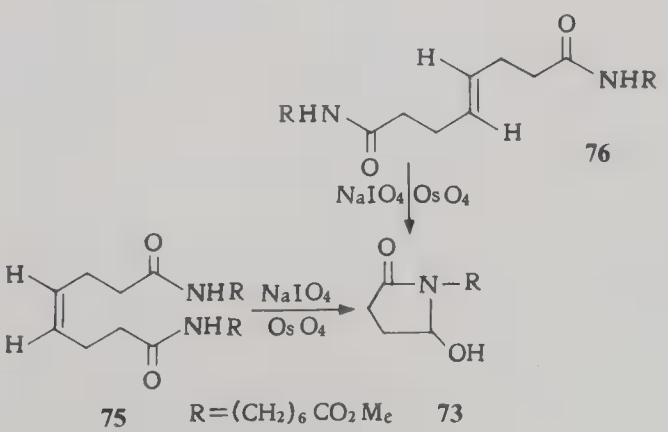
Primary natural prostaglandins bear an oxygen function both at C−11 and C−9. Chinn *et al.*[226] synthesized certain 9-deoxy-11-oxygenated prostanoids[227,228] to examine possible biological activity as a function of chemical structure. In the synthesis of such an active class of compounds osmium tetroxide plays an important role to convert β, γ-unsaturated ketone (**68**) into β-keto aldehyde (**69**) which is in equilibrium with S-*cis*-enol (**70**).



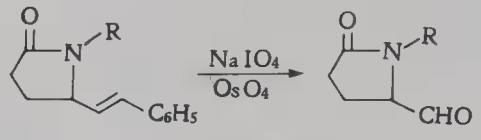
(ii) An interesting biologically active azaprostaglandine has been prepared by Barco *et al.*,[229] viz., 11-deoxy-8-aza prostaglandin E_1 (**71**) from pyroglutamic acid via synthon (**72**).[230,231] The synthesis of synthon (**72**) has been reported by two alternative approaches[232]—one starting from the ω-carbinol lactam (**73**) and the other starting with isoxazole acid (**74**).



In this synthesis osmium tetroxide converts **75** or **70** into the hydroxy lactam **73** (about 90% yield) in the presence of $NaIO_4$,[143]

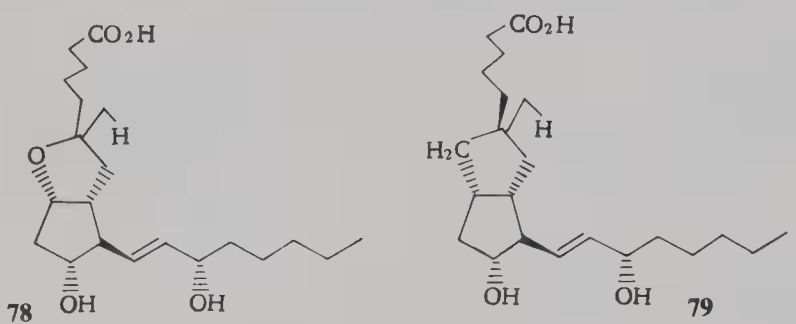


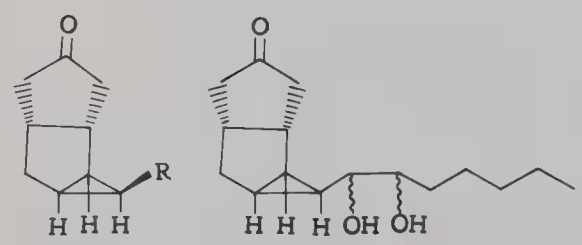
whereas in the second approach osmium tetroxide $NaIO_4$ converts **77** into **72**.



77 R=$(CH_2)_4CO_2Me$ **72**

(iii) A recently discovered metabolite prostacyclin [PGI_2(**78**)] from arachidonic acid is a potent inhibitor of human platelet aggregation and a relaxer of certain vascular tissues.[233,234] In the synthesis of 6a-carbaprostaglandin[235] I_2(**79**), which is stereoisomer of the naturally occurring prostacyclin [FGI_2(**78**)], compound **80** has been hydroxylated catalytically with osmium tetroxide in the presence of *N*-methyl-morpholine oxide dihydrate[136] to give the isomeric *cis* glycols (**81**) in quantitative yield.

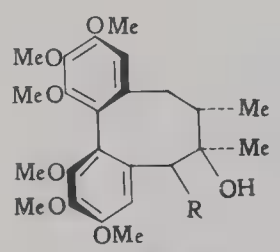




80 **81**

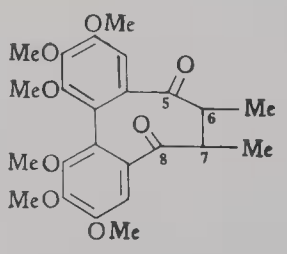
R, CH= CH C_5H_{11}

(iv) A bisbenzocyclo-octadiene Lignan[236] [±schizandrin] (**82**), the main biologically active Lignan component obtained from the fruits of *Schizandra Chinensis Baill*,[237,238] has been synthesized starting from the diketone **83**. In this synthesis the hindered double bond of **84** reacts with osmium tetroxide in pyridine to afford the diol **85** on attacking at the less hindered site.

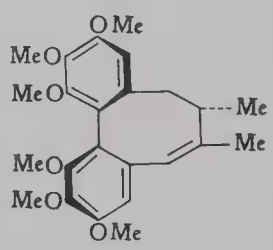


82 R=H

85 R=OH



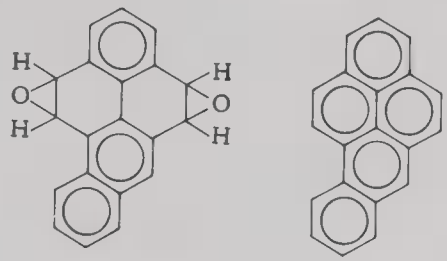
83



84

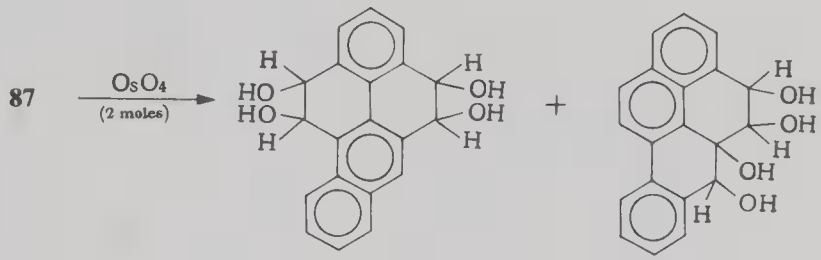
(v) David *et al.*[239] have used osmium tetroxide in the synthesis of 3-*O*-(2-acetamido-2-deoxy-α-D-galactopyranosyl)-D-galactose,[239] the terminal structure in the blood-group A.

(vi) Benzo[α] pyrene (BAP) is a potent carcinogen[240] and an environmental pollutant. The "K-region" diepoxide, 4,5:11,12-diepoxy-4,5:11,12-tetrahydrobenzo[α] pyrene (**86**) was synthesized through osmium tetroxide oxidation of the hydrocarbon **87**

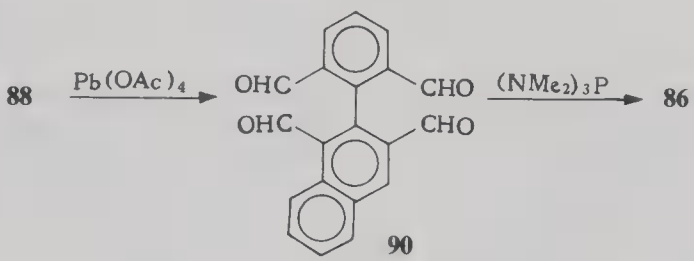


86 **87**

according to the scheme given below:



88 **89**

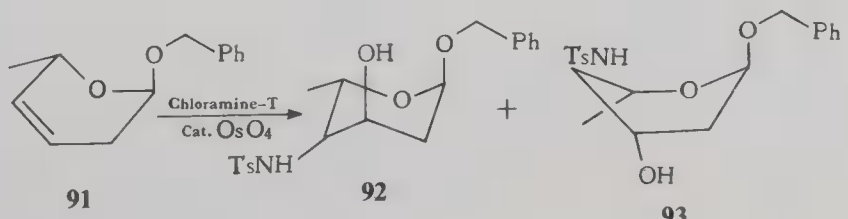


90

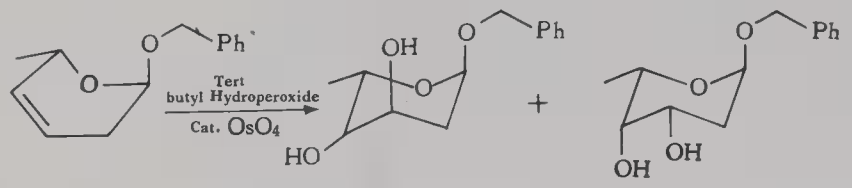
[K-region: double bonds in polycyclic aromatic hydrocarbons are regions of high electron density similar to that of the 9,10 bond of phenanthrene.]

(vii) Current *et al.*[241] have prepared *trans*-2-benzyloxy-3,6-dihydro-6-methyl-2H-pyran (**91**), which is a useful precursor of a number of the 2,6-dideoxyglycoside structures occurring in several natural products. For example adriamycin, a potent antileukemia drug, consists of the aglycone adriamycinone coupled to the 3-amino-2,3,6-trideoxy sugar daumosamine.

Hydroxyamination of **91** by chloramine-T, silver nitrate, and a catalytic amount of osmium tetroxide results in the formation of two isomeric compounds **92** and **93**, whereas **91** is also converted to the isomeric diols **94** and **95** by *tert*-butyl hydroperoxide, tetraethyl ammonium acetate, and a catalytic amount of osmium-tetroxide.



91 **92** **93**



91 94 95

(viii) The chemistry of osmium tetroxide has also attracted attention in the field of proteins and amino acids. Bahr[25] pointed out that certain amino acids are quite reactive with osmium tetroxide under mild conditions. Studies have been carried out to examine the oxidation of lysine, histidine, methionine, cystine, and tryptophan with osmium tetroxide.[37,242–246] Cross-linking[247,248] of proteins has been suggested during the reaction with osmium tetroxide. The liquefaction of protein gels upon long exposure to osmium tetroxide has also been observed due to peptide bond cleavage, which has been confirmed by Pollard *et al.*[245,249] Ford *et al.*[250] have shown that the reactivity of osmium tetroxide is greatly affected by certain ligands like pyridine. Very recently Deetz *et al.*[251] have reported the cleavage of peptide bonds and the pronounced effects of the ligand during a kinetic study of the reactions of osmium tetroxide with amino acids and proteins.

(ix) Midden *et al.*[42] have used osmium tetroxide with yeast $tRNA^{Tyr}$ to prepare its specific, single-site derivative where osmium is attached covalently to the isopentenyl adenosine residue at the side 3′ of the anticodon.

4. EXPERIMENTAL CONSIDERATIONS AND PROCEDURES

In this section an attempt is made to evaluate the various experimental conditions such as concentrations, temperature, pH, solvent, etc. in the light of oxidant, co-oxidant, and substrate for various types of reactions.

Osmium tetroxide is very toxic. Its vapor attacks the eyes and may cause temporary blindness, conjunctivitis, and corneal ulceration. It also attacks the nose, throat, and bronchial passages. Fortunately it has a characteristic and powerful odor. There is no evidence for cumulative poisoning by the compound. Since almost all the osmium compounds are very easily oxidized to the tetroxide, great care is necessary in working with them and a well-ventilated fume cupboard is essential. There are a number of reviews[253–256] on the toxicology of osmium.

4.1. Osmium Tetroxide in Alkaline Medium

Osmium tetroxide, a pale yellow solid of m.p. 40.6°C and b.p. 131.2°C, is the most common compound of osmium. It can be prepared by burning osmium metal[252] in air or by oxidation of osmium compounds of lower valency states with a wide variety of oxidizing agents; nitric acid is the most commonly used reagent for its synthesis.

Osmium tetroxide is moderately soluble in water, whereas in alkaline medium it exists as octahedral complexes[4–6,18] of the form *trans*-$OsO_4(OH)(H_2O)^{1-}$ and $OsO_4(OH)_2^{2-}$. At lower alkali concentration osmium tetroxide assumes the former and at higher alkali concentrations the latter structure. It can be represented as

$$OsO_4(OH)(H_2O)^{1-} + OH^- \rightleftharpoons OsO_4(OH)_2^{2-} + H_2O$$

When osmium tetroxide is dissolved in higher alkali concentration it forms $OsO_4(OH)_2^{2-}$ according to the following equation:

$$OsO_4 + 2OH^- \rightleftharpoons OsO_4(OH)_2^{2-}$$

4.2 Oxidation of Alkenes by Criegee's Method

4.2.1. In the Absence of Bases

According to Criegee's classical procedure alkenes[16–21] are treated with a stoichiometric amount of osmium tetroxide in an inert solvent (e.g., ether, dioxane, benzene, or cyclohexane) at room temperature and the mixture is allowed to stand at room temperature or cooled for several days or weeks. An osmic ester is formed which in some cases precipitates from the reaction mixture and in some other cases must be isolated by evaporation of the solvent. The osmic(VI) ester hydrolyzes in a reducing medium like alkaline formaldehyde or aqueous–alcoholic sodium sulfite giving *cis*-diol and osmium.

4.2.2. In the Presence of Bases[17,21,24–42]

The hydroxylation of flavone acetate is carried out in the following manner: 300 mg of flavone acetate is dissolved in 10 ml of dry benzene and to it is added a solution of osmium tetroxide, prepared by dissolving 195 mg of OsO_4 in a mixture of 2.80 ml of dry benzene and 0.30 ml of pyridine. The light yellow color of the solution darkens immediately, and after 10 min a precipitate appears. The mixture is kept at room temperature for about four days till all the solid is deposited. After this the whole content is diluted with 30 ml of ether and kept overnight. The solid is filtered off and washed with ether. It is then dissolved in 20 ml of ethylene dichloride and shaken with 10 ml of 2% aqueous potassium carbonate solution. The ether soluble part (flavone salt) when crystallized from ethyl acetate yields colorless crystals (m.p. 246–248°C).

4.3. General Procedure for the Cleavage of Osmate Esters

In order to prepare diols from alkenes,[96] 100 g (3.94 m mol) of osmium tetroxide is stirred with 3.9 mmol of an alkene dissolved in 15 ml of pyridine up to the appropriate time. While stirring this mixture a solution of 1.8 g of sodium bisulfite, 30 ml of water, and 20 ml of pyridine is added (sodium sulfite, water, and pyridine are kept in the ratio of 2:3:35 in the final mixture). In 30 min a clear orange solution is obtained. Chloroform is used to extract the product. This chloroform extract is dried over sodium sulfate or potassium carbonate. The solvent is evaporated *in vacuo* to yield the diol product. Tables I and II indicate the range of yields at varying conditions.

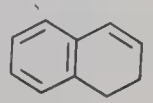
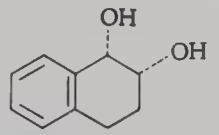
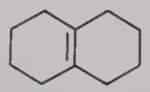
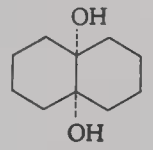
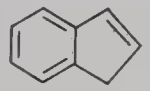
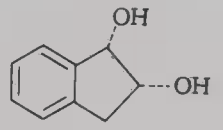
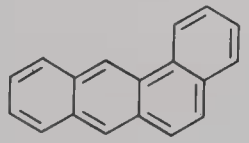
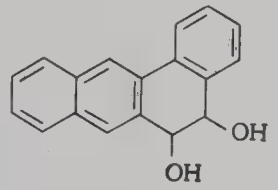
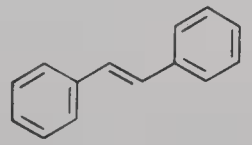
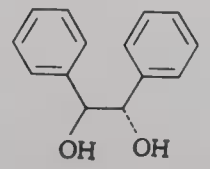
4.4. OsO_4-Catalyzed *cis*-Hydroxylation of Alkenes

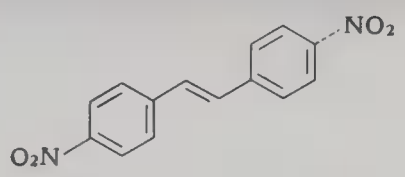
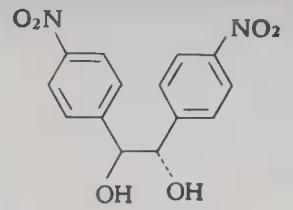
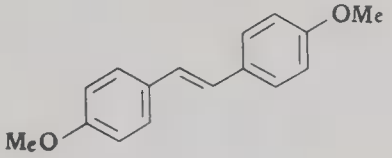
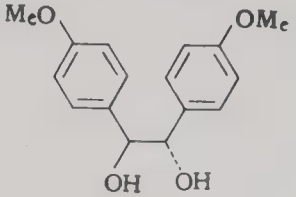
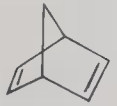
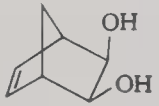
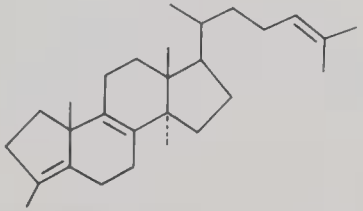
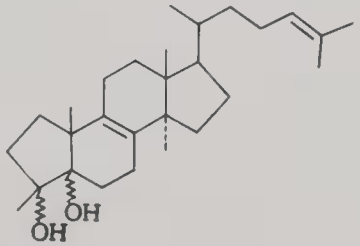
4.4.1. Oxidation of Cyclohexene with OsO_4/H_2O_2[102–108]

The H_2O_2 reagent is prepared as follows: to a mixture of 100 ml of pure *tert*-butyl alcohol and 25 ml of 30% hydrogen peroxide anhydrous sodium sulfate (or better, anhydrous magnesium sulfate) is added in small portions. Two layers separate. The alcohol layer, which contains most of the hydrogen peroxide, is removed and dried with anhydrous magnesium sulfate, followed by anhydrous calcium sulfate. The resulting liquid is a solution of 6.3% hydrogen peroxide in *tert*-butyl alcohol.

Cyclohexene (peroxide free, b.p. 81–83°C) (8.2 g) is mixed with 55 ml of the reagent and a solution of 15 mg of osmium tetroxide in anhydrous *tert*-butyl alcohol is added. The mixture is cooled to 0°C. The whole mass is kept overnight and the initial orange color disappears. The solvent and the unused cyclohexene are removed by distillation at atmospheric pressure. The residue is fractionated under reduced pressure. The fraction collected at b.p.

TABLE I. Noncatalytic *cis*-Hydroxylation of Alkenes in the Absence of Pyridine

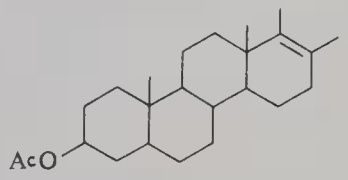
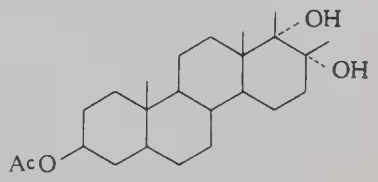
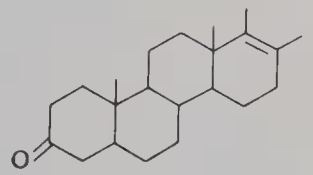
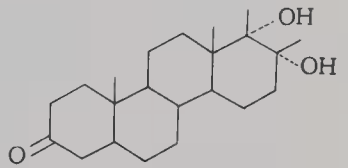
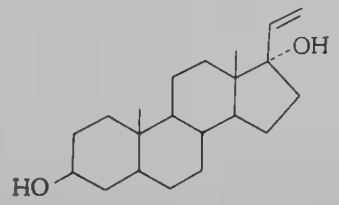
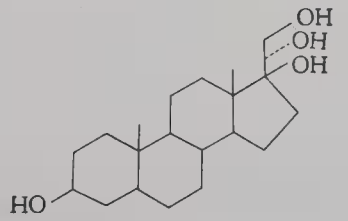
Substrate	Product	Yield (%)	Solvent, time[a]	Hydrolysis method	Reference
		78[b] (89)[c]	Diethyl ether, 24 h	Na_2SO_3	16
		81[b] (90)[c]	Diethyl ether, 24 h	Na_2SO_3	16
		66[b] (99)[c]	Diethyl ether, 24 h	Na_2SO_3	16
		—	Chloroform	—	69
		48[e]	Cyclopentane, 4 days, 20°C	$NaHSO_3$	70

		32	Dioxane, 5 days, 20°C	$NaHSO_3$	70
		37	Dioxane, 5 days, 20°C	$NaHSO_3$	70
		21	Diethyl ether	H_2S	71
		—	Diethyl ether, 24 h	$LiAlH_4$	65

[a] Conditions used for the preparation of osmium(VI) ester complex.
[b] *cis*-diol yield from corresponding osmium(IV) complex.
[c] In parentheses yield of osmium(VI) ester complex.
[d] Debromination using zinc metal.
[e] *cis*-diol (90%) in the presence of pyridine.

Table continued

TABLE I. *Continued*

Substrate	Product	Yield (%)	Solvent, time[a]	Hydrolysis method	Reference
		89	Dioxane, 10 days	H_2S	73
		76	Dioxane, 10 days	H_2S	73
		—	Diethyl ether, 96 h	Na_2SO_3	74

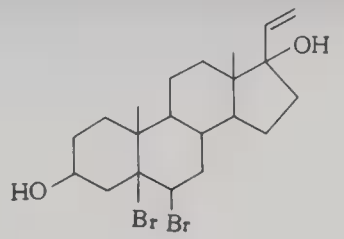
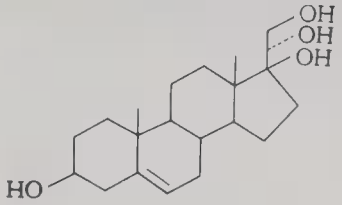
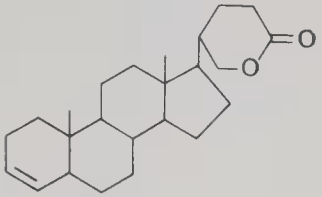
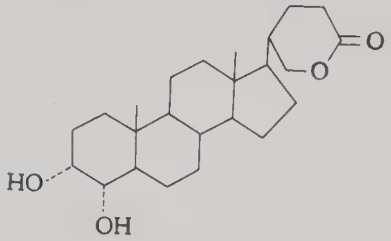
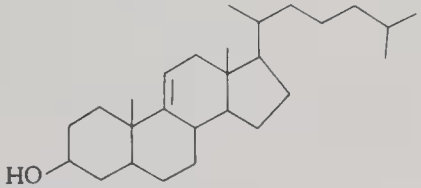
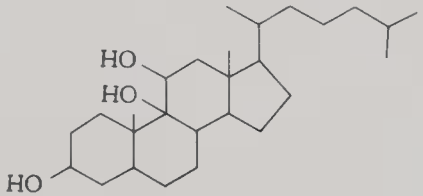
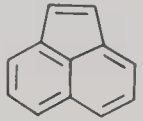
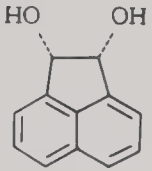
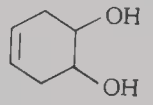
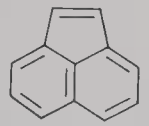
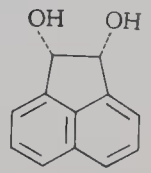
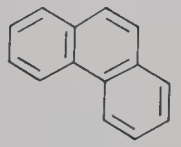
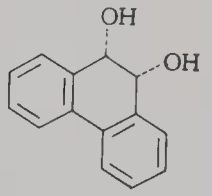
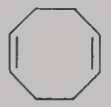
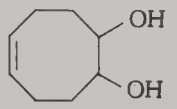
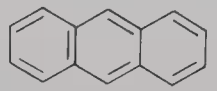
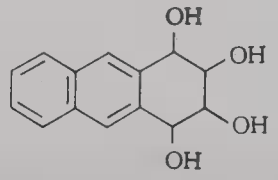
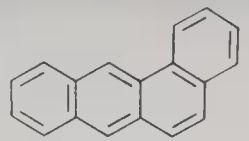
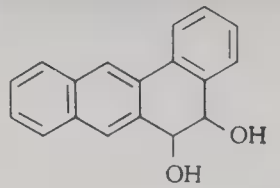
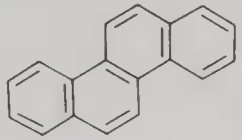
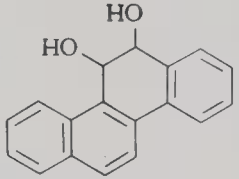
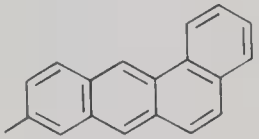
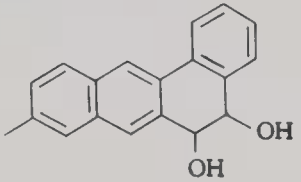
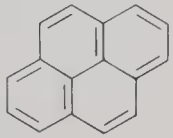
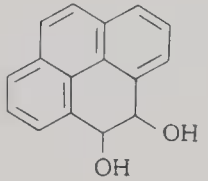
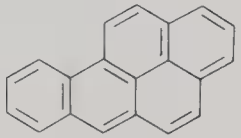
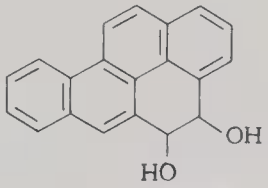
		69[d]	Diethyl ether, 90 h	Na_2SO_3	74
		84	Diethyl ether, 90 h	$NaHSO_3$	75
		60 (90)[c]	Diethyl ether, 48 h	Na_2SO_3	76
		84[b] (98)[c]	Diethyl ether, 24 h	Na_2SO_3	16

TABLE II. Noncatalytic *cis*-Hydroxylation of Alkanes in the Presence of Pyridine

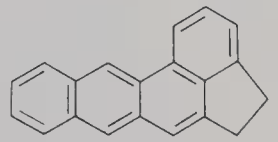
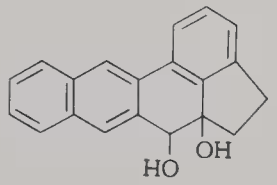
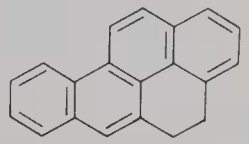
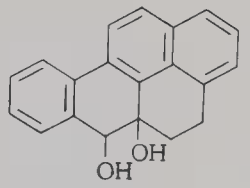
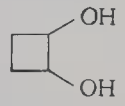
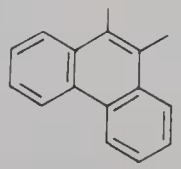
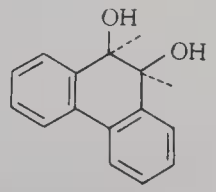
Substrate	Product	Yield (%)	Solvent, time[a]	Hydrolysis method	Reference
		100[b]	Diethyl ether, 30 min	KCO_3/KOH	17
		94[c]	Diethyl ether	Mannitol/KOH	17
		64[c]	Benzene, 2 days	Mannitol/KOH	17, 77–79
		14	Diethyl ether	H_2S	80
		76	Diethyl ether	Na_2SO_3	81
		—	Benzene, 1 week	Mannitol/KOH	78, 79

		—	Benzene, 2 days	Mannitol/KOH	78, 79, 82
		—	Benzene, 2 days	Mannitol/KOH	78, 79
		—	Benzene, 2 days	Mannitol/KOH	78, 79
		—	Benzene, 2 days	Mannitol/KOH	78, 79
		—	Benzene, 1 week	Mannitol/KOH	78, 79

[a] Experimental conditions used in the preparation of Os(VI) ester complexes.
[b] Osmium(VI) ester complex yield in parentheses.
[c] *cis*-diol yield from the corresponding osmium(VI) complex.

Table continued

TABLE II. *Continued*

Substrate	Product	Yield (%)	Solvent, time[a]	Hydrolysis method	Reference
		—	Benzene, 2 days	Mannitol/KOH	82
		52	Pyridine	$NaHSO_3$	83
			Pyridine, 8 days	$NaHSO_3$	84
		41 100[b]	Diethyl ether, 1.5 h,0°C	KOH	85
		79 100[b]	Benzene, 7 days	Na_2SO_3	85

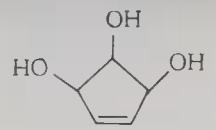
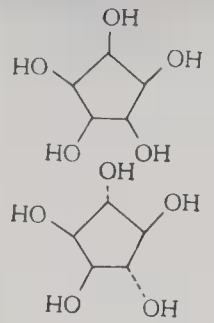
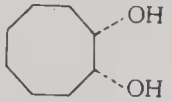
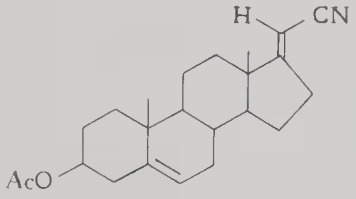
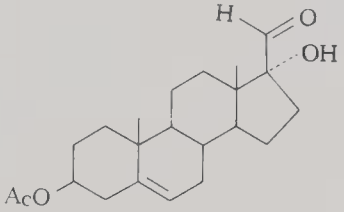
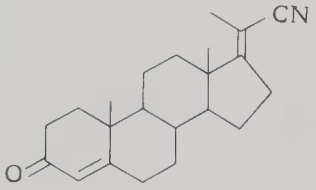
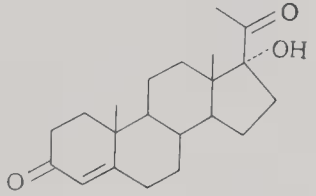
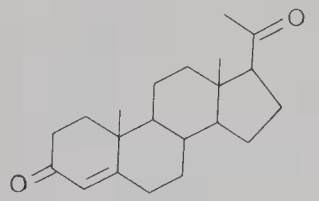
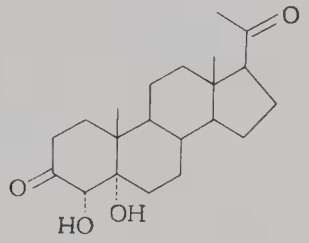
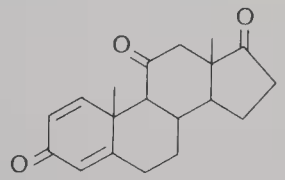
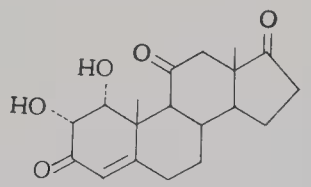
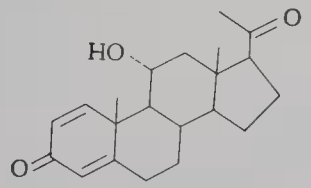
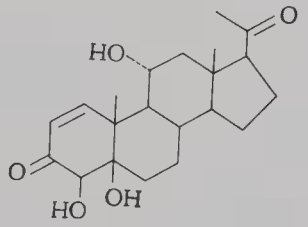
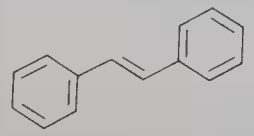
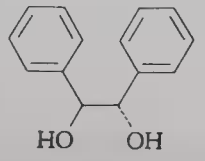
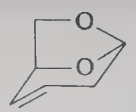
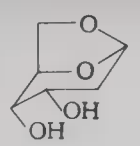
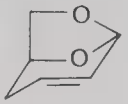
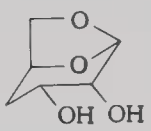
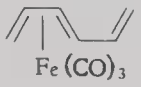
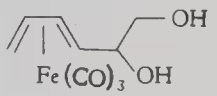
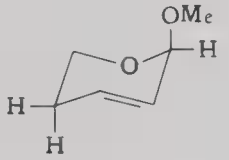
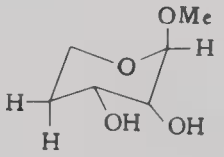
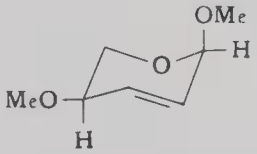
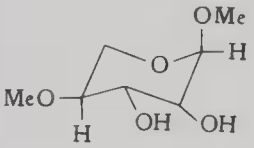
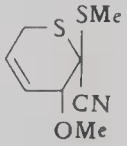
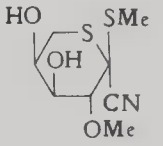
		35 17	Benzene, 3 days	H_2S	86
		38 93[b]	Diethyl ether, 24 h	Na_2SO_3	87
		19	Pyridine	$NaHSO_3$	88
		2	Pyridine	$NaHSO_3$	88

Table continued

TABLE II. *Continued*

Substrate	Product	Yield (%)	Solvent, time[a]	Hydrolysis method	Reference
		67	Dioxane, 18 h	$NaHSO_3$	89
		55	Pyridine	H_2S	90
		23	Pyridine	H_2S	90
		90	Cyclopentane	$NaHSO_3$	70

		92	Pyridine, 15 h	$NaHSO_3$	38
		87	Dioxane, 24 h	H_2S	38
		96	Pyridine, 15 h	$NaHSO_3$	38
		10	Pyridine, 23 h	Na_2SO_3	39
		93 73	Pyridine, 20 h —	$NaHSO_3$ $NaHSO_3$	41 41
		65	Pyridine, 21 h	$NaHSO_3$	72

120–140°C/15 mm solidifies immediately. This material is recrystallized from ethyl acetate. The yield of pure *cis*-1,2-cyclohexane-diol (m.p. 90°C) is 5.0 g (44%). Table III represents the *cis*-hydroxylation of some important alkenes by hydrogen peroxide.

4.4.2. Oxidation with OsO_4/Metal Chlorates

For the preparation of diols via *cis*-hydroxylation, metal chlorates[119–123] have been used as co-oxidants; barium chlorate is the most efficient, giving better yields. However, procedures involving potassium chlorates and silver chlorate are also given in this section.

4.4.2a. Oxidation of Crotonic Acid to Dihydroxybutyric Acid by Osmic Acid/Barium Chlorate. In this method barium chlorate is used in two ways:

I. Addition of the Total Quantity of Chlorate in One Operation. Barium chlorate (15.6 g) (25% excess) and 2.5 ml of osmic acid solution (1%) are added to 1 liter of water and then 20 g of crotonic acid is dissolved in this medium. The solution is kept at room temperature in the dark for an hour. Barium oxalate is separated by filtration. Again the filtrate from barium oxalate is extracted twice with 200 ml of benzene. The concentration of the water solution at reduced pressure results in a thin syrup. The syrup is dissolved in 1 liter of water and then, to remove all the volatile acids, the solution is distilled. The residue is dissolved in 300 ml of water and the excess of barium chlorate is reduced by passing through sulfur dioxide gas. Thus, the barium sulfate formed is removed by filtration and the filtrate is concentrated at reduced pressure to two-thirds of its volume. Barium hydroxide and silver oxide are used to remove completely sulfuric and hydrochloric acids.

The solution thus purified contains dihydroxy butyric acid and about 20% of chlorohydroxy butyric acid. After evaporation of the solvent and drying at 40°C/10 mm for several hours, the residue (22 g) is crystallized from ethyl acetate 20 ml (yield 8.4 g) (m.p. 73.5°C).

The mother liquor is diluted with ethylacetate to 50 ml and then shaken with 50 ml of water. This solution is evaporated under reduced pressure and the residue is dried and crystallized from ethyl acetate (yield 2.0 g) (m.p. 72.5).

Thus the total yield is 10.4 g of white crystals (m.p. 73°C) (38%). Recrystallization gives 9.4 g of *dl*-dihydroxybutyric acid (m.p. 74–74.5°C).

II. Gradual Addition of Chlorate during Oxidation. In the second method crotonic acid (20 g) is dissolved in 1 liter of water (which contains 5 ml of a 1% osmic acid solution). In this solution gradually 15.6 g of barium chlorate is added in three weeks in about 0.4 g lots on appearance of the brown color. Crotonic acid is completely oxidized in about four weeks. The reaction mixture is processed as discussed in (I). The yield of the oxidized product is 24.9 g and dihydroxy butyric acid is 13.5 g (m.p. 72°C) (45%).

4.4.2b. Oxidation of Crotonic Acid with OsO_4/Potassium Chlorate. In 1 liter of water 5 ml of a 1% osmic acid solution is mixed and then 20 g of crotonic acid is dissolved. In this medium potassium chlorate (12 g) is added gradually in about 0.5 g lots whenever the solution becomes brown. Decrease in the acidity (24%) is observed after four weeks when the oxidation is completed. Benzene is used to extract the solution and excess of potassium chlorate is reduced with sulfur dioxide gas. Barium hydroxide is used to precipitate the sulfuric acid as barium sulfate; potassium chloride remains in solution. The residue obtained after evaporation of water is dissolved into 20 ml of absolute alcohol and then about 600 ml of ethyl acetate is added until no more precipitation occurs.

Precipitate. The precipitate is treated with 150 ml of hot absolute alcohol and potassium chloride is removed during hot filtration. White crystals (10.5 g) are obtained on

cooling. The filtrate contains traces of chlorohydroxybutyric acid (m.p. about 104–106°C). The product is recrystallized from absolute ethanol.

In 400 ml of water 3 g of the double salt is dissolved and then 11 ml *N* sulfuric acid is added. The solution is then distilled to dryness at reduced pressure. The residue is dissolved in ethyl acetate in the usual manner. In two crops 2.0 g of crystals (74°C) of *dl*-dihydroxybutyric acid are obtained (60% theoretical).

Ethyl Acetate Solution. A residue (14.8 g) is obtained by the removal of ethyl acetate at reduced pressure which results in 3.2 g crystals (m.p. 73°C) from ethyl acetate. Chlorohydroxy butyric acid (20%) is obtained from the mother liquor.

4.4.2c. Oxidation of Crotonic Acid with Osmic Acid/Silver Chlorate. Crotonic acid (20 g) is dissolved in 1 liter of water containing 18.3 g of silver chlorate and 2.5 ml of a 1% osmic acid solution. The reaction mixture is cooled at room temperature. The solution turns milky and silver chloride gets precipitated.

A slight amount of bromine water is added to the sample after five days. A slight pressure in the flask develops at the end of the oxidation. The silver chloride is removed by filtration (silver oxalate is also obtained in small amounts). The filtrate is extracted with benzene and evaporated at reduced pressure. The crystals obtained are dissolved in water. After evaporation of the water the residue is treated with 100 ml absolute alcohol and the crystals are separated by filtration (4.5 g of silver salt of dihydroxy butyric acid).

This salt (8 g) obtained from the 20 g of crotonic acid in different experiments is dissolved in water and the calculated amount of hydrochloric acid is added. The residue (4.0 g of syrup) gives 3.1 g crystals (m.p. 74°C).

Alcoholic Solution. At reduced pressure the alcoholic solution is evaporated, the residue is treated with ethyl acetate, and the solution is filtered. The filtrate is distilled to dryness. A pale yellow syrup (23 g) gives 12.8 g of crystals (m.p. 74°C) in two crops from ethyl acetate (total yield was 54% of the theoretical). The mother liquor contains about 5% of the crotonic and chlorohydroxy butyric acid.

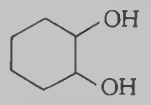
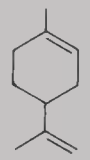
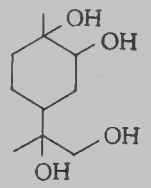
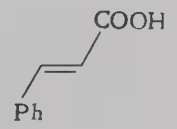
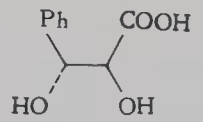
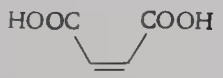
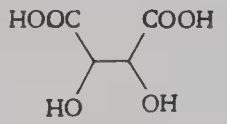
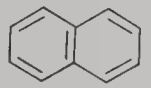
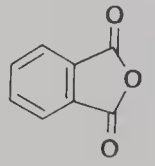
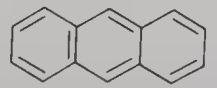
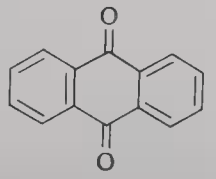
In other cases when the silver salt is not removed, the oxidation takes about two weeks, and when some more silver chlorate is used (20 g silver chlorate and 20 g crotonic acid), the yield of dihydroxy butyric acid increases to 60%.

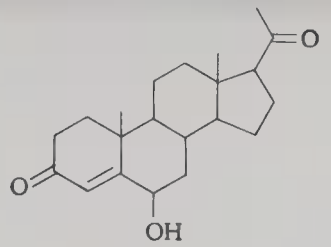
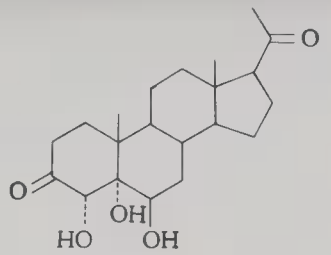
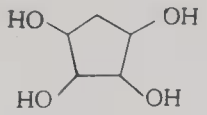
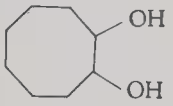
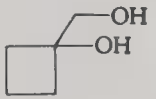
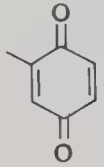
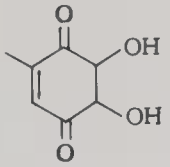
4.4.2d. Oxidation by Gradual Addition of Silver Chlorate. In this method again 20 g of crotonic acid is dissolved in 1 liter ice-water containing 10 ml of a 1% osmic acid solution. Crystallized silver chlorate (18 g) is added in four weeks keeping the solution in ice-water in the following manner. The oxidation in the beginning will be fast and only 0.5 g chlorate is added in the first instance. The milky solution obtained in a few minutes turns brown in 3 h. After this 1 g of chlorate in 0.5-g portions is added on every succeeding day for about two weeks. The oxidation becomes slower and 0.5 g chlorate is added when the solutions turns yellow. In the end the reaction mixture is left at room temperature for a number of days. When the solution remains colorless after addition of 18 g of chlorate this indicates that the substrate is completely oxidized. During this process the initial acidity remains the same and a trace of chlorinated compound is obtained. Silver chloride (13.15 g) is obtained after filtration and washing with dilute hydrochloric acid. A very small amount of oxalic acid also separates from the hydrochloric acid filtrate.

The solvent is evaporated under reduced pressure and the excess of silver chlorate is reduced by sulfur dioxide in the usual manner. A colorless viscous syrup (26.7 g) is obtained. The yield of dihydroxybutyric acid crystallized from ethyl acetate in three crops is 23.05 g (m.p. 74°C) (about 82%).

Recrystallization from 40 ml of ethyl acetate gives 20.8 g of pure material (m.p. 74.5–75°C) and 2.7 g ofcrude substance (about 78%). Table IV represents the data on metal chlorates.

TABLE III. Osmium Tetroxide-Catalyzed *cis*-Hydroxylation of Alkenes in the Presence of Hydrogen Peroxide

Substrate	Product	Yield (%)	Solvent, time	Reference
		58	*t*-BuOH, 12 h, 0°C	103
		35	*t*-BuOH, 12 h, 10–15°C	103
		56	*t*-BuOH, 12 h, 0°C	102
		30	*t*-BuOH, 12 h, RT[a]	102
		—	acetone/*t*-BuOH, 18 days	110
		58	acetone/*t*-BuOH, 4 months	110

		35	*t*-BuOH, 9 days, RT	89
		61	*t*-BuOH, 3 days, 0°C	111
		11	*t*-BuOH, 42 h, 0–5°C	112
		39	*t*-BuOH, 2 days, 0°C	113
		66	water/dioxane, 4 h, 25°C	114

[a] RT, Room temperature.

Table continued

TABLE III. *Continued*

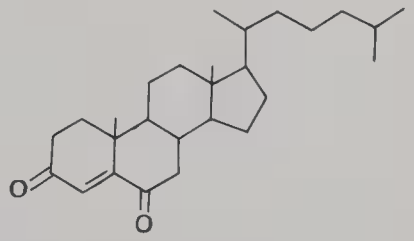
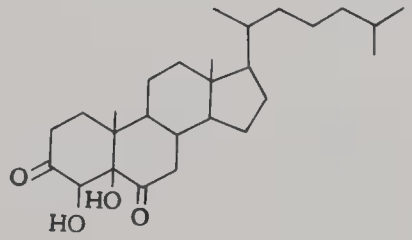
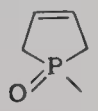
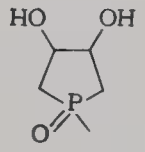
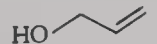
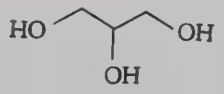
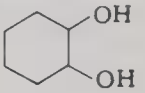
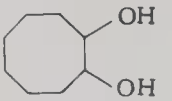
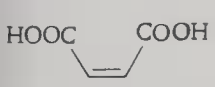
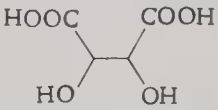
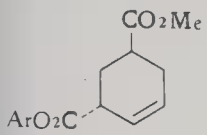
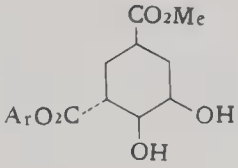
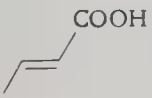
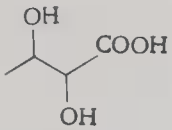
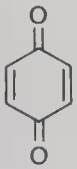
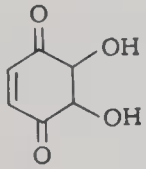
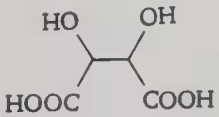
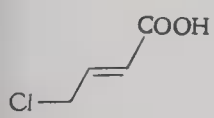
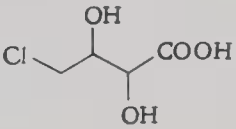
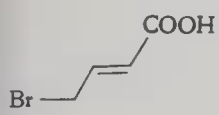
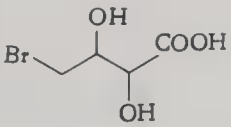
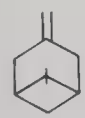
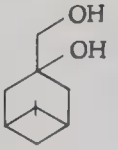
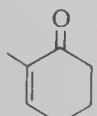
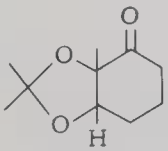
Substrate	Product	Yield (%)	Solvent, time	Reference
		—	diethyl ether, 12 h, RT	115
		100 67	water, 50°C water, 1.5 h	116 117
		60 56, 68, 100	*t*-BuOH, 3 h *t*-BuOH, 2 h, 70°C; 2 days, RT; 1 h, RT	102 118

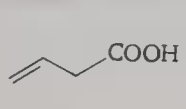
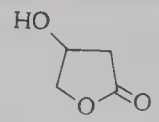
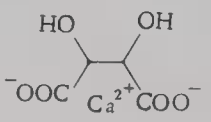
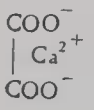
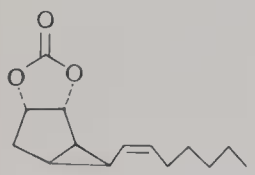
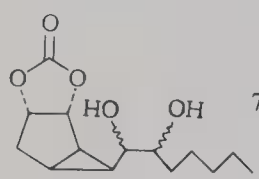
TABLE IV. Osmium Tetroxide-Catalyzed *cis*-Hydroxylation of Alkenes in the Presence of Metal Chlorates

Substrate	Product	Yield (%)	Conditions	Reference
		76	$NaClO_3$, water, 11 h, 50–55°C	117
		46	$NaClO_3$, water, 9 h, 50°C	124
		30	$NaClO_3$, acetic acid, water, *t*-BuOH, dioxane, 74 h, 80°C	112
		98	$NaClO_3$, water, 7–10 h, 40–50°C	125
		84–88	$NaClO_3$, water RT	122
		38,[a] 83	$AgClO_3$, water, 2 weeks, 0°C–RT	120
		50	$NaClO_3$, 54 h, RT, aqueous 1 NHCl	126
		49	$NaClO_3$, 110 h, 50°C, aqueous 1 NHCl	127
		78	$Ba(ClO_3)_2$, water, 32 h	128
		75	$Ba(ClO_3)_2$, water	129
		70	$Ba(ClO_3)_2$, water, 24 h	130
		50	$NaClO_3$, 4 h, diethyl ether/ dioxane/water	131
		65	$Ba(ClO_3)_2$, tetrahydrofuran/water, 10°C	123

[a] Catalytically oxidized with barium chlorate.

Table continued

TABLE IV. *Continued*

Substrate	Product	Yield (%)	Conditions	Reference
		35	$Ba(ClO_3)_2$, water, 3 days, 35°C	129
Pyromucic acid		—	$NaClO_3$, water, 60 h, 50°C	127
				
		75	$NaClO_3$, tetrahydrofuran, water	136

4.4.3. *Oxidation of Octene to Threo-4,5-dihydroxy Octane with OsO_4/tert-Butyl Hydroperoxide*[132–134]

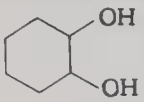
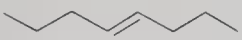
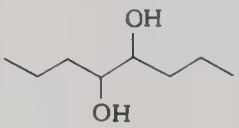
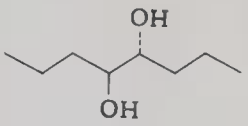
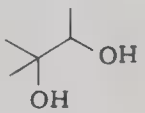
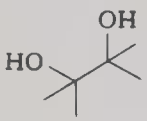
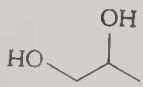
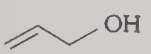
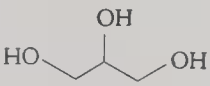
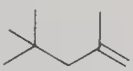
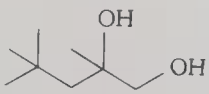
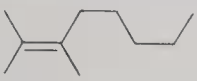
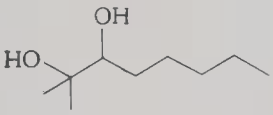
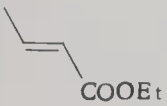
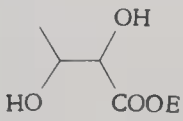
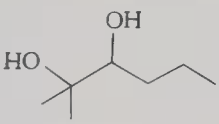
A mixture containing acetone (200 ml), (E)-4-octene (11.2 g, 100 mmol), $Et_4NOAc \cdot 4H_2O$* (25 mmol), and 18 ml of 90% *tert*-butyl hydroperoxide is stirred at room temperature in a 1-liter Erlenmeyer flask stirrer, until the Et_4NOAc is completely dissolved. The resulting solution is cooled in an ice bath, and then 10 ml (50 mg or 0.2 mmol OsO_4) solution of osmium tetroxide in *tert*-butyl alcohol is added in one portion. The solution at once becomes brownish purple. After 1 h the reaction mixture is brought to room temperature and stirred overnight keeping the stopper loose. To the resulting mixture 400 ml of ether is added while stirring in an ice bath. Then 50 ml of freshly prepared 10% sodium bisulfite is added in one portion. The organic layer becomes colorless when brought to room temperature. After stirring for 1 h the aqueous layer is saturated with sodium chloride and the organic layer is separated and washed with brine. The combined aqueous layers are extracted twice with 10 ml of ether and dried on evaporation of the solvent. The residue (an oil) is distilled, resulting in 11.8 g (81%) of threo-4,5-dihydroxyoctane. The results are listed in Table V.

4.4.4. *Oxidation of Cyclohexene to cis-Cyclohexane-1,2-diol with OsO_4/N-Methyl Morpholine*[136–139] *N-Oxide*

N-methyl morpholine-*N*-oxide (18.2 g), 50 ml water, 20 ml acetone and 0.8 g osmium tetroxide in 8 ml *tert*-butyl alcohol is mixed and then 10.1 ml (10 ml mol) distilled cyclohexene is added. The reaction mixture is maintained at room temperature and stirred overnight under nitrogen. Sodium hydrosulfite (1 g), magnesium silicate (12 g), and 80 ml of water are added and then the Mg silicate is filtered. Sulfuric acid (1 *N*) is used to neutralize the filtrate to pH 7. The acetone is evaporated under vacuum and the pH is adjusted to 2. The solution is saturated with sodium chloride and extracted with ethyl acetate. The aqueous phase is concentrated by azeotropic distillation with *N*-butanol and further extracted with

* Et_4NOAc can be generated *in situ* from Et_4NCl and anhydrous NaOAc in acetone.

TABLE V. Osmium Tetroxide Catalyzed *cis*-Hydroxylation of Alkenes in the Presence of *tert*-Butyl Hydroperoxide

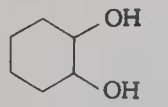
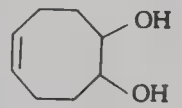
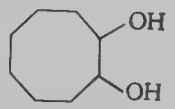
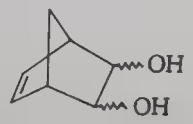
Substrate	Product	Yield (%)	Conditions	Reference
		62	*t*-BuOH/ET_4NOH	132
		52, 45, 51	Acetone/ET_4NOH	133
		73	*t*-BuOH/ET_4NOH	132
		81, 78, 74	Acetone/ET_4NOAc	133
		61 63 72	*t*-BuOH/ET_4NOH *t*-BuOH/ET_4NOH *t*-BuOH/ET_4NOH	132 132 132
		—	—	135
		—	—	135
		—	—	134
		69	*t*-BuOH/Et_4NOH	132
		58, 71, 72	Acetone/Et_4NOAc	130
		67	*t*-BuOH/Et_4NOH	132

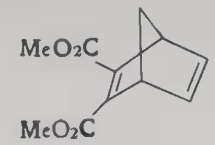
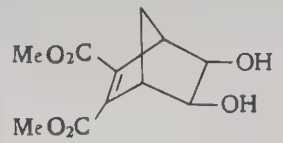
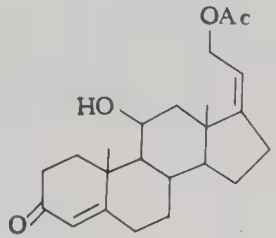
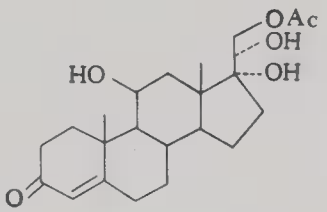
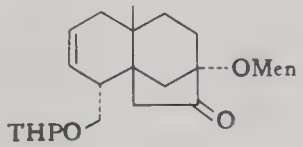
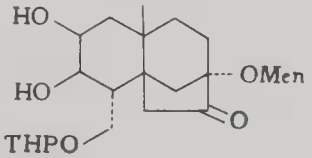
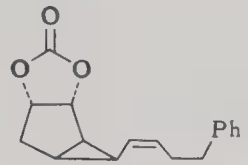
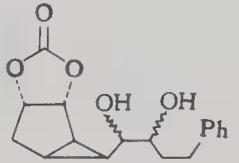
ethyl acetate. The combined ethyl acetate layers are dried and evaporated yielding 11.2 g of a crystalline solid (96.6%). After recrystallization from ether 10.6 g (91%) *cis*-1,2-cyclohexene diol (m.p. 95–97°C) is obtained. The detailed results are given in Table VI.

4.4.5. Oxidation of Cyclohexene to Adipaldehyde with OsO_4/Sodium Periodate

To a mixture containing ether (15 ml), water (15 ml), cyclohexene (0.405 g), and osmium tetroxide (65.4 mg) finely powdered sodium metaperiodate[140–141] (2.32 g) is gradually added in 40 min under stirring. During the reaction period the temperature is maintained at 24–26°C. After 80 min the initially dark reaction mixture changes to pale

TABLE VI. Osmium Tetroxide Catalyzed *cis*-Hydroxylation of Alkenes in the Presence of *N*-Methylmorpholine *N*-Oxide

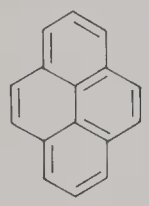
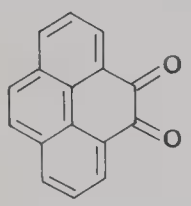
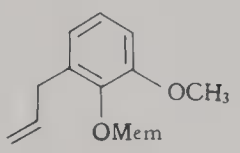
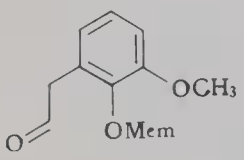
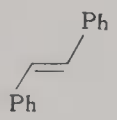
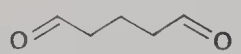
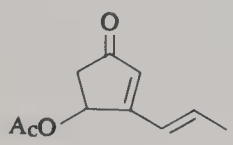
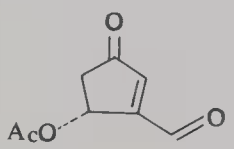
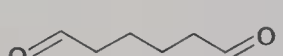
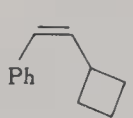
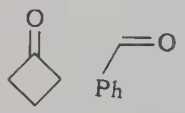
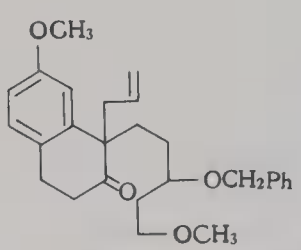
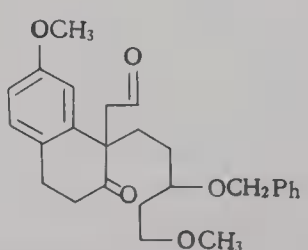
Substrate	Product	Yield (%)	Conditions	Reference
		91	Aqueous acetone/*t*-BuOH	136
		31	Aqueous acetone/*t*-BuOH	136
		79	Aqueous acetone/*t*-BuOH	136
		25	Aqueous acetone/*t*-BuOH	136

		—	—	139
		78	10:3:1 *t*-BuOH/tetrahydrofuran/water	133
		89	1:2.5 Water/acetone, 80 h, 23°C	138
		95	Aqueous acetone/*t*-BuOH	136

yellow and a considerable amount of sodium iodate separates. The mixture is extracted thoroughly with diethyl acetate. The combined organic layer is filtered through a small amount of sodium sulfate. The solution is then treated with 2,4-dinitrophenyl hydrazine (2.5 g) and 5 drops of concentrate hydrochloric acid. After 1 h the immediately precipitated yellow product is separated and washed with ethyl acetate and ether (1.81 g) (77% yield). Adipaldehyde bis-2,4-dinitro-phenyl hydrazone is obtained as yellow needles after repeated recrystallization of the sample by nitromethane.

Similar procedures can be used with other alkenes, only other solvent systems may be needed. The data obtained with various alkenes are given in Table VII.

TABLE VII. Osmium Tetroxide-Catalyzed Oxidation of Alkenes in the Presence of Sodium Periodate

Substrate	Product	Yield (%)	Conditions	Reference
		10, 23	—	142
		74	3:1 Tetrahydrofuran/ water, 2 h, 0–23°C	138
		85	Dioxane/water	143
		76	Diethyl ether/water	143
		86	Acetone/water	144
		77	Diethyl ether/water	143
		—	Dioxane/water, 25°C	145
		97	Tetrahydrofuran/water	140

4.5. Oxidation of Alkenes by Imido Reagent[169–174,178]

4.5.1. Preparation of Tert-Butyl Imido/Osmium Reagent.

In the preparation of *tert*-butyl-imido reagent (46a), 10.0 g (39.4 mmol) osmium tetroxide and 50 ml olefin free pentane are stirred in a 200-ml flask, till most of the osmium tetroxide dissolves. Then 4.2 g (39.5 mmol) *tert*-butylamine is added. The contents start to boil owing to the rapid exothermic reaction and a large mass of red-orange crystals settle at the bottom of the flask. The solvent is removed under reduced pressure after stirring the mixture for 30 min. Care must be taken because the solid is volatile and hence the vacuum should be maintained for only a small interval of time. At room temperature the content is kept up to 16 h in the dark (overnight). A yellow solid (91%) is obtained (*t*-butylimido-OsO_3).

A similar procedure is adopted for the preparation of 1-adamantylimido (**46b**) and 2-methyl-2-butyl-imido (**46c**) with the following amount of solvents and reagents: 1-admantyl-imido, 6.0 g (23.6 ml) OsO_4, 15 ml olefin free methylene chloride, 3.57 g (23.6 mmol) admantyl amine, in 75 ml methylene chloride, 30 ml pentane, time 6 h, yield 91% (yellow solid); 2-methyl-2-butyl imido (**46c**), 5.0 g (19.6 mmol) OsO_4, 20 ml olefin free pentane, 2.30 ml (19.6 mmol) *tert*-amylamine, time 18 h, yield 87% (yellow solid).

4.5.2. Oxyamination of Olefins—General Procedure

One equivalent of olefin is stirred with a catalytic amount of tri-oxo (alkylimido) osmium(VIII) 0.1 *M* solution in olefin free methylene chloride or pyridine. The reaction mixture becomes dark at rates depending on the olefin. The reaction mixture is kept in the dark for 12 h to 2 days depending on the olefin. The cleavage of the resulted osmate ester is carried out by one of the following methods.

4.5.2a. Bi-sulfite Method. To each millimole of osmate ester, 10 ml of pyridine and a solution of 0.5 g of sodium bisulfite in 8 ml of water are added. The reaction mixture is kept for at least 12 h at room temperature while stirring. Sometimes when the reaction is slow a better result might be obtained at 60–80°C. The aminoalcohol product derived from the olefin is extracted with 40 ml of chloroform per millimole of osmate ester and then twice with 12 ml of chloroform. Table VIII gives the comparative yields.

4.5.2b. Lithium Aluminum Hydride Method. The brownish-black osmate ester is dissolved in anhydrous ether and cooled in an ice bath under nitrogen. Ten equivalents of $LiAlH_4$ are added to 25 ml mmol of osmate ester while stirring. The reaction mixture is processed according to the following procedures. For every gram of $LiAlH_4$, an equal amount of water is slowly added to the reaction mixture. To the above solution again the same amount of 15% aqueous sodium hydroxide is added slowly, followed by three times this amount of water. In order to get the maximum yield the whole mass is stirred at least for 12 h; thereafter the mixture is filtered. The residue of osmium and aluminum salts is washed with anhydrous ether. Table VIII indicates the yield.

4.6. Oxidation of Alkenes by OsO_4/Chloramine-T

4.6.1. Phase Transfer Method[180–183]

One millimole of olefin, 5 ml chloroform, 0.50 ml (0.01 mmol) of osmium tetroxide, 352 mg (1.25 mmol) chloramine-T trihydrate, 11.4 mg (0.05 mmol) of benzyl triethyl ammonium chloride, and 5 ml of distilled water are kept in a 25-ml one-neck round-bottomed flask, equipped with magnetic stirrer and a reflux condenser. The whole mixture is

TABLE VIII. Amino Alcohols from Alkylimidoosmium Compounds

Olefins	Product (amino alcohol)	Percent yield: Diol	Percent yield: Amino alcohol
Cyclohexene	*cis*-2-(*tert*-Butylamino) cyclohexanol	—	85[a]
Cyclohexene	*cis*-2-(1-Admantylamino) cyclohexanol	—	79[a]
1-Phenyl cyclohexene	2-(*tert*-Butylamino)-1-phenyl cyclohexanol	8	65[a]
1-Methyl cyclopentene	2-(*tert*-Butylamino)-1-methyl cyclopentanol	—	66[a]
1-Decene	n-$C_8H_{17}(OH)CHCH_2NH(t\text{-Bu})$	6 <1	63[b] 89[a]
Styrene	$C_6H_5CHOHCH_2NH(t\text{-Bu})$	Trace	37[b]
α-Methylstyrene	$Ph(Me)C(OH)CH_2NH(t\text{-Bu})$	<1	93[b]
α-Methylstyrene	$Ph(Me)C(OH)CH_2NH$(1-admantyl)	<1	62[b]
1-Phenyl-2-methyl propene	$PhCHNH(t\text{-Bu})C(OH)Me_2$	0	88[a]
2-Methyl-1-tridecene	n-$C_{11}H_{23}(Me)C(OH)CH_2NH(t\text{-Bu})$	<1	82[b]

[a] In pyridine.
[b] In CH_2Cl_2.

heated in an oil bath at 55–60°C. The mixture is constantly stirred and the progress of the reaction is tested by the disappearance of olefins with TLC or GLC. When the reaction is completed, sodium bisulfite (104 mg or 1 mmol) is added and the mixture is refluxed for 3–6 h to effect the reductive cleavage of the trace of osmate esters. After reduction is completed two phases separated. The flask and separatory funnel are washed with 10 ml of chloroform. The combined organic phase is washed with saturated brine solution containing 1% sodium hydroxide till the $TsNH_2$ is extracted, usually once or twice. A clear yellow solution is obtained by treating again with saturated brine and drying with $MgSO_4$. Crude β-hydroxy-*p*-toluene sulfonamide is obtained on concentration. The crude product is purified by crystallization.

Procedure A has also been performed without difficulty on a 1 mol scale. For convenience, the large-scale reactions are performed five times more concentrated (with respect to both $CHCl_3$ and H_2O phases and OsO_4 catalyst solution). Thus, cyclohexane 82.2 g (1 mole) resulted in 205 g (76%) pure oxyaminated product. In this case the product derived from cyclohexene is crystalline and begins to crystallize if the chloroform phase is allowed to cool. Hence phases are separated while the solution is slightly hot. This problem does not arise in the dilute procedure. The results are given in Tables IX and X.

4.6.2. Tert-Butyl Alcohol Method

The olefin (1 mmol), 5 ml of *tert*-butyl alcohol, 0.50 ml (0.01 mmol) of osmium tetroxide catalyst solution, and 352 mg (1.25 mmol) of chloramine-T trihydrate are stirred in a 10-ml one neck round-bottomed flask at 55–60°C. Chloramine-T is only slightly soluble under these conditions. Olefin consumption is tested by TLC or GLC. When all olefin has reacted, 11.1 mg (0.03 mmol) of sodium borohydride is added with constant stirring for 1 h at room temperature. The reaction mixture is concentrated (rotary evaporator) to remove solvent *tert*-butyl alcohol. The residue is extracted with 20 ml of methylene chloride. The

resulting solution is washed with saturated brine containing 1% sodium hydroxide until the whole of $TsNH_2$ is extracted (usually once or twice) and once with saturated brine and dried (over $MgSO_4$) to result in a clear yellow solution. Crude β-hydroxy-*p*-toluene-sulfonamide is obtained after concentrating the solution. The crystallization results in the purification of the crude product.

This procedure has also been performed with 1 mole at five times the concentration described above for the 1 mmol experiments. In this case the problem of crystallization as it was observed in procedure A does not arise. The pure oxyamination product 198 g (65%) was obtained from 118.2 g (1 mole) of α-methylstyrene. The detailed results are given in Tables IX and X.

4.7. Oxidation of Alkenes by OsO_4/*N*-chloro-*N*-argento Carbamates[181,182,187]

N-chlorosodiocarbamate 1,5 mmol, 0.51 g (3 mmol) silver nitrate, and 10 ml of reagent grade acetonitrile are mixed in a 25-ml round-bottomed vessel. A slightly yellow suspension results at room temperature after stirring the mixture for more than five minutes. 81 ml (4.5 mmol) of water, 1 mmol of olefin, and 2.54 mg (0.01 mmol) of osmium tetroxide in *tert*-butyl alcohol are added to the yellow suspension. The brown milky suspension is stirred for several hours at room temperature (depending upon the olefin consumption). The presence of olefin is tested by TLC or GLC. In order to precipitate the remaining silver ion, 0.25 ml (1.5 mmol) of saturated sodium chloride solution is added and the solid sodium chloride is removed by filtration. The filtrate, thus obtained, is refluxed with 4 ml of 2.5% aqueous sodium bisulfite for 3–6 h. The final mixture, thus obtained, is concentrated and the aqueous residue is extracted with three 10-ml portions of methylene chloride. The organic phase is

TABLE IX. Osmium Tetroxide-Catalyzed Oxidation of Alkenes by Chloramine-T

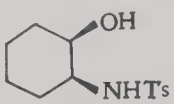
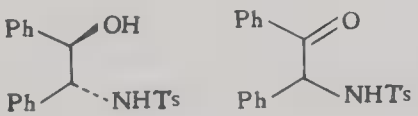
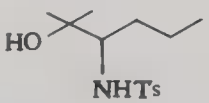
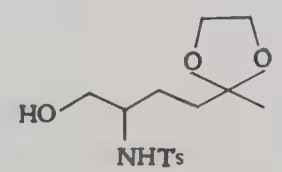
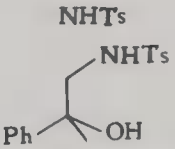
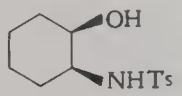
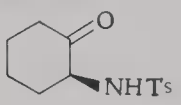
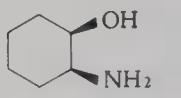
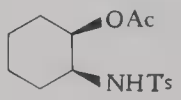
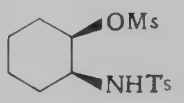
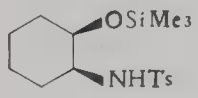
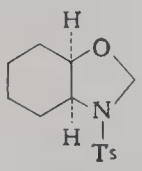
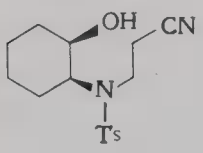
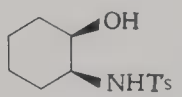
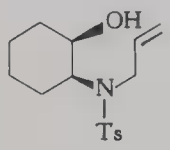
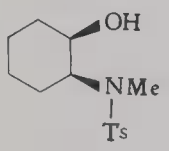
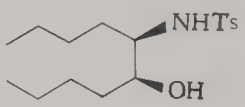
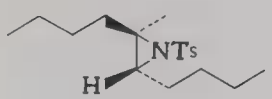
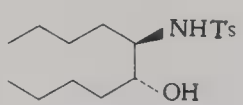
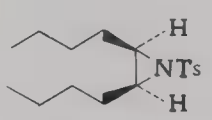
Substrate	Product	Yield (%)	m.p. (°C)	Reaction time (h)
1-Decene		62, 16	55–57	12
Cyclohexene		75	158	12
E-Stibene		71, 9	148, 142	12
2-Methyl-2-hexene		67	103	24
2-Methyl-2-hepten-6-ethyleneketal		83	100	24
α-Methylstyrene		65	95	16

TABLE X. Transformations of the Hydroxysulfonamides of Cyclohexane

Substrate	Product	Yield (%)	Experimental conditions
		100	Acetone, RT
		97	Liquid ammonia, sodium, 1 h
		100	Acetic anhydride, ethylacetate, 5 h
		98	Triethlamine in THF, methanesulfonyl chloride, 1 h, 0–20°C
		100	Hexamethyldisilazane in THF, 15 h, RT
		95	Formaldehyde in HCl and ethanol, 1 h, refluxed
		75	Dioxane, KOH, acrylonitrile, 5 h, refluxed
		98	Allylbromide, K_2CO_3, refluxed in acetone, 15 h
		87	Potassium *tert*-butoxide, methyl iodide, 70°C, 15 h
		93	THF triethylamine, methanesulfonyl chloride, 0°C
		90	THF, triethylamine, methanesulfonyl chloride, 0°C

dried with $MgSO_4$ and crude hydroxy carbamate results after concentration. The regioisomers are separated by silica gel chromatography. The crude product is purified by recrystallization. The results obtained with various metals are given in Table XI.

4.8. Oxidation of Alkynes[81]

4.8.1. Preparation of Osmium Tetroxide–Amine Adducts

Osmium tetroxide (1 g) is added in an aqueous solution or emulsion of amine. The solution is stirred for five minutes and the yellow or orange product is filtered off. Good yields (70%–90%) are obtained on washing with water and drying *in vacuo*. With hexamethylene tetramine ($C_6H_{12}N_4$) and quinuclidine crystalline products are obtained from carbon tetrachloride as bright red needles and platelets, respectively.

4.8.1a. Osmium (VI) *Esters from Alkynes.* A solution of diphenyl-acetylene (0.13 g) in ether or THF is added dropwise to the solution of $OsO_4 \cdot C_5H_5N$ (0.5 g) in ether or tetrahydrofuran (THF) with constant stirring. A brown product (45%) is filtered after 5 min, washed with ether, and dried in vacuum.

A similar procedure is adopted with isoquinoline.

4.8.1b. Hydrolysis of the Complex $Os_2O_4(O_4C_{14}H_{10})(NC_5H_5)_4$ *to Benzil.* The complex (0.6 g) and ethanol are mixed with a solution of sodium sulfite (1 g) acidified with HCl to pH 7.3. The liquid is allowed to cool after refluxing for 3 h. The precipitate of the osmium complex is filtered and the filtrate is continuously extracted with ether. The extract is dried over $MgSO_4$, evaporated *in vacuo*, and benzil is obtained in 65% yield.

4.8.2. Catalytic Oxidation of Diphenylacetylene

To osmium tetroxide (0.05 g) and 1.5 g of potassium chlorate a solution of 0.67 g diphenylacetylene in *tert*-butyl alcohol (10 ml), acetone (10 ml) and water (3 ml) is added while stirring. The reaction mixture is cooled after refluxing at 56°C for 24 h and extracted with ether (3×20 ml). Pure benzil (79%) is obtained by the usual working up procedure. In Table XII some of the hydrolysis products are listed.

4.9. Oxidation of Dienes

In the case of dienes[80,81] all experiments are performed in a dry nitrogen atmosphere since the products are hydroscopic.

TABLE XI. Reactivity of Styrene with Different Ethyl *N*-chloro-*N*-metallocarbamates

Metallic salts	Reaction time (h)
$Zn(NO_3)_2$, $ZnCl_2$, $CdCl_2$	10–20
$Cu(OAc)_2$, $Cd(OAc)_2$, $Zn(OAc)_2$, $Cd(NO_3)_2$, $AgNO_3$	5–10
$Hg(OAc)_2$, $HgCl_2$, $Hg(NO_3)_2$	<2

TABLE XII. Hydrolysis Product of Oxo-osmium (VI) Esters of Alkynes

Substrate	Product	Yield (%)	Oxo-osmium (VI) ester
Phenylacetylene	Benzoic acid	58	$Os_2O_4(O_4C_8H_6)(NC_5H_5)_4$
Diphenylacetylene	Benzil	64	$Os_2O_4(O_4C_{14}H_{10})(NC_5H_5)_4$
Methyl-phenylacetylene	1-Phenyl-propane-1,2-dione	55	$Os_2O_4(O_4C_9H_8)(NC_5H_5)_4$

4.9.1. Preparation of OsO_4/Pyridine Complexes $Os_2O_4(O_4R)L_4$

Osmium tetroxide (0.3 g) in ether (10 ml) containing 0.25 g pyridine is added dropwise to 0.05 g 2,3-dimethyl-buta-1,3-diene while stirring. A brown precipitate is filtered after 5 min and washed with ether. The pure product (60%) is obtained by recrystallizing from dichloromethane and ether.

A similar procedure is adopted to prepare the isoquinoline complexes by taking 0.4 g OsO_4, ether (10 ml), isoquinoline (0.5 g), and cyclo-octa-1,5-diene (0.08 g) in ether (5 ml). The yield of the pure product is 65%.

Hydrolysis of the Complex trans-OsO_2 $(O_2C_8H_{12})(NC_5H_5)_2$ to Cyclooctene-5,6-diol. To a solution of K_2SO_3 (2 g) in 40 ml water and 5 ml ethanol 1.9 g of the complex is added. The whole mixture is heated under reflux for 2 h and then allowed to cool. The osmium gets precipitated and is filtered off. The product is extracted from the filtrate with ether and dried over $MgSO_4$. Evaporation *in vacuo* results in *cis*-cyclooctene-5,6-diol in 76% yield.

4.10. Oxidation of Quinones

The hydroxylation of quinones[114] is carried out in the following way. Sodium chlorate (20.0 g) in solvents like water, tetrahydrofuran (THF), water–dioxane, or acetic and a 1.3-ml solution of 1% osmium tetroxide are mixed. The solution is added drop by drop to the 0.1-mol solution of quinone maintained at 25°C. After 4–75 h (depending upon the quinone taken), the product is extracted in petroleum ether. Crystallization results in pure hydroxy quinone.

4.11. Oxidation of Steroids[89,90,192–203]

Osmium tetroxide (1.05 mol) is added to a solution of 2.5% cholest-4-ene (1 mole in pyridine), the whole content is kept for 48 h at 25°C, and then an aqueous sodium disulfite 10% (5 mol) is added to the mixture. The resulting mass is stirred for 1 h and then extracted with benzene or chloroform. The combined extracts are washed with aqueous sodium chloride and dried.

On 150 g silica gel, 1.45 g of the hydroxylation product of cholest-4-ene is adsorbed and eluted with ethylacetate-benzene (1:1), resulting in 0.339 g of 4α,5α-diol. Further elution in the same solvent gives 1.076 g of 4β,5β-diol.

4.12. Oxidation of Pyrane[41]

cis-2,5-dimethoxy-5,6-dihydro-2H-pyren (0.563 g, 3.9 mmol) dissolved in 9 ml of pyridine is added in 4 ml of dry pyridine containing 1.0 g (3.39 mmol) osmium tetroxide at

room temperature. The solution is stirred for 20 h at the same temperature. The whole mass is treated with the solution of sodium bisulfite (1.0 g) dissolved in 20 ml of pyridine and 30 ml of water. It is then stirred for an additional 4 h. Methylene chloride (6 × 25 ml) is used to extract the orange solution. Potassium carbonate is used to dry the extract. Distillation at 70°C and 0.05 mm pressure results in 0.51 g (73%) methyl-4-*O*-methyl-α-DL-lyxopyranoside as a colorless syrup.

A similar procedure has been followed for the preparation of methyl-4-deoxy-β-DL-erythro-pento-pyranoside, with the difference that after decomposition of the osmate ester the solution is extracted continuously with methylene chloride. The distillation results in a viscous liquid (93%) of the above compound.

4.13. Synthesis of a β-Keto Aldehyde[226–228] (**69**) from a β, γ-Unsaturated Ketone (**68**)

4-Hydroxy-7-(4-oxo-1-cyclo-hexenyl) heptanoic acid γ-lactone (**68**) is used by dissolving 0.5 g (2.25 mmol) in 10 ml of dioxene. It is added to 1.0 g of osmium tetroxide in 10 ml of dioxane. The whole content is stirred for 20 h and then hydrogen sulfide is bubbled for 40 min. Celite is added and the resulting mixture is filtered. The filter cake is washed with ethanol under reduced pressure and the combined filtrate and washings are distilled to dryness to afford an oil 0.5 g (83%) of the corresponding diastereoisomeric mixture of diols.

The diol mixture 0.10 g (0.7 mmol) is dissolved in 2 ml of methanol and 0.1 ml of pyridine and added to 0.19 g of periodic acid in 0.8 ml of water. At room temperature the whole mass is stirred for 15 min and then diluted with water followed by extraction with methylene chloride. The extract is successively washed with water, dried over sodium sulfate, and distilled to dryness under reduced pressure. A tautomeric mixture of **69** and **70** is obtained in 78% yield.

4.14. Synthesis of **73**, Methyl-7-(2-hydroxy-5-oxo-1-pyroridinyl) Heptonoate from **75** or **76**[230–232]

Osmium tetroxide (0.001 g) is added to a stirred solution of amides **75** or **76** (1.95 g, 4.29 mmol) in 40 ml dioxane and 13 ml water. After 10 min the color of the solution turns brownish and then sodium metaperiodate (2.06 g, 9.2 mmol) is added, keeping the temperature of the solution 25°–26°C. The whole reaction mixture is stirred for 3 h at the same temperature. The precipitated solid is filtered and the filtrate is evaporated *in vacuo* (1 mm Hg). The residue is dissolved in 15 ml of $CHCl_3$, dried, and evaporated *in vacuo* resulting in 91% yield of **73**.

A similar experimental procedure is followed for the synthesis of **72**, methyl-7-methyl-7-(2-formyl-5-oxo-1-pyroridinyl) heptanoate by taking 0.58 g (1.76 mmol) of **77**. The crude reaction mixture is subjected to chromatography over silica gel and elution with ether (Et_2O), then with methanol resulting in 77% aldehydo ester **72**.

4.15. Synthesis of **80**, (1′Rs,2′Rs)-8-oxo-3 endo-(1′,2′-dihydroxyheptyl)tricyclo-4.3.0.0-nonane[233–235] from **79**

In the synthesis of **80** a solution of 5.93 g (25.52 mmol) of **79**, 8-oxo-3-endo(*cis*-1-hepenyl)tricyclo-4.3.0.0.-nonane, 75 ml of acetone, 5 ml of water, 3.12 ml solution of osmium tetroxide in *tert*-butyl alcohol (30 mg/ml), and 3.98 g (20.98 mmol) of *N*-methyl-morpholine[136] oxide dihydrate is stirred up to 2 h at room temperature. Again 4.0 g of sodium bisulfite is dissolved in 20 ml of water and then added in the above solution. The whole content is stirred for 30 min, then diluted with brine and extracted with ethyl acetate.

The extract is washed with brine and dried over sodium sulfate. 7.15 g of crude **80** is obtained as an oil after concentrating the extract *in vacuo*.

For purification the following process was adopted. A 48 mm × 36 in. column was slurry packed with 300 g of silica gel in 20% acetone in methylene chloride. The sample was applied in methylene chloride and eluted with 20% acetone in methylene chloride. The fractions, 50 ml each, were combined to yield 6.71 g (99%) of pure **80**, a very viscous colorless oil.

4.16. Synthesis of "K-Region" Diepoxide (**86**)

In the synthesis of "K-region" diepoxide, 4,5:11,12-diepoxy-4,5,11,12-tetrahydrobenzo-(α)-pyrene (**86**), 2 g (2 mmol) of osmium tetroxide dissolved in 15 ml of freshly distilled dry pyridine is added to a solution of BaP 1.0 g (1 mmol) in 25 ml of pyridine. The dark-brown solution thus obtained is stirred for 12 days under nitrogen. Then an additional 0.35 g of osmium tetroxide is added and again stirred for another 4 days. Sodium bisulfite (4 g) in 60 ml of water is then added to the reaction mixture and stirred for 4 h. CH_2Cl_2 (500 ml) is used to extract the resulting mixture several times. The organic layer is then washed with water and evaporated under reduced pressure to remove CH_2Cl_2 and pyridine. The residue, when treated with 75 ml of CH_2Cl_2, results in 0.87 of a reddish solid after filtration. The reddish solid (0.2 g) is then refluxed with 30 ml of CH_2Cl_2 and filtered. Repeated crystallization of the residue from THF and hexene results in 0.05 g of **87**.

A solution of tetrol (0.32 g) **87** in 100 ml of 1:1 benzene/pyridine is stirred with $Pb(OAc)_4$ (1.0 g) for 4 h at room temperature. Water (50 ml) is added and the solution is extracted with 250 ml of CH_2Cl_2. The extract is dried and evaporated to remove all the solvents. Creamy-white flakes (0.22 g) **89** are obtained by treating the above extract with CH_2Cl_2/hexane (4.1).

Tetraldehyde (0.15 g) **89** in 8 ml of dry benzene is refluxed with 0.5 ml of freshly distilled tris-(di-methyl-amino)-phosphine for 1 h. The brown solution thus obtained is concentrated to 4 ml by flushing with nitrogen. Greenish-yellow crystals were deposited on addition of a few drops of hexane. The diepoxide **85** (0.015 g, 11.2%) is recrystallized by a dioxane–hexane mixture as tiny pale-yellow needles.

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13

Thallium(III) Salts as Oxidants in Organic Synthesis

Alexander McKillop and Edward C. Taylor

1. INTRODUCTION

Only thallium and indium of the group IIIB elements are known to exist as the monovalent ions under normal conditions. By contrast with indium(I) salts, however, which are very readily oxidized to the trivalent state and the chemistry of which is not at all well developed, thallium(I) salts are stable. Indeed, it has been accurately stated that "... for thallium the Tl^{I}–Tl^{III} relationship is a dominant feature of the chemistry."[1] This is certainly true with respect to the utility of Tl(III) as an oxidant in organic chemistry. The reduction potential E^0 for $Tl^{3+} + 2e \rightarrow Tl^{+}$ in aqueous solution under standard conditions is $+1.25$ V,[2] but clearly more powerfully oxidizing Tl(III) species can be obtained by variation in the anion associated with the metal and by appropriate choice of reaction conditions. In the terms of the organic chemists, the thermodynamically favorable reduction of Tl(III) to Tl(I) is one of the most important "driving forces" in thallium(III)-mediated oxidations.

Thallium is one of the post-transition, heavy metal elements and is flanked by mercury and lead. Not surprisingly, therefore, certain aspects of the chemistry of thallium are more or less closely related to aspects of the chemistry of both mercury and lead, for example, oxymetallation and electrophilic aromatic metallation reactions. Moreover, Hg^{2+}, Tl^{3+}, and Pb^{4+} are isoelectronic and Tl^{3+} is a more powerful oxidant than Hg^{2+} but a less powerful oxidant than Pb^{4+}. By contrast with Pb^{4+}, especially in the form of lead(IV) acetate, however, Tl^{3+} was virtually uninvestigated as a potential oxidant for organic substrates prior to 1970. That situation has changed dramatically during the last ten years. Thallium(III) salts are now widely utilized for a wide range of oxidations, many of which, for all practical purposes, are both unique to the element and the methods of choice for the given transformations. Many of these reactions proceed via formation of organothallium

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intermediates, most of which are very unstable, while others almost certainly proceed via formation of O–Tl, S–Tl, and N–Tl bonds. That is, a discrete chemical intermediate is formed which contains thallium, and which subsequently undergoes decomposition with concomitant reduction of thallium(III) to thallium(I). In yet other cases, however, no direct bond formation to thallium is involved; instead, the essential function of the thallium(III) is as an electron acceptor. In such cases, the very unstable thallium(II) ions which are formed presumably undergo rapid disproportionation to thallium(I) and thallium(III) ions.

So far, there has been relatively little detailed kinetic and mechanistic investigation of thallium(III)-induced oxidations of organic substrates. Plausible "curly arrow" reaction pathways have been advanced for the majority of oxidation reactions, and some kinetic, mechanistic and stereochemical evidence has been cited in support of some of them. In general, however, the mechanisms suggested in this chapter for individual reactions are speculative. Even so, it is now evident that, in terms of mechanism, studies during the last few years have clearly demonstrated that oxidation by thallium(III) is in certain instances at least much more complex than had been generally appreciated. In the early 1970s, oxidation by thallium(III) was tacitly assumed to proceed by two-electron transfer mechanisms, and such mechanisms may very well be operative in many cases. In 1973, however, Elson and Kochi reported that treatment of certain alkyl substituted aromatics with thallium(III) trifluoroacetate (TTFA) resulted in the formation of radical cations via a one-electron transfer process.[3] Similar observations had been made at approximately the same time by the present authors, who subsequently described in 1977 a very useful method for the preparation of a wide range of symmetrical biaryls based on the ease with which electron rich aromatic substrates could transfer a single electron to thallium(III).[4] Thallium(III)-induced electron transfer reactions have been extended considerably during the last few years and are currently the subject of much interest and research effort.

Because of the often complicated nature of thallium oxidations it is not easy to classify the reactions clearly in terms of substrate and product classes. Therefore, the individual oxidation reactions described in the following discussion have been grouped under three general headings, viz., (1) one-electron transfer oxidations, (2) two-electron oxidations, and (3) oxidations of uncertain mechanism. Reaction types have been indicated within each category. Assignment of a particular transformation to a given category is obviously based solely on currently available evidence, and, in view of the dearth of detailed mechanistic evidence, it is quite probable that some reassignments will be necessary in the near future as a consequence of detailed physical organic study of individual reactions. Reactions discussed under heading (3) are either (a) those for which no mechanism was postulated by the original investigators, but for which a plausible mechanism can be drawn; or (b) those which can equally well be explained on the basis of a one-or two-electron transfer process; or (c) those for which no obvious and/or plausible mechanism can as yet be advanced.

2. SCOPE AND LIMITATIONS

2.1. One-Electron Transfer Reactions

There is considerable current interest in methods both for the generation of aromatic radical cations and for exploitation and utilization of these highly reactive species in organic synthesis. Generation of aromatic radical cations is normally carried out most conveniently using one of two general procedures, namely, anodic oxidation or reaction of an aromatic substrate with a metal salt which can function as a one-electron acceptor, such as Fe(III), Co(III), Ce(IV), etc. It is now known that Tl(III), especially in the form of TTFA, can function highly efficiently as a one-electron acceptor.

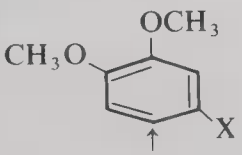
2.1.1. Dehydrodimerization of Aromatic Compounds

Reaction of a wide variety of aromatic substrates with TTFA results in formation of arylthallium di(trifluoroacetates), the products of formal electrophilic aromatic thallation [Eq. (1)], and this area of organothallium chemistry has recently been comprehensively

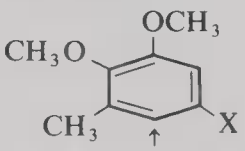
$$ArH + Tl(OCOCF_3)_3 \longrightarrow ArTl(OCOCF_3)_2 \qquad (1)$$

reviewed.[5] Reaction of electron-rich aromatic substrates with TTFA, on the other hand, does not result in thallation but leads to intermolecular oxidative dehydrodimerisation and formation of biaryls in good to excellent yield.[4,6] The postulated mechanism is outlined in Scheme 1. That is, the initial step is one-electron transfer from the electron-rich aromatic substrate **1** to thallium(III), which results in generation of an aromatic radical cation **2**; electrophilic substitution of the aromatic substrate **1** by **2** then gives **3**, oxidative aromatization of which gives the biaryl **4**.

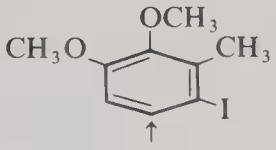
This very simple synthesis of symmetrical biaryls has been examined in some detail and the scope and limitations largely defined.[6] Typical yield data are indicated for compounds **5**–**17**, where the arrow indicates the position of coupling; note that the reactions are completely regiospecific and that 2,2′,6,6′-tetrasubstituted biaryls can readily be prepared in high yield. These oxidations are very rapid—a few seconds to a few minutes at room temperature



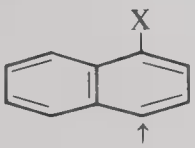
5 X = Br, 80%
6 = CH_3, 74%



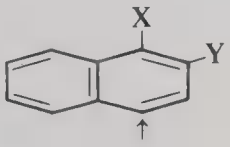
7 X = Br, 99%
8 = CH_3, 74%



9 83%

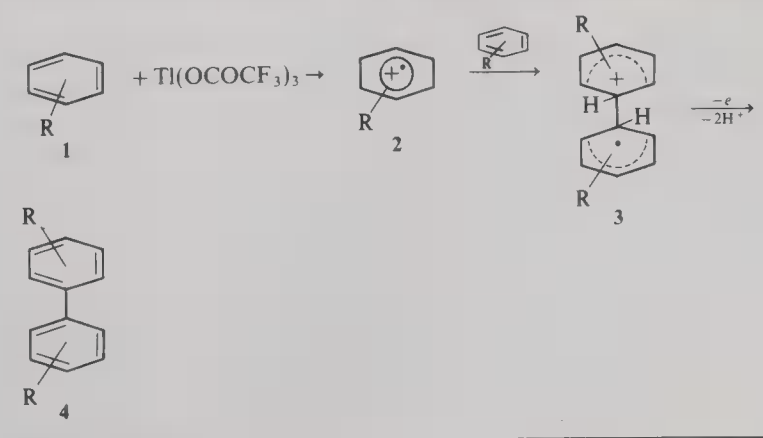


10 X = I, 94%
11 = CH_3, 100%
12 = $(CH_3)_2CH$, 76%
13 = CH_3O, 88%
14 = C_6H_5, 83%



15 X = CH_3O, Y = CH_3, 92%
16 X = CH_3, Y = Cl, 82%
17 X = CH_3O, Y = Br, 80%

SCHEME 1

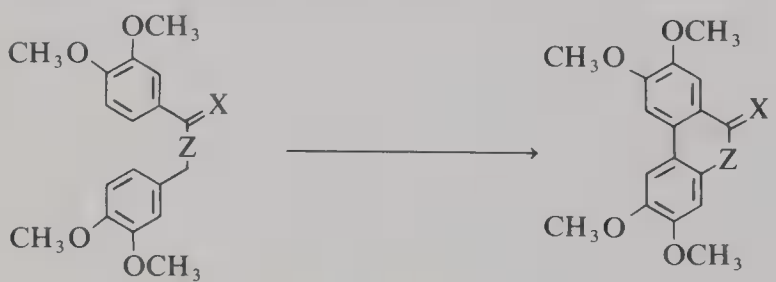


or below in most cases—and isolation and purification of products is extremely simple. A variety of solvents can be used, such as trifluoroacetic acid, carbon tetrachloride, methylene chloride, or acetonitrile, although with the last three a catalytic amount of boron trifluoride etherate apparently must also be used.

In keeping with the proposed mechanism (Scheme 1), aromatic substrates which contain powerful electron-withdrawing groups (CN, COOR, NO_2) fail to react with TTFA to give biaryls. The TTFA method, therefore, is complementary to the classical Ullmann biaryl synthesis, which usually gives satisfactory yields only when the aromatic halides contain powerful electron-withdrawing groups and is normally an inefficient reaction for the preparation of binaphthyls. Consequently, the TTFA method is particularly suitable for the synthesis of natural products. The biaryl subunit, usually containing hydroxy or alkoxy substituents, occurs very commonly in a wide range of natural products, especially the alkaloids, and a key step in total synthesis is frequently a biaryl forming reaction. Phenol oxidative coupling has of course been very widely applied in natural product synthesis, but in practice yields are often very poor and complex mixtures of products are by no means uncommon. Attempts to overcome these deficiencies and limitations during the last decade or so have led to considerable improvements in certain biaryl forming reactions, especially the use of vanadium(V) reagents popularized by Kupchan and his co-workers for Scholl-type reactions.[7]

2.1.2. Intramolecular Cyclizations

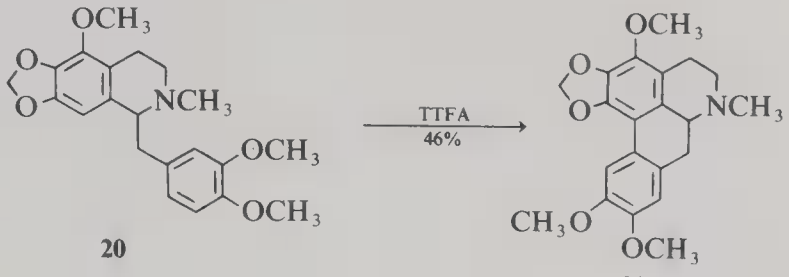
Recent studies have established that TTFA is most probably at least as efficient a reagent as, and certainly more selective than, say, vanadium oxytrifluoride for intramolecular nonphenolic oxidative couplings.[8] Thus, treatment of 1,3-bis-(3,4-dimethoxyphenyl)propane (**18a**) with TTFA in carbon tetrachloride containing a catalytic amount of boron trifluoride etherate results in smooth oxidative coupling to give the bridged biphenyl **19a** in 81% yield. Oxidation of **18b–18d** gives **19b–19d** in yields of 80%, 43%, and 58%, respectively, and all of



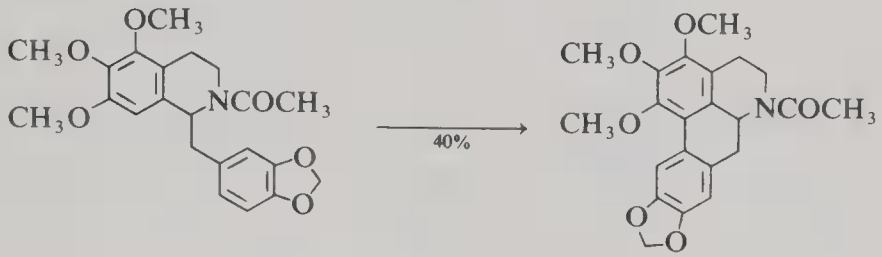
18 (a) $X = H_2$, $Z = CH_2$
(b) $X = H_2$, $Z = O$
(c) $X = H_2$, $Z = NCH_3$
(d) $X = O$, $Z = NCH_3$

19

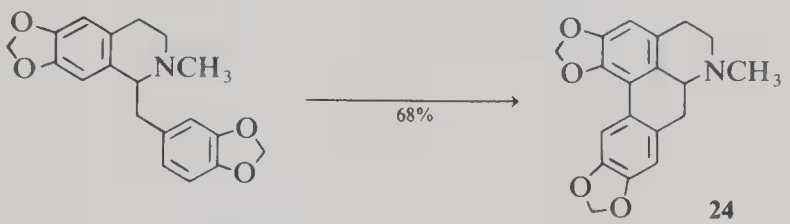
these reactions are believed to proceed via radical cation formation followed by direct intramolecular electrophilic aromatic substitution. Aporphine and homoaporphine alkaloids can be readily prepared using the same general approach. Thus, ocoteine (**21**), 3-methoxy-*N*-acetylnornantenine (**23**), neolitsine (**24**), kreysigine (**26a**), and *O*-methylkreysigine (**26b**) have been synthesized as outlined in Eq. (2)–(5). Note that in the case of kreysigine the benzyl ether protecting group is conveniently cleaved under the reaction conditions. In these reactions the first step is again believed to be electron transfer and radical cation formation (Scheme 2). However, the question of direct versus bridgehead coupling (followed by rearrangement) of **27** to give **28** has not been resolved. The evidence available indicates that direct coupling probably occurs in the case of kreysigine and *O*-methylkreysigine. Reaction of **29** with TTFA, on the other hand, results in formation of the homoproaporphine **30**; dienone-phenol rearrangement of the latter gives multifloramine **31**.



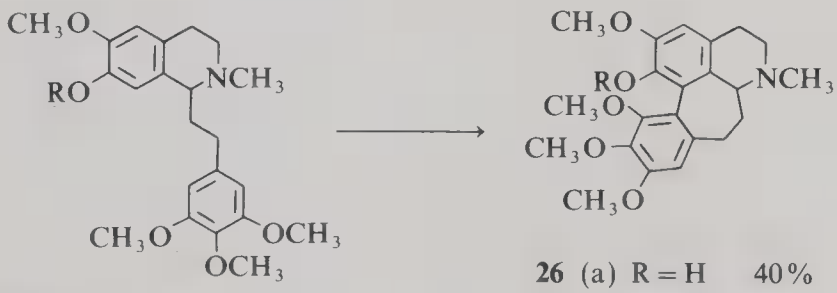
20 **21** (2)



22 **23** (3)



24 (4)



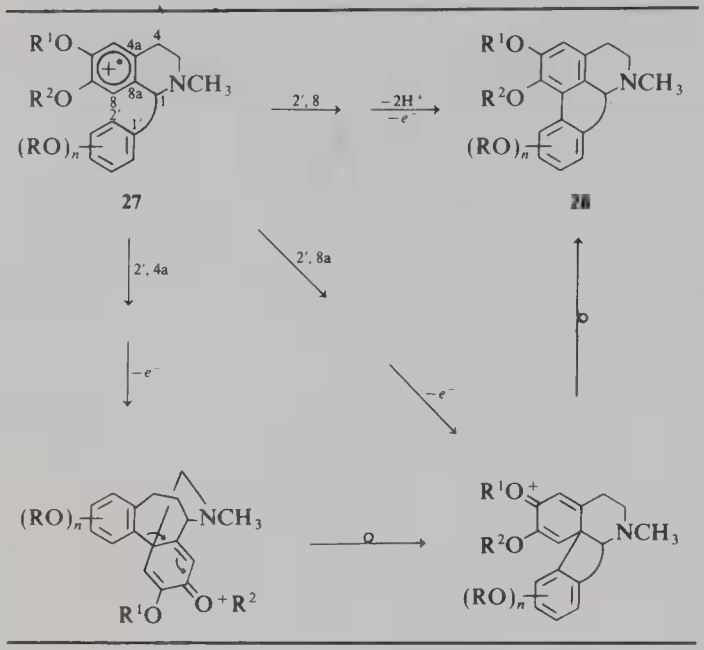
25 (a) $R = CH_2C_6H_5$
(b) $R = CH_3$

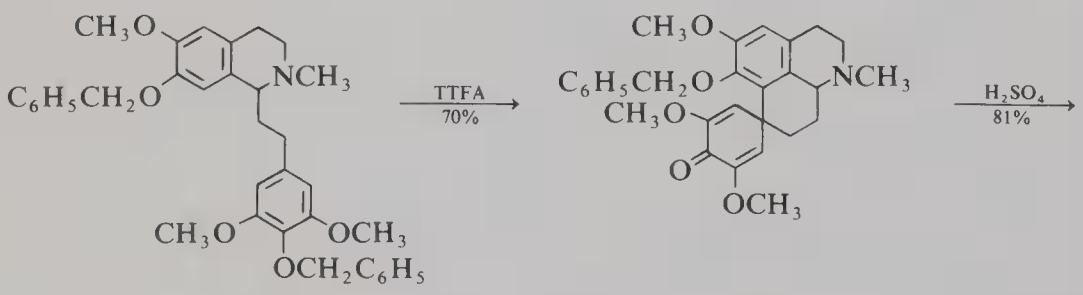
26 (a) R = H 40%
(b) $R = CH_3$ 46%

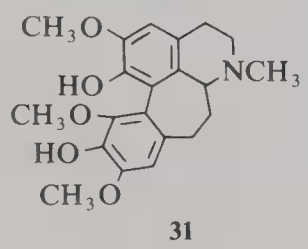
(5)

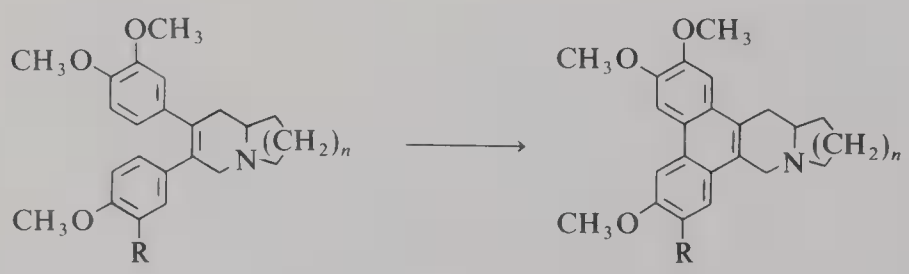
It is as yet too early to attempt to assess the range of applicability of these TTFA-induced oxidations in natural product synthesis. Already, however, there are clear indications that TTFA may well prove to be the reagent of choice for such reactions. Thus, Herbert[9] has shown that oxidation of septicine (**32a**) and julandine (**32b**) gives tylophorine (**33a**) and cryptopleurine (**33b**) in 95% and 69% yield, respectively. The latter case is especially interesting as the intramolecular electrophilic substition reaction occurs *meta* to the methoxy substituent. During studies on the total synthesis of juncusol, Kende and Curran found that reaction of the 1,2-diarylethane (**34**) with TTFA resulted in both ring closure and dehydrogenation to give the crude phenanthrene **35** directly in 58% yield.[10] Ring closure to form an eight-membered ring has been described by Cambie *et al.*,[11] who obtained the isostegane derivative **37** in 82% yield by oxidation of matairesinol dimethyl ether (**36**), while McDonald and Wylie have prepared the dibenz[*df*]azonine (**39a**) and the dibenz[*df*]azecine (**39b**) in a similar manner in 36% and 60% yield, respectively.[12] That is, oxidative coupling of compounds of the type $ArCH_2(X)_nCH_2Ar$, where $n = 0-4$, results in formation of 6–10-membered rings in moderate to excellent yield.

SCHEME 2





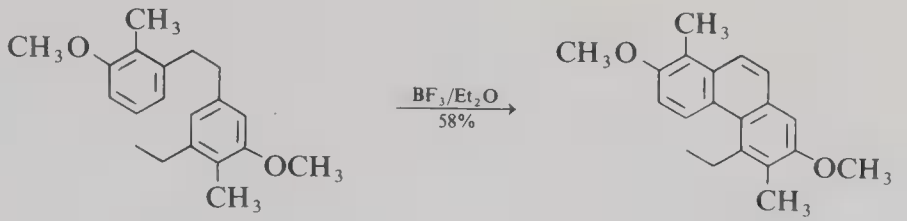




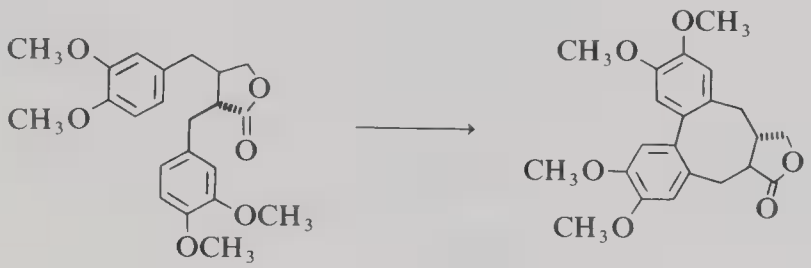
(a) R = OCH_3, $n = 1$

(b) R = H, $n = 2$

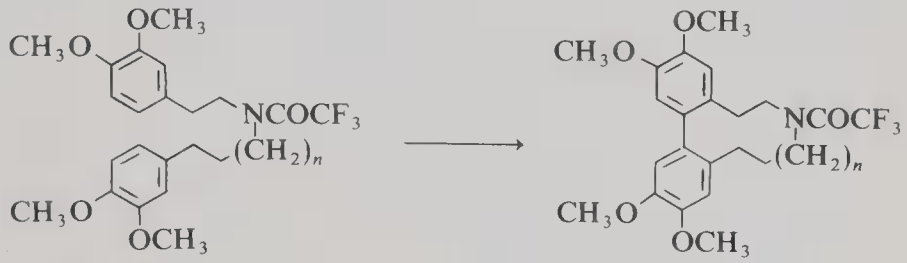
There is one important experimental feature associated with aromatic radical cations generated using metal salt oxidants, namely, that in almost all reactions some overoxidation of starting material and/or product occurs to give tarry, resinous materials, the amount of



34 35



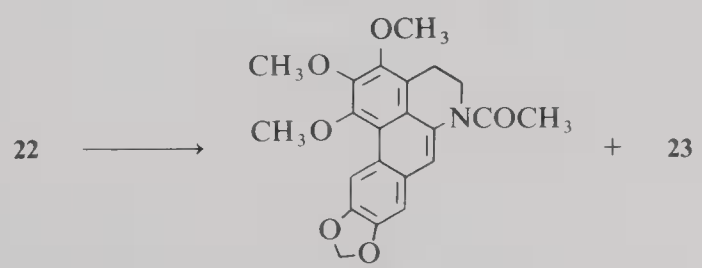
36 37



38 39

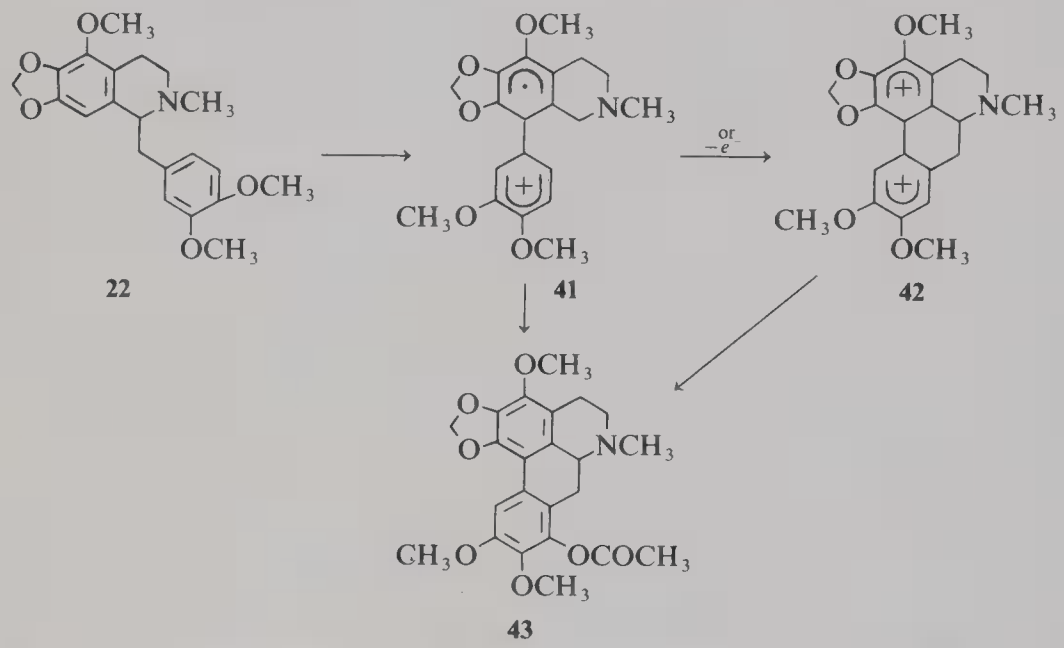
(a) $n = 0$
(b) $n = 1$

which can vary significantly with the particular metal salt used. In the above-TTFA reactions the amount of such byproducts is often very little and their presence does not normally present any difficulties whatsoever in the isolation and purification of the desired products. Apart from this gross overoxidation, however, the TTFA oxidations are remarkably free of "side reactions"; indeed, only three have been recorded, all of which involve overoxidation, and one of which is discussed later (see p. 709). The remaining two are the dehydrogenation of dihydrophenanthrenes and the direct acetoxylation of an aromatic ring. In the oxidation of both **22** and **34** dehydrogenation of the initially formed dihydrophenanthrene was observed. In the former case, the 6a,7-dehydro derivative **40** was formed in 31% yield, together with 40% of the desired alkaloid **23**; this did not present a serious problem, however, as reduction of **40** with amalgamated zinc in ethanol/hydrochloric acid gave the alkaloid **23**.[8] In the latter case, only the phenanthrene **35** was isolated. Clearly, oxidative coupling of 1,2-diarylethanes can be expected to give at least some of the corresponding phenanthrene. The second, more interesting, and unexpected side reaction was recorded during the synthesis of ocoteine (**21**) where, in an attempt to reduce the amount of overoxidation encountered with



40

TTFA, the 1-benzyl-1,2,3,4-tetrahydroisoquinoline (**20**) was reacted with thallium(III) acetate rather than the more powerfully oxidizing TTFA. The exclusive product was acetoxyocoxylonine (**43**), formation of which can be explained on the basis that acetate ion, being substantially more nucleophilic than trifluoroacetate ion, reacts with either the radical cation (**41**) or the dication (**42**). Aromatic nuclear acetoxylation has been observed on occasion with other metal salts; the generality and/or synthetic utility of thallium(III) acetate for such reactions with simple aromatic substrates remains to be investigated.

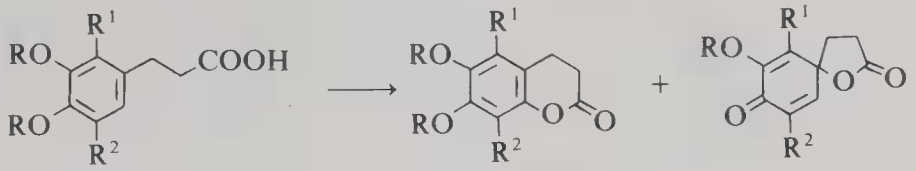


Intramolecular oxidations can be generalized as outlined in Eq. (6), where Nu is an electron rich aromatic ring. In principle, however, Nu could be any one of a wide range of nucleophiles, and both the length and nature of the chain of atoms separating Nu from the aromatic ring can be varied substantially. In practice, it has already been demonstrated that the radical cation **44** can be trapped as outlined in Eq. (6) when Nu is a carboxylic acid, alcohol, or tosylamide group.

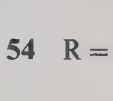
44 (6)

Oxidation of 3-(3,4-dimethoxyphenyl)propionic acid (**45**) with TTFA in TFA containing a catalytic amount of boron trifluoride etherate is instantaneous at −20°C; quenching of the reaction by immediate addition of *t*-butanol gives a mixture of the dihydrocoumarin (**46**) and the spirocyclohexadienone (**47**) in a ratio of 2:1.[13] If methanol rather than *t*-butanol is used to quench the reaction, the ester **48**, which is derived from the dihydrocoumarin **46**, is obtained together with **47**. In an analogous fashion, TTFA oxidation of 3-(3,4-diethoxyphenyl)propionic acid **49** gives the dihydrocoumarin **50** and the spirocyclohexadienone **51** in a ratio of 1:10. Oxidation of **52** and **54** likewise gives the dihydrocoumarins **53** and **55**, respectively, whereas the spirocyclohexadienone **57** was the only product isolated from the oxidation of **56**. The failure to observe dihydrocoumarin formation in the latter instance is presumably a reflection both of steric hindrance to ortho substitution and facile demethylation of the doubly flanked methoxy group; such selective demethylation is a known TTFA-induced reaction.[14,15] Oxidation of 3-(4-methoxyphenyl)propionic acid (**58**) interestingly results in both inter- and intramolecular coupling to give **59**.

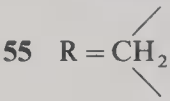
It is suggested that formation of dihydrocoumarins such as **46** and spirocyclohexadienones such as **47** in the above transformations proceeds as outlined in



45 $R = CH_3$, $R^1 = R^2 = H$
46 $R = CH_3$, $R^1 = R^2 = H$
47 $R = CH_3$, $R^1 = R^2 = H$
49 $R = C_2H_5$, $R^1 = R^2 = H$
50 $R = C_2H_5$, $R^1 = R^2 = H$
51 $R = C_2H_5$, $R^1 = R^2 = H$
52 $R = CH_3$, $R^1 = OCH_3$, $R^2 = H$
53 $R = CH_3$, $R^1 = OCH_3$, $R^2 = H$

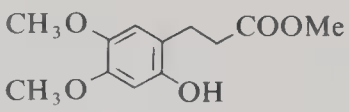


54 $R^1 = R^2 = H$



55 $R^1 = R^2 = H$

56 $R = CH_3$, $R^1 = H$, $R^2 = OCH_3$
57 $R = CH_3$, $R^1 = H$, $R^2 = OCH_3$



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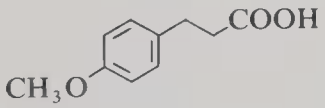
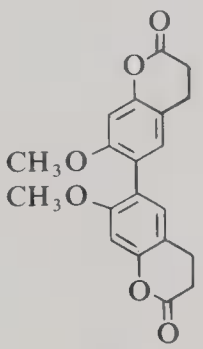


58

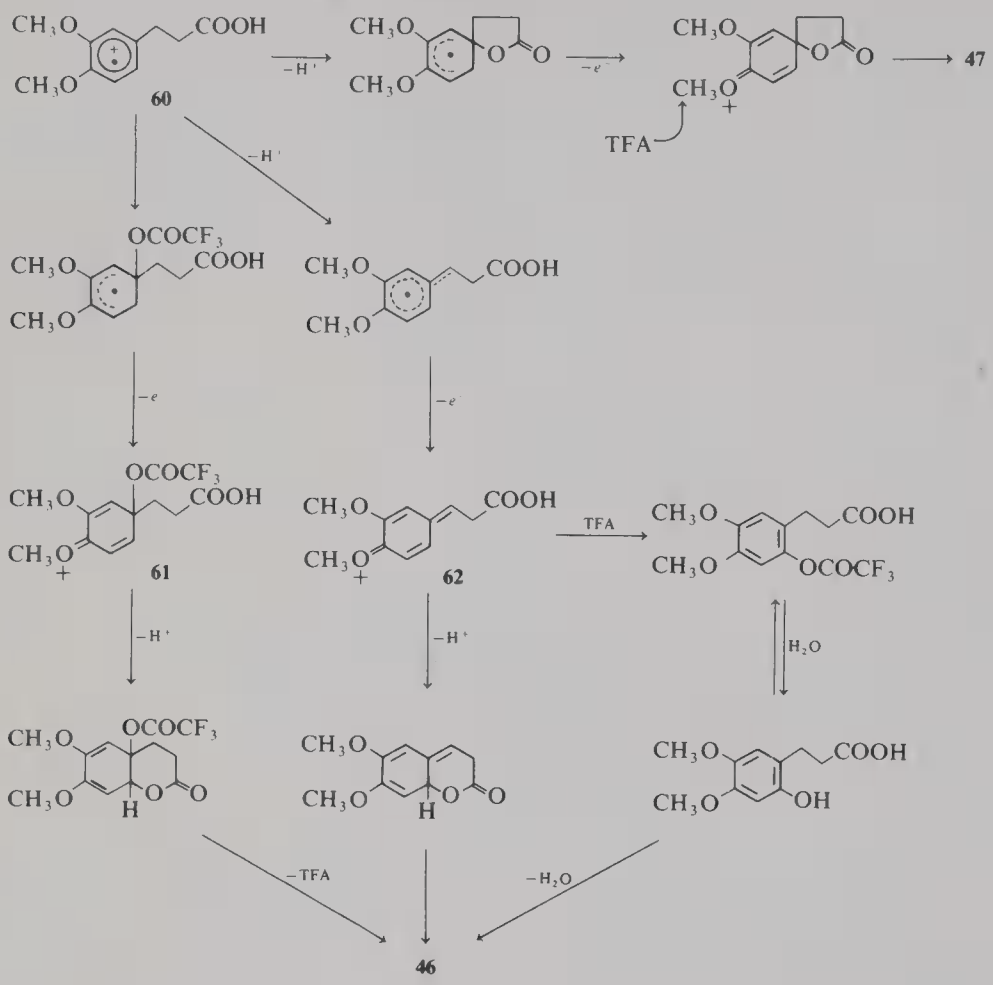


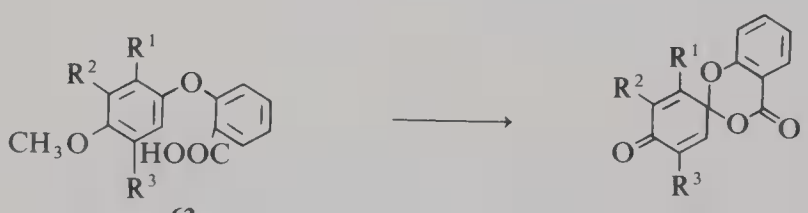
59

Scheme 3.[13] The most significant aspects of these suggested mechanisms are that whereas the spirocyclohexadienone **47** is postulated to arise by direct intramolecular capture of the radical cation **60**, formation of the dihydrocoumarin **46** is postulated to involve two separate one-electron transfer processes and intramolecular cyclization of the carboxyl nucleophile to a positively charged intermediate **61** or **62**, or both. Alternative mechanisms can be advanced for the formation of both **46** and **47**, but the evidence currently available is most in keeping with the pathways outlined in Scheme 3.

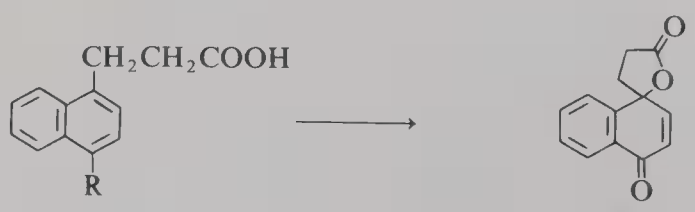
Extension of the above TTFA oxidations to closely related substrates has produced a number of very interesting results. Reaction of the diaryl ether carboxylic acids **63** with TTFA, for example, gives the spirocyclohexadienones **64** in moderate to good yield,[16] while oxidation of the naphthalenylalkanoic acids **65a**, **65b**, **67a**, **67b**, **69**, and **71** gives the spirocyclic lactones **66a**, **66b**, **68a**, **68b**, **70**, and **72**, respectively.[13] Formation of **66b**, **68b**, and **72** from **65b**, **67b**, and **71** is particularly interesting and presumably involves solvent capture of a radical cation or cation intermediate during the oxidation. In contrast to the reactions of **69** and **71**, which result in the formation of six-membered spirocyclic heterocyclic rings, no such products have been isolated from the reactions of the homologous 5-arylvaleric acids. The methoxy substituted substrate **73a** undergoes extensive degradation to give mainly tarry products together with a small amount of 1,4-naphthoquinone. The methyl substituted sub-

SCHEME 3

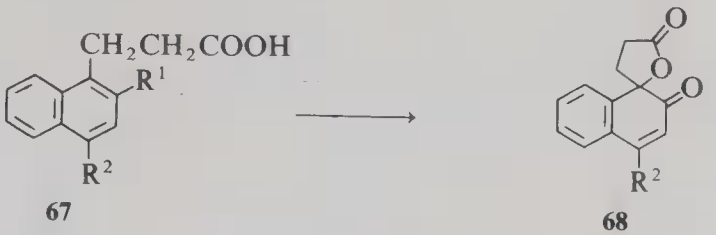




(a) $R^1 = R^2 = R^3 = H$, 53%
(b) $R^1 = R^3 = H$, $R^2 = OCH_3$, 36%
(c) $R^1 = H$, $R^2 = R^3 = OCH_3$, 60%

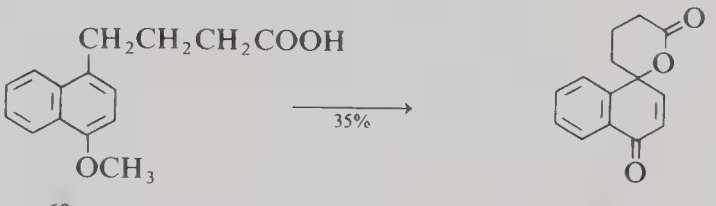


(a) $R = OCH_3$, 74%
(b) $R = H$, 36%

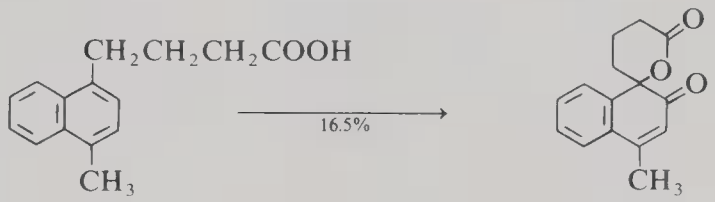


67 **68**

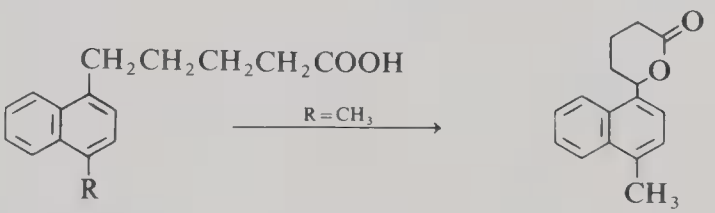
(a) $R^1 = OCH_3$, $R^2 = H$, 18%
(b) $R^1 = H$, $R^2 = CH_3$, 52%



69 **70**



71 **72**



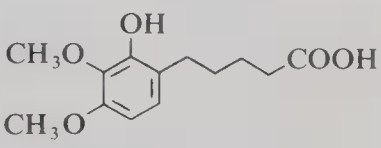
73a,b

(a) $R = OCH_3$
(b) $R = CH_3$

74

75 **76**

(a) R = H
(b) $R = OCH_3$



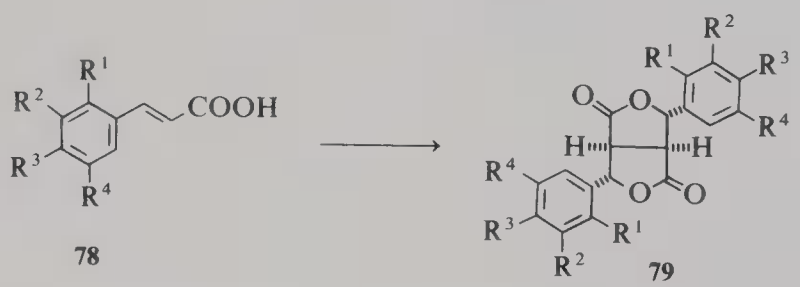
77

strate **73b**, on the other hand, gives the lactone **74** in 54% yield, and an exactly analogous reaction occurs with **75a**, **75b**, which give the lactones **76a**, **76b** in low yield. It has been suggested that in these oxidations the initially formed radical cation undergoes deprotonation followed by further one-electron transfer to give a benzylic carbenium ion which is trapped intramolecularly by the carboxyl group. Of these latter transformations, the

oxidation of **75b** is especially interesting as the phenol **77** is formed in 29.5% yield together with the spirocyclic lactone **76b**. The phenol **77** is almost certainly formed in a manner analogous to the formation of acetoxyocoxylonine **43** from **20**, i.e., by solvent capture of the intermediate radical cation.

Oxidation of a variety of ω-aryl *n*-alkanols with TTFA has been studied and the results are broadly similar to those outlined above for arylalkanoic acids.[13] Both intramolecular trapping of the radical cation by the hydroxyl group and reaction at the benzylic position have been observed, although product yields are in general substantially lower than for the arylalkanoic acids. Trapping of radical cation intermediates with nitrogen nucleophiles has been successful so far only with the tosylamides of β-arylethylamines, and gives mixtures of indoles and dihydroindoles.[15] Clearly, much more detailed investigations are required with both alcohol and nitrogen nucleophiles before any proper assessment can be made of the real synthetic utility of these oxidative cyclization reactions.

There has been almost no study so far of the effect of variation of the chain separating the aromatic ring and the nucleophile [see Eq. (6)] on the overall course of oxidation with TTFA. The one study which has been reported clearly demonstrates, however, that major changes in reaction products can arise as a result of apparently relatively minor changes in the nature of the bridge. Thus oxidation of *p*-alkoxycinnamic acids (**78**) with TTFA in TFA/methylene chloride containing boron trifluoride etherate is instantaneous at room temperature and results in oxidative dimerization to give the biologically active 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane-4,8-diones (**79**) in low to moderate yield.[17–19] Even though the

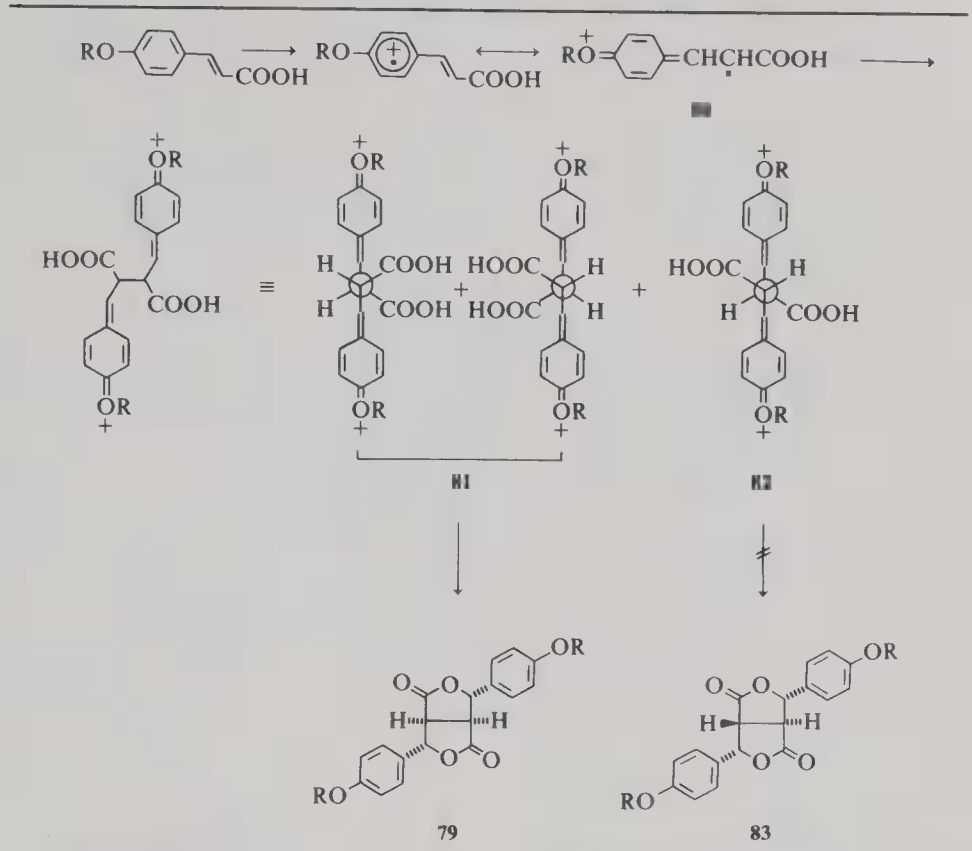


78 **79**

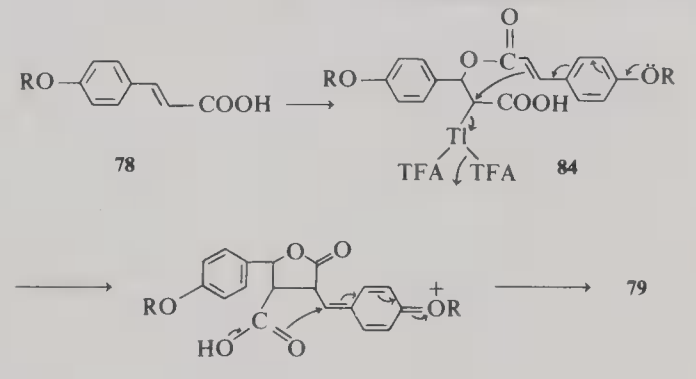
	R^1	R^2	R^3	R^4	%
(a)	CH_3O	CH_3O	CH_3O	H	39
(b)	H	CH_3O	CH_3O	CH_3O	54
(c)	H	CH_3O	CH_3O	H	47
(d)	H	OCH_2O		H	31
(e)	H	CH_3O	HO	H	12

yields are at best moderate, this does represent a very simple one-step synthesis of these interesting lignan natural products from readily available starting materials. A plausible mechanism for this oxidative dimerization is outlined in Scheme 4, which involves dimerization of the initially formed radical cation resonance contributor **80** to a mixture of **81** (*dl* pair) and **82** (*meso*). Intermediate **81** can cyclize to the *cis*-fused product **79**, which has the aromatic substituents in the thermodynamically most stable configuration, but intermediate **82** apparently does not undergo analogous cyclization as formation of the highly strained *trans*-fused bis-lactone **83** has not been observed. This in part at least could account for the moderate yields of oxidation products. A reasonable alternative mechanism which does not involve one-electron transfer can be advanced for this oxidative dimerization and is outlined in Scheme 5. Here, the initial reaction is oxythallation (q.v.) of the cinnamic acid **78** to give **84**, which can undergo intramolecular cyclization as shown. There is some experimental evidence to indicate that this latter pathway may also be operative in these oxidative dimerizations.

SCHEME 4

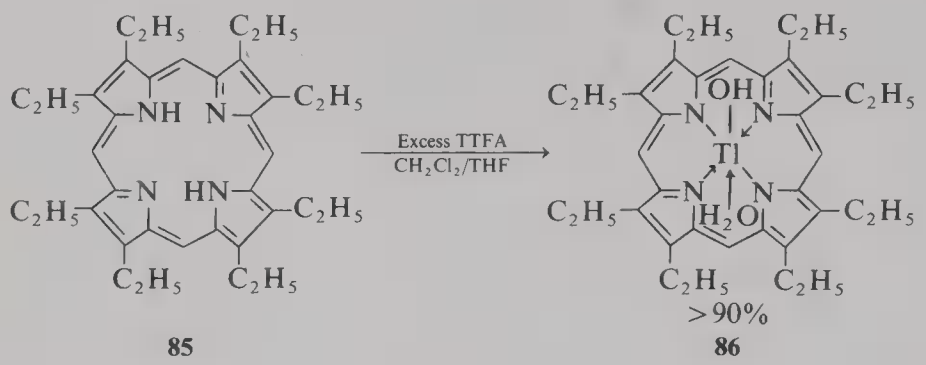


SCHEME 5



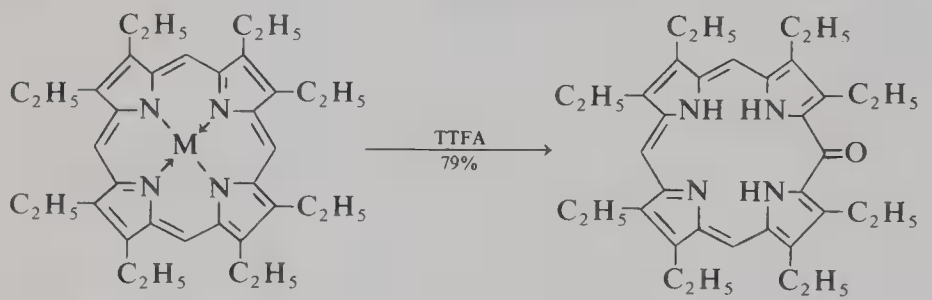
2.1.3. Oxidation of Porphyrins

All of the TTFA oxidations discussed thus far have involved rather simple aromatic substrates and, with two exceptions, proceed via inter- or intramolecular trapping of a radical cation or cation intermediate by either an electron rich aromatic ring or a suitably positioned carboxyl, alcohol, or tosylamide group.The two exceptions are the nuclear oxygenation reactions **22** → **43** and **75b** → **77**. By contrast, Smith and his colleagues have carried out detailed studies of the oxidation of porphyrins and chlorins with TTFA and have developed useful and in many cases high yielding procedures for the stereospecific oxygen of *meso* positions. Reaction of octaethylporphyrin **85** with TTFA gives the corresponding thallium(III) complex **86**, which is largely resistant to further oxidation; prolonged treatment of **85** with TTFA in trifluoroacetic acid and dichloromethane does, however, result in some oxidation to give a



85 **86**

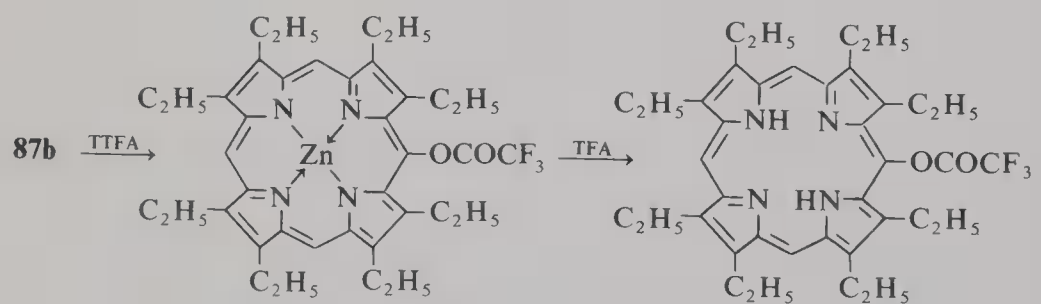
mixture of the α,γ-dioxo, α, β, γ-trioxo, and the tetraoxa (octaethylxanthoporphyrinogen) products.[20] Treatment of the magnesio complex **87a** or, better, the zinc(II) complex **87b** with TTFA, on the other hand, results in smooth oxidation and formation of octaethyloxophlorin **88** in 79% yield.[21] Oxidation of other *meso*-unsubstituted porphyrins proceeds similarly,



87a M = Mg
87b M = Zn

88

while a variety of *meso*-substituted substrates are oxidized stereospecifically to *meso*-disubstituted products.[22–25] Oxidation of all four *meso* positions of octaalkylporphyrins can be effected. The zinc(II) complex of *meso*-tetraphenylporphyrin still undergoes oxidation at the *meso* positions, but yields are much lower and ring cleavage products are also formed. One-electron transfer processes are certainly involved in these reactions, and if a solvolytic isolation procedure is avoided, the actual reaction products, the *meso*-trifluoroacetoxy derivatives, can often be isolated in excellent yield, e.g., **87b** → **89** → **90**. Whether the

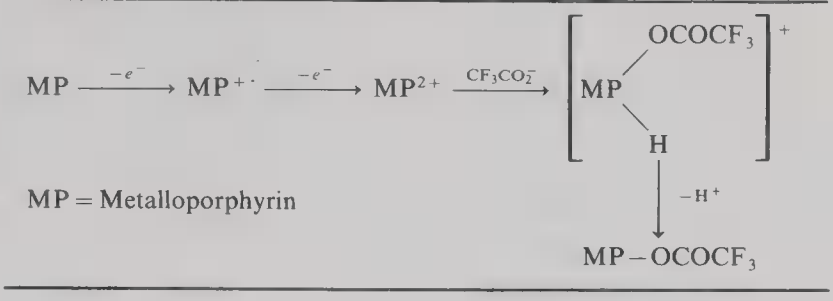


89 **90**

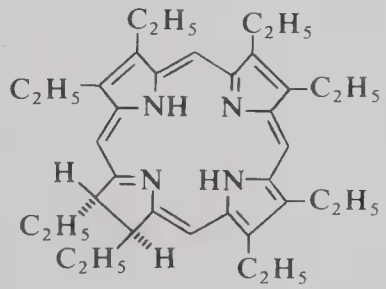
oxidation proceeds by reaction of trifluoroacetate ion with the radical cation derived from the porphyrin or with the dication remains, however, something of a moot point (Scheme 6).

Oxidation of chlorins (7,8-dihydroporphyrins) with TTFA is also of considerable interest and importance.[26] Reaction of the octaethyl compound **91** with excess of TTFA, for example, gives a mixture of products, the major one of which is the aromatic thallium(III) complex **86** formed by dehydrogenation of the 7- and 8-positions; only 3% of the chlorin thallium(III) complex is obtained. The product of real interest, however, is the

SCHEME 6

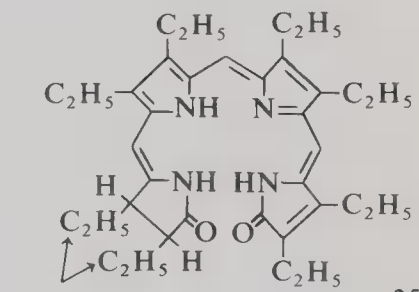


dihydrobiliverdin **92**, as cleavage of metalloporphyrins to their open chain bile pigment counterparts is a reaction of considerable biological importance and one for which only two other laboratory procedures are available. The mechanism for the formation of **92** from **91** is complex and involves initial stereospecific *meso*-trifluoroacetoxylation of the chlorin by TTFA and ultimate oxidative ring cleavage by oxygen. Smith *et al.* have also developed important procedures for the specific oxidative removal of one pyrrole ring from the thallium(III) complexes of bilitrienes.[27,28] While these latter reactions certainly appear to proceed by radical cation mechanisms, the thallium does not function as a formal oxidant in the sense of the other reactions discussed above; rather, its unique role [the Zn(II), Cu(II), and Ni(II) complexes, and the free base, are stable under the reaction conditions] is to act as an electron acceptor in the final photochemical stage of the transformation and undergo reduction to thallium(I).



91

$\xrightarrow[THF/CH_2Cl_2]{TTFA}$ **86** +



trans **92** 25%

2.2. Two-Electron Transfer Reactions

2.2.1. Oxythallation Reactions, General Features

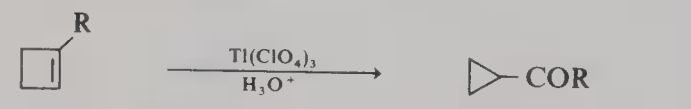
Oxymetallation is the general term used to describe the overall addition reaction that takes place when an olefin acetylene or allene is reacted with an electrophilic metal salt. Oxymercuration is the most familiar and widely studied of the oxymetallation reactions and is of considerable synthetic utility. In recent years, however, oxythallation has been studied

intensively and the result has been the development of a wide range of novel and synthetically important oxidation procedures. By contrast with oxymercuration, which in the case of olefins almost invariably results in the formation of stable organomercurials, oxythallation seldom gives stable organothallium products. Monoalkyl organothallium derivatives of the type $RTlX_2$ are generally very unstable and undergo spontaneous decomposition under the reaction conditions. In many cases, the decomposition of oxythallation adducts proceeds via carbonium ion-like intermediates and the overall transformation involves oxidative rearrangement of the carbon skeleton of the substrate. The general principles, scope, and limitations of oxythallation have been described in some detail recently,[5] and consequently the following discussion highlights only the most important and general aspects of the subject.

In practical terms oxythallation is simple and straightforward, and most reactions go to completion rapidly at room temperature. The most commonly used reagent is thallium(III) nitrate (TTN),[29] which can be used in a range of solvents such as methanol, 1,2-dimethoxyethane, trimethyl orthoformate (TMOF),[5,30,31] acetic acid, aqueous mineral acids, or, in admixture with methanol and/or TMOF, as a supported reagent on Montmorillonite K-10 clay and other inert inorganic supports.[5,31,32] Thallium(III) acetate, trifluoroacetate, sulfate, and perchlorate have been used to some extent[5]; the acetate and trifluoroacetate salts are, however, not in general particularly effective oxidants, while reactions with the sulfate and perchlorate, which are effective oxidants, are necessarily almost always carried out in aqueous acidic media. Oxythallation using thallium(III) acetate or trifluoroacetate frequently gives mixtures of products, partly or largely as a result of acetate or trifluoroacetate ion rather than the solvent participating inter- or intramolecularly during either the addition process or the subsequent decomposition of the oxythallation adduct. Such complications are not observed with the sulfate or perchlorate salts but have been noted on occasion with TTN, particularly when very poorly or non-nucleophilic solvents have been employed.

2.2.2. Oxythallation of Double and Triple Bonds

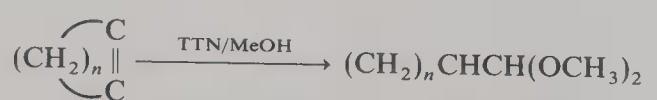
The rapid and high yield transformation of cyclohexene into the dimethyl acetal of cyclopentanecarboxaldehyde on reaction with TTN in methanol illustrates the Tl(III)-induced oxidative rearrangement of a simple olefin (Scheme 7).[29] This general approach in fact constitutes a simple and by now quite widely used procedure for the rapid and direct oxidative ring contraction of cyclobutenes, cyclohexenes, and cycloheptenes; typical examples are shown in Eqs. (7)–(11). As expected, the reaction is of no synthetic utility for ring con-



(7)

Ref. 33

R = H, 75%–85%
R = CH_3, 88%–92%

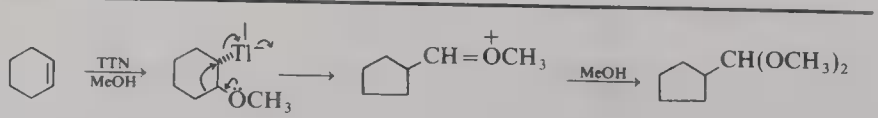


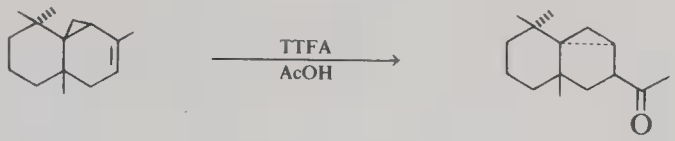
(8)

Ref. 29

$n = 4$, 85%
$n = 5$, 86%

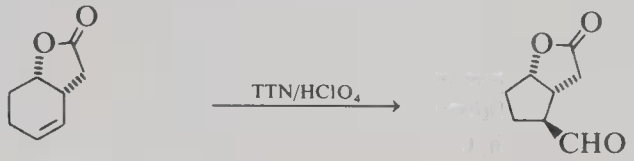
SCHEME 7





(9)

Ref. 34 76%



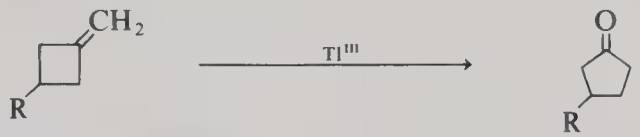
(10)

Refs. 35, 36 >50%

(11)

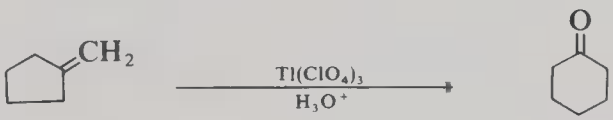
Ref. 37 66%

traction of cyclopentenes, which give complex mixtures of products, while the scope and limitations with respect to large ring olefins remain to be firmly established. In contrast to these ring contractions, reaction of methylenecycloalkanes with thallium(III) salts can result in smooth ring expansion and formation of cycloalkanones. Again, as expected, these oxidative rearrangements are most favored where the overall transformation involves relief of ring strain, i.e., four- to five- and five- to six-membered ring transformations; examples are shown in Eqs. (12)–(14).



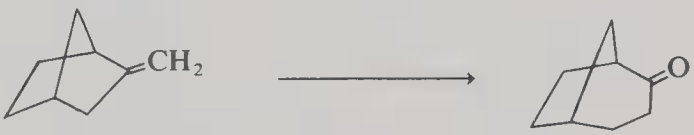
(12)

Ref. 33, R = H, 77%–81%
Ref. 38, R = CN, 81%



(13)

Ref. 33 78%–82%

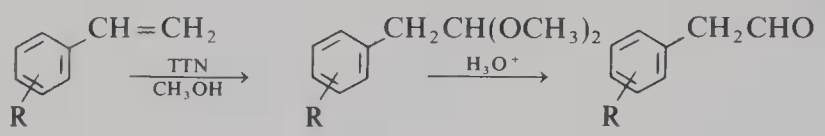


(14)

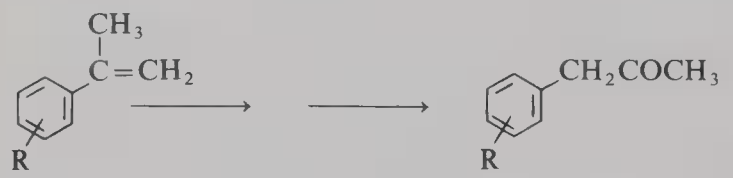
Ref. 38, $Tl(ClO_4)_3/H_3O^+$, 50%
Ref. 39, TTN/MeOH, 68%

In principle, Tl(III)-induced oxidative rearrangement of simple acyclic olefins should constitute a facile procedure for the direct conversion of an olefin into an aldehyde or ketone. In practice, however, mixtures of products are normally obtained unless the olefin contains at least *either* one substituent which is a good migrating group *or* a good nucleophile which can participate intramolecularly during the reaction. Thus, oxidation of a simple *n*-alkene with TTN or other thallium(III) salts usually gives a mixture of carbonyl compound(s), 1,3-diol derivatives, and epoxide depending on the reaction conditions and the solvent used, and

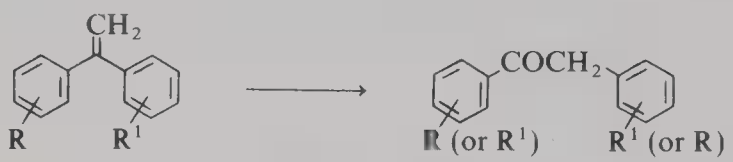
is seldom of any significance.[5,40] By contrast, oxidative rearrangement of styrenes constitutes a simple and valuable procedure for the high yield preparation of arylacetaldehydes from readily available starting materials [Eq. (15)].[29,32,41–47] α-Methylstyrenes and α-methylstilbene react analogously to give arylacetone derivatives [Eq. (16)],[29,44] while 1,1-diarylethylenes are smoothly transformed into deoxybenzoins in almost quantitative yield [Eq.(17)].[29,44] In the latter case, both possible isomeric deoxybenzoins can be obtained if the aromatic rings in the diarylethylene contain different substituent groups and therefore have different migratory aptitudes. In accord with the generally accepted mechanism of oxythallation, results from kinetic and product distribution studies are consistent with a mechanism in which electron-releasing substituents in one of the aromatic rings strongly favor migration of that aryl group and in which C–Tl bond cleavage is concerted with aryl migration.[44]



(15)

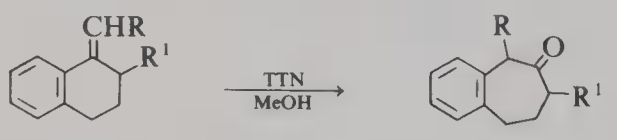


(16)



(17)

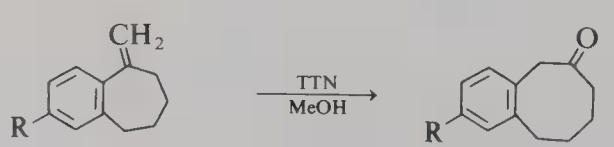
The presence of a good migrating substituent or of a suitably situated nucleophile in the olefin can be used to advantage to overcome thermodynamically unfavorable situations. Ring expansion of a methylenecyclohexane to a cycloheptane or of a methylenecycloheptane to a cyclooctane, for example, involves an increase in steric strain and is thus normally unfavorable. With the benzo-fused methylenecycloalkanes **93** and **95**, however, smooth oxidative ring expansion to **94** and **96**, respectively occurs on treatment with TTN [Eqs. (18) and (19)].[48] As the methylenecycloalkanes are readily prepared by Wittig reaction of the



93 **94**

(18)

R = CH_3, R^1 = H, 95%
R = C_2H_5, R^1 = H, 96%
R = R^1 = CH_3, 81%
R = H, R^1 = CH_3, 95%

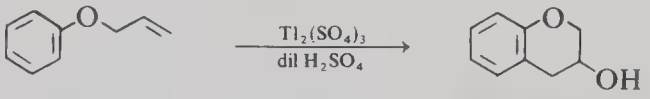


95 **96**

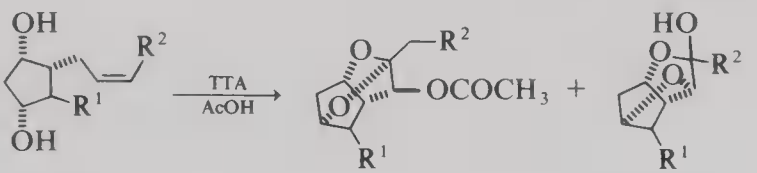
(19)

R = H, 82%
R = CH_3O, 100%

corresponding cycloalkanones, this is a general and highly efficient procedure for the ring expansion of cyclic aryl alkyl ketones whereby a methylene carbon, which may be substituted, is selectively inserted between the aromatic ring and the carbonyl group.[48–51] Product control by intramolecular participation of a suitably situated nucleophile is illustrated by the direct transformation of allyl phenyl ether into 3-hydroxychromane [Eq. (20)] and of the methyl ester of prostaglandin $F_2\alpha$ (**97**) into the dioxatricyclic systems **98** and **99** [Eq. (21)].[52,53] Carbon–carbon double bonds,[54–58] aromatic rings,[59,60] the alcohol,[41,52,53,61–68] carboxyl,[69–72] ester,[69] carboxamido,[69] and amino groups[73,74] have all been shown to participate intramolecularly in oxythallation reactions, and this general concept, while by no means yet defined with respect to scope and limitations, is one of considerable current interest and importance, especially in natural product chemistry.



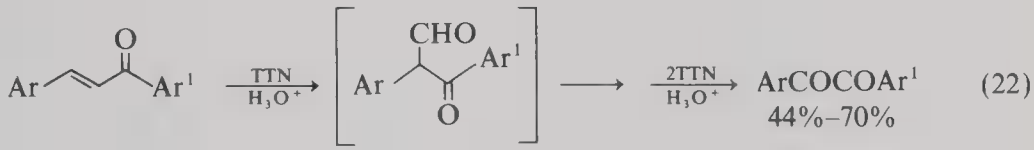
60%–70% (20)



97 **98** 24% **99** 51% (21)

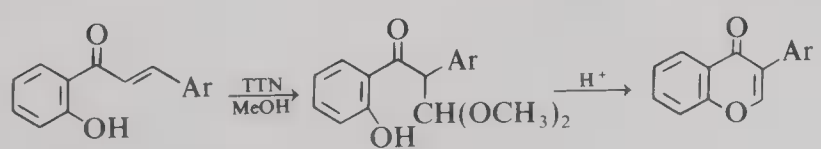
$R^1 = CH{=}CHCHC_5H_{11}$
OH
$R^2 = (CH_2)_3COOCH_3$

Olefins in conjugation with electron-withdrawing groups are relatively poorly nucleophilic, and it was rapidly established that such substrates either did not undergo oxythallation on treatment with TTN, as for example esters of cinnamic acids, or gave mixtures of products, as for example with cinnamaldehydes.[29] An intermediate situation was found to obtain with chalcones, and by the use of either prolonged reaction times and/or heating of the reaction mixture, oxidative rearrangement was found to occur in moderate to good yield [Eq. (22)].[75] Moreover, if the Ar^1 ring contains an *ortho*-situated hydroxy group

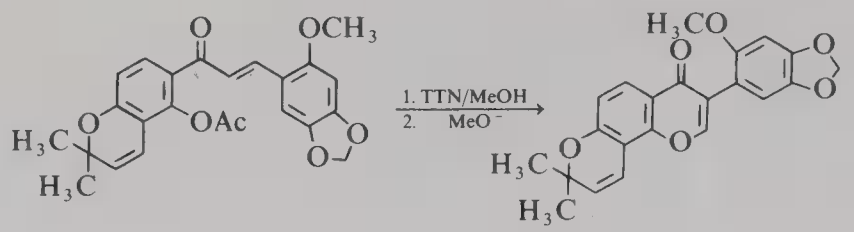


(22)

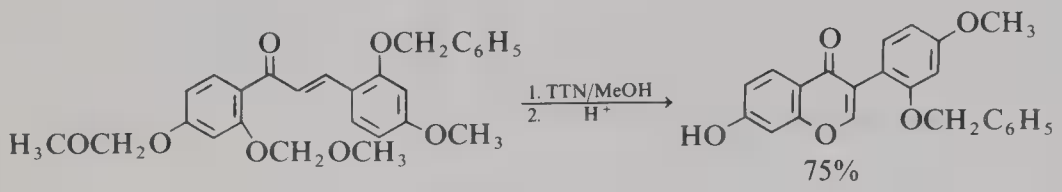
and the reaction is carried out in methanol, then intramolecular transacetalization of the 3,3-dimethoxy-1,2-diarylpropan-1-one (**100**) obtained by oxidative rearrangement of the chalcone[75,76] followed by loss of methanol results in formation of an isoflavone [Eq. (23)].[77,78] This general approach has now been developed into a simple, effective, and widely used preparative route to isoflavones[79–94]; typical examples are shown in Eqs. (24) and (25).[95,96] 1,3-Diaryl-1,3-propanediones, which are effectively fully enolized, undergo



100 (23)

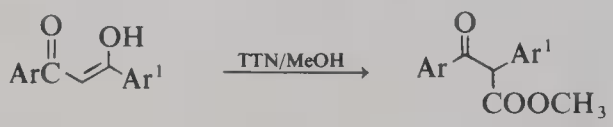


(24)

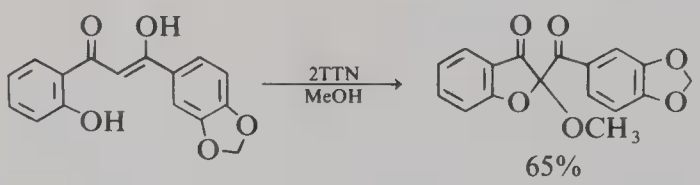


(25)

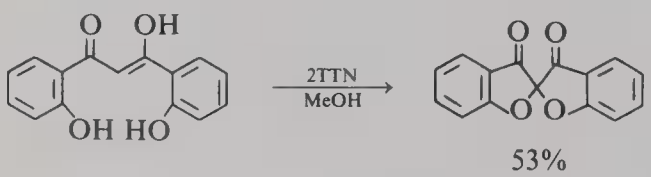
chalcone-like oxidative rearrangement on treatment with TTN in methanol to give methyl 3-oxo-2,3-diarylpropanoates [Eq. (26)]; the latter can react further with TTN to give a variety of products, and hence careful attention must be paid to the reaction conditions.[97] As with chalcones, the intermediate oxythallation adduct can be trapped intramolecularly by a suitably positioned ortho hydroxy group [Eqs. (27) and (28)]. The reactions of a variety of arylidene and diarylidene ketones with TTN have been examined; in some cases good to excellent yields of products of oxidative rearrangement have been obtained [Eqs. (29) and (30)], but in others complex mixtures of products were formed.[98]



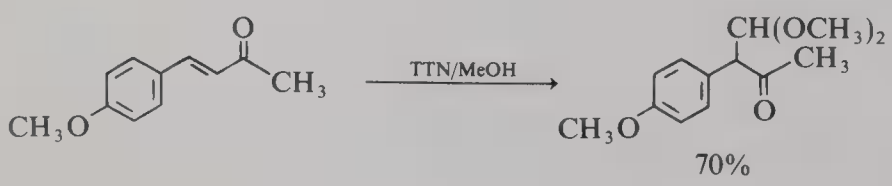
(26)



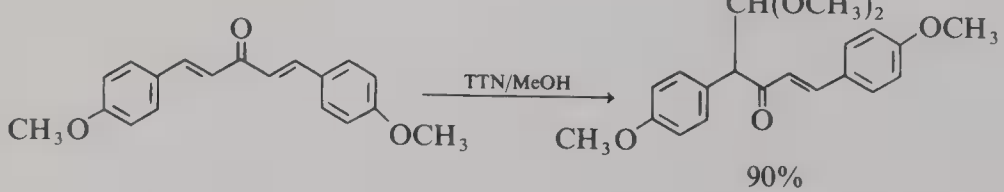
(27)



(28)



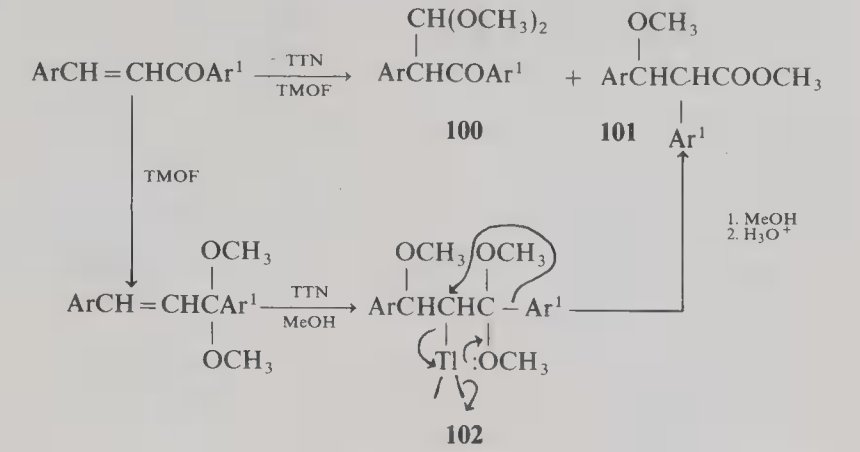
(29)



(30)

Despite the successful development and exploitation of the above isoflavone synthesis, most attempts to apply the oxythallation principle to simple α,β-unsaturated aldehydes,

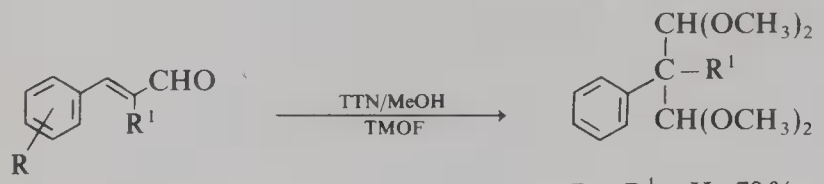
SCHEME 8



ketones, and esters gave negative or at best indifferent results of little practical value. Consequently, modifications of the standard procedures had to be developed, and two such have proved to be highly successful. The first involves the use of TTN in TMOF, either alone or in admixture with methanol,[5,30,31] and the second the use of the TTN/TMOF/methanol reagent supported on montmorillonite K-10 clay.[5,31,32] Use of these reagent combinations has not only successfully extended the oxythallation/oxidative rearrangement principle to α,β-unsaturated systems but has led to the discovery of several novel oxidative transformations. Thus, oxidation of chalcone with TTN in TMOF rather than methanol as solvent gives a 1:1 mixture of **100**, the expected product of rearrangement, and methyl 2,3-diphenyl-3-methoxypropanoate (**101**).[99,100] The latter product arises by previously unprecedented oxidative rearrangement of chalcones involving migration of the Ar^1 group as outlined in Scheme 8. As the oxythallation reaction which leads to **100** is slow due to deactivation of the carbon–carbon double bond by the carbonyl group, acetalization of the latter by TMOF, which is catalyzed by both TTN and the acidic medium, is a competing reaction. When the acetal has formed, however, deactivation of the carbon–carbon double bond ceases; it is then of a simple styrene type and hence oxythallation is rapid. The Ar^1 group in the oxythallation adduct **102** subsequently migrates in preference to the Ar group because of stabilization of the intermediate carbonium ion by the geminal methoxy groups. Evidence in support of the main features of this mechanism is readily available: independent preparation of the dimethyl acetal of chalcone followed by oxidation with TTN in TMOF gives methyl 2,3-diphenyl-3-methoxypropanoate (**101**, $Ar=Ar^1=C_6H_5$) in quantitative yield.[99,100] Further studies have shown that it is possible by appropriate choice of reaction conditions, positioning of activating substituents, and/or initial conversion of the chalcone to the corresponding acetal to effect selective rearrangement of either the Ar or the Ar^1 group.[100]

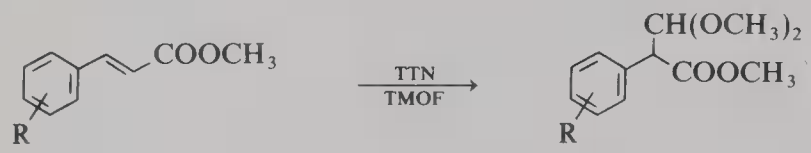
Both cinnamaldehydes and methyl cinnamates also undergo facile oxidative rearrangement on treatment with either TTN in TMOF/methanol[30] or with the TTN/K-10 reagent[32] to give arylmalondialdehyde tetramethyl acetals and methyl α-dimethoxymethylarylacetates, respectively. Yields are excellent, and typical examples are shown in Eqs. (31) and (32). That is, readily available chalcones, cinnamaldehydes, and methyl cinnamates can be transformed easily, rapidly, and in high yield into the acetal protected forms of the much less readily available and unstable (to retro-Claisen condensation) 1,3-dicarbonyl compounds **103–105**; the latter, as the corresponding ketals, have been utilized for the synthesis of a wide range of heterocycles.[101]

Ketones rapidly enolize under the acidic conditions of oxythallation and the resultant electron rich olefinic double bond readily undergoes oxythallation. By far the most important reaction of this type is with aryl alkyl ketones. Oxidation of acetophenone with TTN in acidic methanol, for example, gives methyl phenylacetate (94%) and ω-



(31)

R = R¹ = H, 79%
R = 4-CH_3O, R¹ = H, 84%
R = 4-O_2N, R¹ = H, 63%
R = H, R¹ = CH_3, 83%
R = 3-O_2N, R¹ = CH_3, 50%

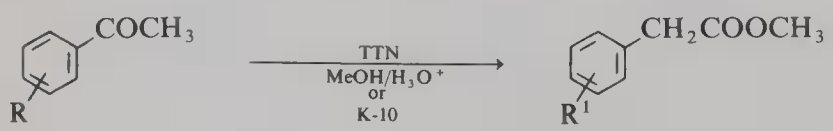


(32)

R = H, 96%
R = 4-CH_3, 96%
R = 4-CH_3O, 90%
R = 2-F, 83%
R = 4-Cl, 96%

(33)

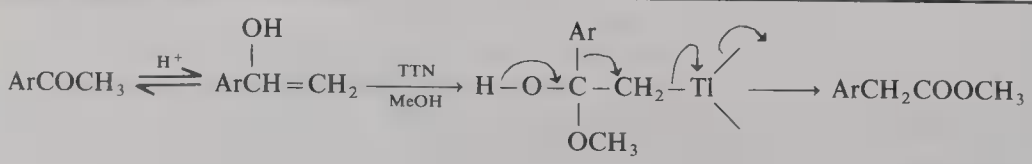
methoxyacetophenone (6%) [Eq. (33)][102,103]; formation of the latter compound is completely suppressed by using the TTN/K-10 reagent.[32] The suggested mechanism for this transformation is outlined in Scheme 9.[102–106] This experimentally simple and high yielding transformation, typical examples of which are shown in Eq. (34),[32,102,103] has been widely



(34)

R = H, 84%
R = 4-Br, 89%
R = 4-F, 88%
R = 4-Me, 86%
R = 2,4,6-$(CH_3)_3$, 81%
R = 4-HO, 64%
R = 2-CH_3O, 62%
R = 3-CH_3O, 68%
R = 4-CH_3O, 89%
R = 3,4-$(CH_3O)_2$, 88%
R = 2,3-CH=CH–CH=CH, 91%
R = 3,4-CH=CH–CH=CH, 89%

SCHEME 9



$$ArCH=CHCOAr^1 \equiv Ar-\underset{\displaystyle CHO}{\underset{|}{C}}HCOAr^1$$

103

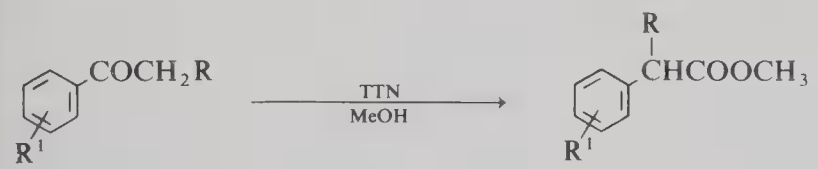
$$ArCH=CHCHO \equiv Ar-\underset{\displaystyle CHO}{\underset{|}{C}}HCHO$$

104

$$ArCH=CHCOOCH_3 \equiv Ar-\underset{\displaystyle CHO}{\underset{|}{C}}HCOOCH_3$$

105

utilized[107–115] for the preparation of a wide range of arylacetic esters, and procedures have been developed whereby the process is rendered catalytic in thallium salt by *in situ* reoxidation of thallium(I) to thallium(III).[116] The general approach can also be extended to the preparation of α-alkylarylacetic esters, some of which, as already mentioned, are of considerable commercial importance as pharmaceuticals. In these cases, use of methanol alone as solvent is often not satisfactory, as significant amounts (up to ca. 30%) of α-methoxy ketones can be obtained as by-products as a result of solvolytic displacement of the thallium substituent from the oxythallation adduct.[103] These problems are, however, completely eliminated either by employing the enol ether of the ketone as substrate[117] or by using the TTN/TMOF/methanol or TTN/K-10 reagent systems, and typical transformations are



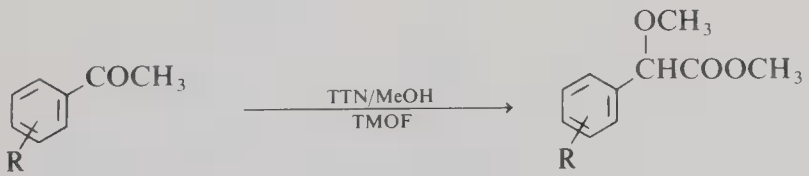
(35)

$R = CH_3$, $R^1 = H$, (TMOF), 98%
$R = C_2H_5$, $R^1 = H$, (K-10), 98%
$R = CH_3$, $R^1 = 4$-  , (H_3O^+), >85%
$R = CH_3$, $R^1 = 3\text{-}C_6H_5CO$, (TMOF), 98%

shown in Eq. (35).[30,32,118–120] Aroylalkanoic acids undergo both oxidative rearrangement and esterification on treatment with the TTN/K-10 reagent [Eq. (36)].[121] Interestingly, oxidation of acetophenones by the TTN/TMOF reagent results not only in oxidative rearrangement

$$PhCOCH_2(CH_2)_nCOOH \xrightarrow{TTN/K\text{-}10} PhCH(CH_2)_nCOOCH_3 \qquad (36)$$

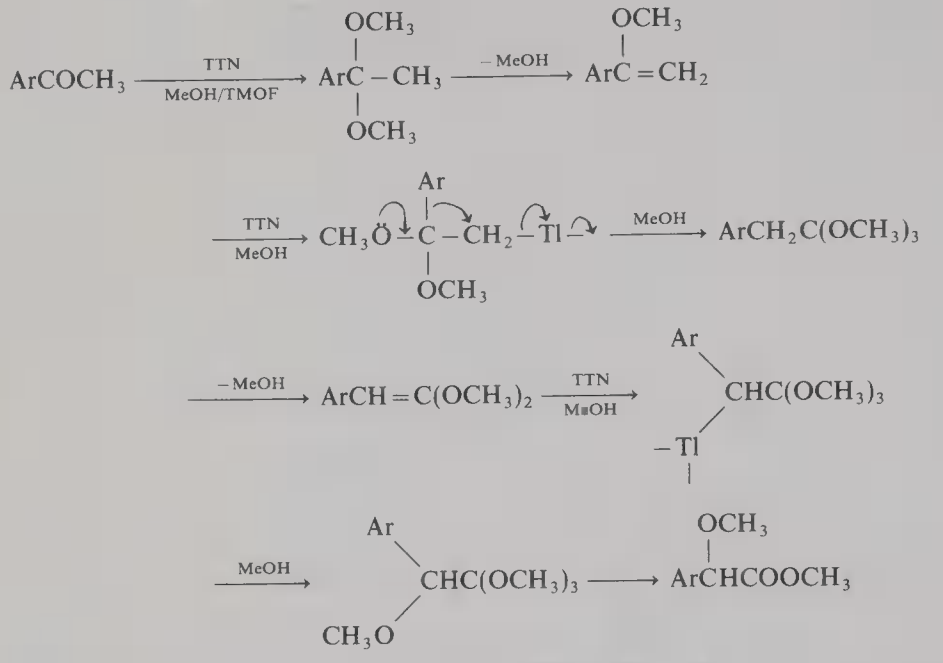
$n = 1$–3



(37)

R = H, 70%
R = 4-CH_3O, 81%
R = 4-O_2N, 87%
R = 3-C_6H_5O, 97%

SCHEME 10

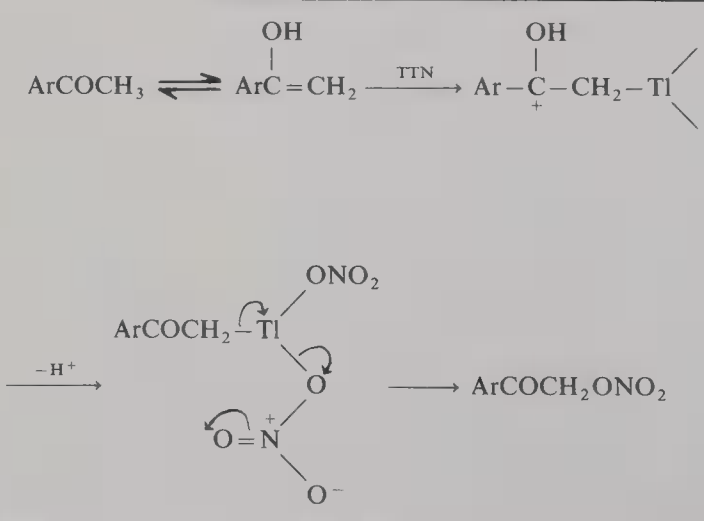


but also in methoxylation and gives methyl α-methoxyarylacetates in excellent yield [Eq. (37)].[30] Two successive methoxythallation reactions are involved, as outlined in Scheme 10.

By contrast to the preceding reactions, all of which involve oxidative rearrangement of the organic substrate, use of non-nucleophilic solvents can give products of unrearranged carbon skeleton. Oxidation of acetophenones with TTN in dimethyl carbonate or acetonitrile, for example, gives excellent yields of the corresponding α-nitrato ketones.[122] In this instance solvothallation is not possible and the mechanism outlined in Scheme 11 has been suggested. With aliphatic ketones the reaction is only useful either where the ketone is symmetrical or where one of the alkyl groups is tertiary.

Oxidation of aliphatic and alicyclic ketones with thallium(III) has been surprisingly little studied, and there is little information available on the mechanisms of the reactions. Reaction of aliphatic ketones and enamines of cyclic ketones with thallium(III) acetate gives α-acetoxy derivatives, but little is known of the scope, limitations, and real synthetic potential of the processes.[123–126] Oxidation of cycloalkanones can give excellent yields of ring contrac-

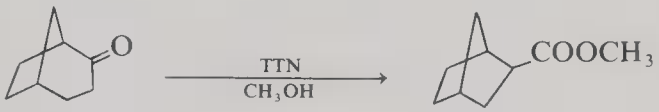
SCHEME 11



ted carboxylic acids or esters[127] as outlined in Eqs. (38)–(40),[128–130] but again the scope and limitations of this potentially very useful reaction remain to be defined. It is, however, clear that factors such as reaction conditions and the nature and position of the carbonyl group with respect to other functional groups in the molecule can have a profound effect on the

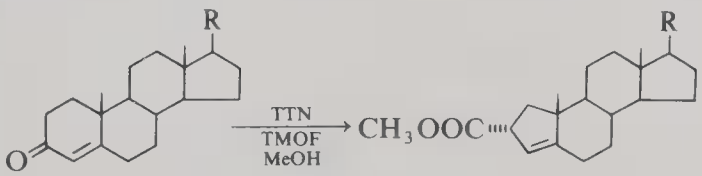
(38)

$TlCl_3/HClO_4$, 80%
TTN/AcOH, 95%



(39)

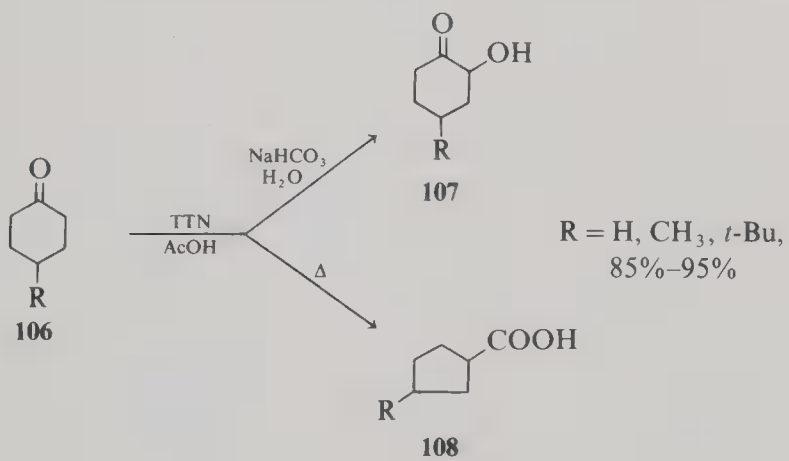
85%



(40)

R = $OCOCH_3$, 75%
R = $COCH_3$, 65%

overall course of reaction.[131–134] The effect of reaction conditions is dramatically illustrated with simple cyclohexanones.[135] Thus, oxidation of **106** with TTN in acetic acid proceeds smoothly and almost instantaneously at room temperature. If the thallium(I) nitrate is then removed and the reaction mixture neutralized with aqueous sodium bicarbonate solution, excellent yields of the acyloins **107** are obtained. If, on the other hand, the reaction mixture after removal of the thallium(I) nitrate is gently warmed, no acyloin is formed; the sole product is the ring contracted carboxylic acid **108**. These reactions have not yet been fully satisfactorily explained.



R = H, CH_3, *t*-Bu,
85%–95%

Mercury(II) catalyzed hydration of acetylenes is a well established and synthetically useful process. Uemura and his colleagues have shown that thallium(III) acetate can perform the same function, but there is no practical advantage in the thallium procedure.[136] The reactions of acetylenes with TTN, on the other hand, are much more interesting, as hydration and formation of ketones are not observed. Instead, these reactions lead to one of four dif-

ferent types of products, depending on the nature of the acetylene.[137] Thus, diaryl acetylenes are smoothly converted into benzils [Eq. (41)] and dialkyl acetylenes to acyloins [Eq. (42)]; terminal acetylenes are oxidized to carboxylic acids with the loss of the terminal carbon atom [Eq. (43)], while alkyl aryl acetylenes undergo oxidative rearrangement to give methyl α-alkylarylacetates [Eq. (44)]. The last reaction represents a very simple procedure

$$ArC{\equiv}CAr^1 \xrightarrow[CH_3OH \text{ or } H_3O^+]{TTN} ArCOCOAr^1 \quad (41)$$

45%–95%

$$RC{\equiv}CR \xrightarrow[H_3O^+ \text{ or } CH_3OH]{TTN} RC(OR^1)-COR \quad (42)$$

$R^1 = H, OCH_3$, 70%–90%

$$RC{\equiv}CH \xrightarrow[H_3O^+]{2TTN} RCOOH \quad (43)$$

55%–80%

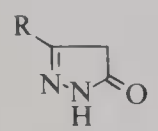
$$ArC{\equiv}CR \xrightarrow[CH_3OH]{2TTN} ArCH(R)COOCH_3 \quad (44)$$

78%–98%

for the preparation of these substituted arylacetic acids, a number of which are important nonsteroidal anti-inflammatory drugs. Reasonable mechanisms, all of which involve oxythallation as the initial step, have been suggested for these acetylene transformations.[137]

2.2.3. Oxidation of Nitrogen Compounds

In contrast to the above oxythallation reactions, which involve addition of the thallium(III) reagent to a C=C or C≡C bond, there is one particular type of oxidation which is believed to proceed via an electrophilic substitution reaction. Reaction of 3-substituted 5-pyrazolones (**109**) with TTN in methanol is rapid at room temperature; two equivalents of oxidant are required for completion of reaction, nitrogen is evolved, and 2-alkynoic esters (**110**) are formed in excellent yield [Eq. (45)].[138,139] The mechanism shown in



109

$$\xrightarrow[MeOH]{2TTN} RC{\equiv}CCOOCH_3 \quad (45)$$

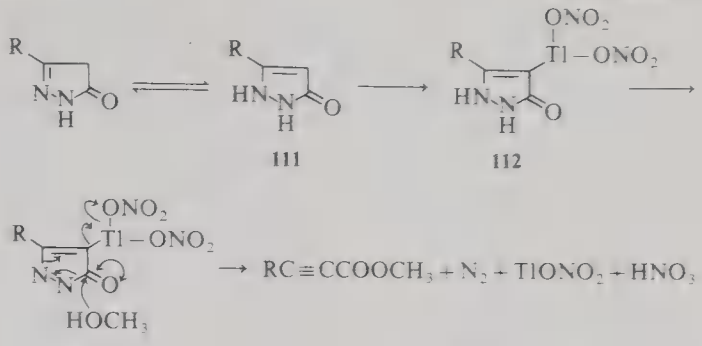
67%–95%

110

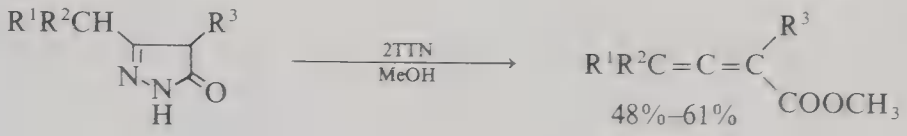
Scheme 12 has been proposed for this transformation,[138] in which it is suggested that TTN functions (a) as an electrophile in the substitution reaction **111** → **112**, and (b) as an oxidant for the NHNHCO group. There is excellent precedent for such reactivity. Thus, the role of thallium(III) as an electrophile in S_EAr reactions is thoroughly well documented[5]; 5-pyrazolones are known to undergo facile electrophilic substitution at the 5-position[140]; enamines (cf. **111**) react readily with thallium(III) salts[124]; and compounds containing the NHNHCO group are postulated to react with thallium(III) salts as shown in Scheme 12.

5-Pyrazolones are almost always prepared by reaction of a β-keto ester with hydrazine. The transformation outlined in Eq. (45) thus represents in a formal sense the dehydration of a β-keto ester. Moreover, in a logical extension of this oxidation, it has been shown that reaction of 3,4-disubstituted 5-pyrazolones (readily prepared by treatment of α-substituted β-

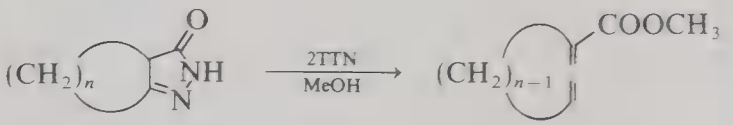
SCHEME 12



keto esters with hydrazine) with TTN in methanol leads directly to allenic esters [Eq. (46)].[141] This transformation can be explained as outlined in Scheme 13, and also formally corresponds to dehydration of the precursor α-substituted β-keto ester. This latter reaction has been successfully extrapolated to the synthesis of cyclic allenic esters [Eq. (47)].[142–144]



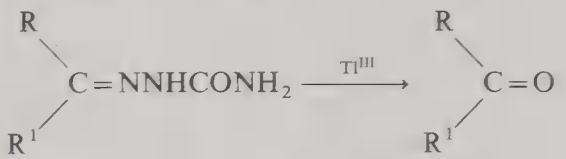
(46)



(47)

$n = 7$–10, 49%–91%

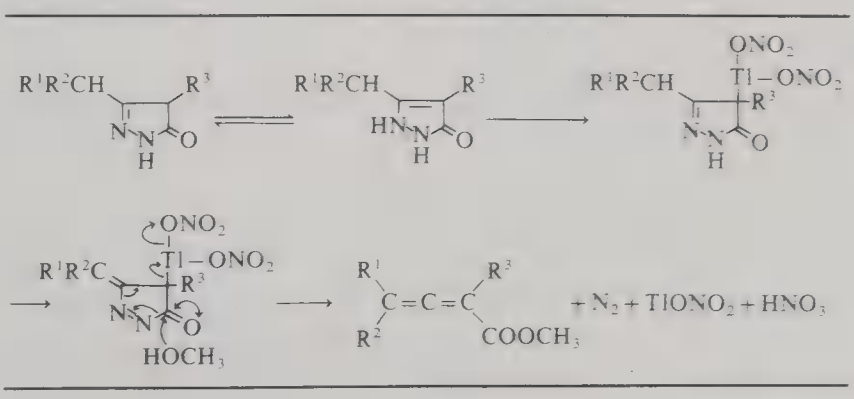
As indicated above, compounds which contain the NHNHCO unit are oxidized by thallium(III). Thus semicarbazones are smoothly converted into aldehydes or ketones on treatment with either TTN[145] or thallium(III) acetate[146] [Eq. (48)], and the latter salt has



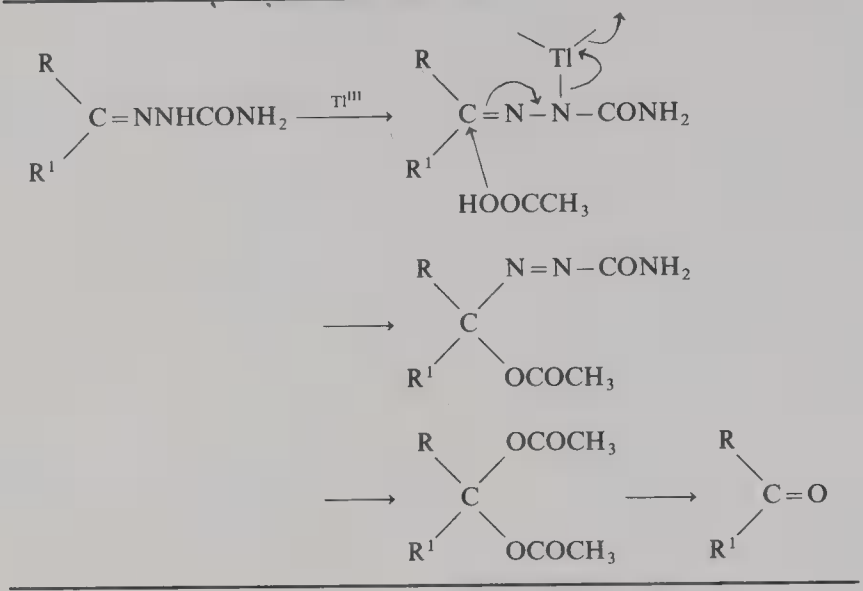
(48)

also been shown to be a good reagent for the analogous regeneration of carbonyl compounds from the corresponding toluene-*p*-sulphonylhydrazones.[146] The mechanism outlined in

SCHEME 13



SCHEME 14

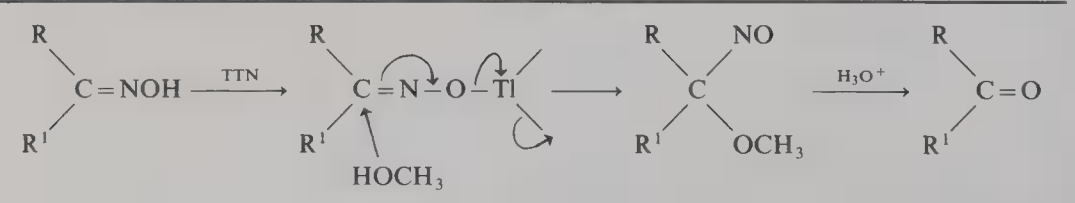


Scheme 14, in which initial formation of an N–Tl bond is postulated, has been advanced for these reactions. Oximes react very rapidly with TTN and aldehydes and ketones are obtained in excellent yield.[145] In this case the mechanism is postulated to involve initial ligand exchange between TTN and the oxime to give **113**, which is converted into the carbonyl compound as shown in Scheme 15. If TTN/TMOF is used in these reactions the rather unstable nitroso ethers **114** can in fact be isolated. There is a fair amount of evidence in support of the mechanism shown in Scheme 15, but there is also some evidence that a one-electron transfer pathway may also be operative. Phenylhydrazones react with TTN much more slowly than oximes, and yields of ketones are moderate. Treatment of phenylhydrazone derivatives of α,β-unsaturated carbonyl compounds with TTN does not result in regeneration of the parent carbonyl compounds, but in oxidative cyclization and formation of 1-phenylpyrazoles in moderate yield.[145]

2.2.4. Oxidation of Organosulfur Compounds

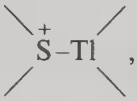
Qualitatively, thallium(III) is one of the softest of the metal ions[147] and it is therefore not at all surprising that thallium(III) acetate, TTFA, and TTN react readily with organosulfur compounds. Thiols are smoothly converted into disulfides in almost quantitative yield on treatment with thallium(III) acetate in chloroform,[148] thioamides are rapidly converted into either the *O*-amides or the corresponding nitriles,[149] and the thallium(III)-promoted hydrolysis of S-alkyl esters is very much faster than the corresponding hydrogen ion-catalyzed reaction.[150] In this latter context, however, it is interesting to note that TTFA

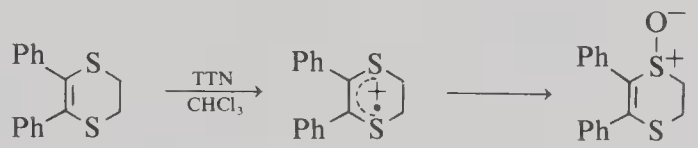
SCHEME 15



113 **114**

has been found to be less efficient than mercury(II) trifluoroacetate in the Masamune esterification procedure.[151]

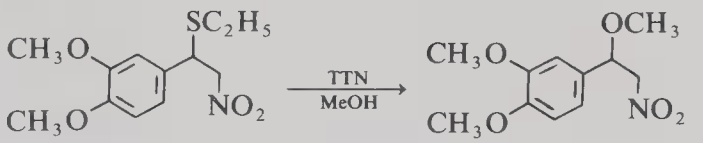
All of these reactions appear to proceed via initial formation of a 1:1 complex between the organosulfur compound and the thallium(III) salt of the type  , and reasonable mechanisms can be suggested for the subsequent transformations of such complexes. A number of interesting and in some cases synthetically important reactions of sulfides and dithioacetals with TTN have been reported where initial formation of similar complexes is either postulated or tacitly assumed. The situation may, however, be more complex, as in at least one case a radical cation mechanism has been established. Thus, oxidation of the dihydrodithiin **115** [Eq. (49)] with TTN in chloroform/methanol gives the sulfoxide **117** in



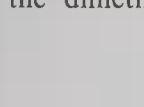
115 **116** **117** 72% (49)

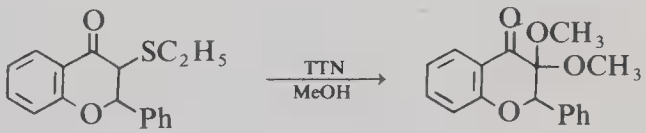
72% yield via the radical cation **116**.[152] Oxidation of a number of other sulfides and selenides under the same conditions gives excellent yields of the corresponding sulfoxides and selenoxides, respectively; the sulfoxides can be further oxidized to sulfones by longer exposure to TTN. The origin of the oxygen atom(s) in the final products is, however, unknown, though it may well be derived from the water of hydration of TTN.

From the few studies available thus far, all of which are in the form of preliminary communications, it is clear that the nature of the products obtained from the oxidation of sulfides by thallium(III) depends on the amount and kind of thallium salt used, the reaction conditions, and the nature of the sulfide. Oxidation of the benzyl sulfide **118** with TTN in methanol, for example, gives the methyl ether **119** [Eq. (50)][153]; similar results are obtained

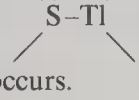


118 **119** 98% (50)

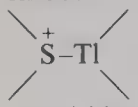
with other alcohols, although in these cases loss of the benzylic substituent and formation of the corresponding nitrostyrene is also observed. The reaction is postulated to proceed via the  intermediate, which can either undergo direct solvolysis or ionize to the benzylic carbonium ion, which could serve as precursor to both types of product. By contrast, oxidation of β-oxido sulfides **120** with TTN in methanol or methanol/chloroform gives either the dimethyl acetals **121** [Eq. (51)] or, in isolated cases, the α-dicarbonyl compound



120 **121** 91% (51)

[Eq. (52)].[154] Yields in this Pummerer type of reaction are good to excellent but the actual mechanism is not known, especially whether a  complex is involved or whether initial oxidation of the sulfide to the sulfoxide occurs.

(52)

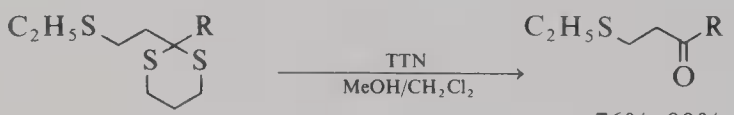
The reactions of dithioacetals also apparently depend on the nature of the substrate. Treatment of α-oxo dimethylthioacetals with TTN in methanol, for example, results in smooth conversion to the corresponding dimethyl acetals, presumably by solvolysis of  complexes.[155] In the absence of an α-oxo substituent, however, 1,3-dithioles and 1,3-dithianes undergo rapid dethioacetalization at room temperature under the same conditions and the corresponding aldehydes and ketones are obtained in generally excellent yield.[156–161] TTFA can also be used for dethioacetalization[162] but fairly detailed studies of this very facile reaction have established that TTN is the reagent of choice. The only potentially serious limitation with respect to other functional groups appears to be with phenols, which are very rapidly oxidized by TTN (see Section 2.3). A wide range of S-acetals has been successfully dethioacetalized, including substrates containing alcohol, ketone, olefin, and acetylene groups, and selective dethioacetalization has also been demonstrated; typical examples are shown in Eqs. (53)–(55).[156,159,160]

73%

(53)

97%

(54)



76%–90%

(55)

2.3. Reactions of Uncertain Mechanisms. Oxidation of Phenols and Derivatives

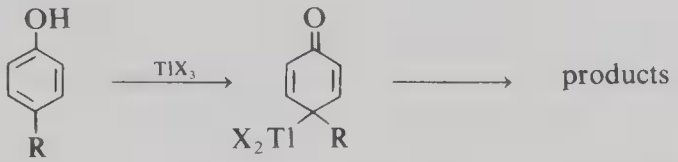
It has been known for almost 50 years that phenols are readily oxidized by thallium(III), but the real synthetic utility of some of these reactions has only been recognized during the last decade. There has been surprisingly little systematic study of these reactions, even though it is obvious from the results available that the products which can be obtained depend on the nature of the phenol, the thallium(III) reagent used, and the reaction conditions. Thallium(III) chloride, oxide, acetate, trifluoroacetate, nitrate, and perchlorate have been variously employed for the oxidation of a wide range of structurally different phenols, but in only a very few instances have the reactions been studied in any detail with respect to the development of optimum experimental conditions, especially the thallium(III) salt used.

Thallium(III)-induced oxidations of phenols are among the most interesting of all thallium(III) oxidations with respect to mechanism. Various different mechanisms have been suggested, some of which might appear to be perfectly plausible as paper exercises, others perhaps less so[163]; in fact, there is either very little or no evidence to substantiate any of them

and the reaction pathways remain more or less obscure. It is particularly interesting to note that while concepts such as ligand exchange between the phenol and the thallium(III) reagent[163–165] [Eq. (56)] and *ipso*-substitution[166] [Eq. (57)] have been invoked to account

$$ArOH + TlX_3 \longrightarrow ArOTlX_2 \longrightarrow \longrightarrow (ArO)_3Tl \qquad (56)$$

$$ArOTlX_2 \longrightarrow \text{products} \longleftarrow (ArO)_3Tl$$



(57)

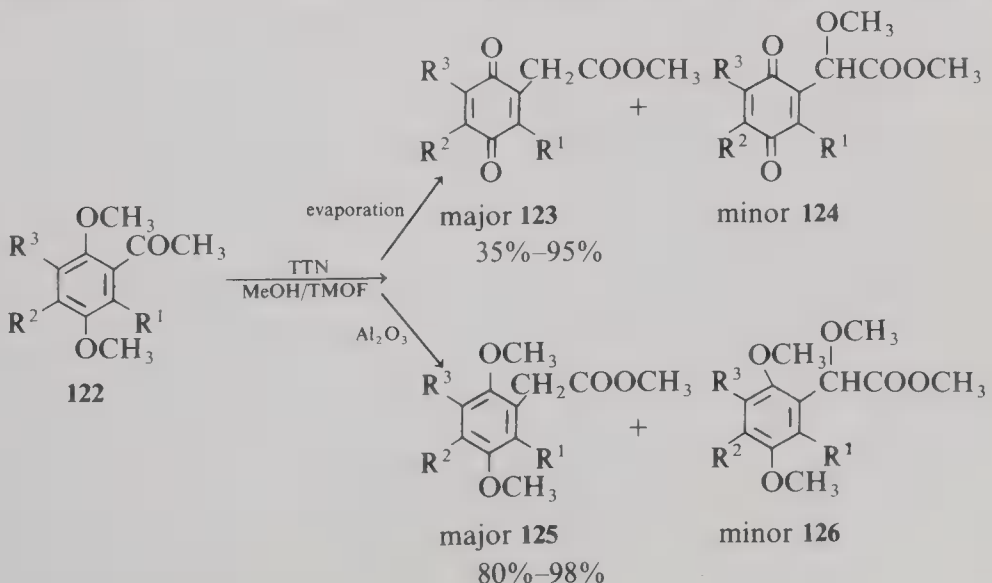
for certain oxidations, almost no serious consideration has been given to the possibility of radical cation mechanisms. The mechanistic ambiguities notwithstanding, certain thallium(III)-induced oxidations of phenols are of considerable synthetic utility. The most important of these are those in which phenols are oxidized either to quinones or to cyclohexadienones and/or which result in intramolecular ring closure to the phenolic ring.

Hydroquinone is oxidized to *p*-benzoquinone by both thallium(III) chloride[164] and acetate,[167] but TTFA[165] and TTN[166] are very much more efficient oxidants. Using these latter reagents, reaction is almost instantaneous at room temperature, yields are excellent, and the process is general. *p*-Benzoquinones are also obtained directly by TTFA oxidation of phenols which have either an amino or a leaving group in the *para* position [Eq. (58)]: a

(58)

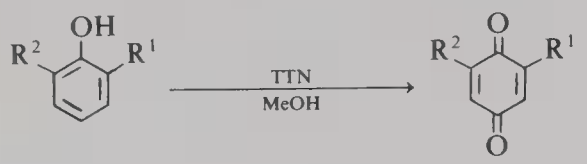
R = *t*-Bu, NH_2, halogen, CH_3COO

special case of this latter type of reaction is the oxidation of 4-*t*-butylphenols, in which the *t*-butyl group is lost as isobutylene.[165] 2,5-Dimethoxyacetophenones are converted to *p*-benzoquinones by treatment with TTN/TMOF in methanol in what appears to be a most unusual reaction.[168] Thus oxidation of **122** is complete within a few minutes at room temperature and if the thallium(I) nitrate is removed by filtration and the filtrate concentrated *in vacuo*, a mixture of **123** and **124** is obtained [Eq. (59)]. If, on the other hand, the reaction is carried



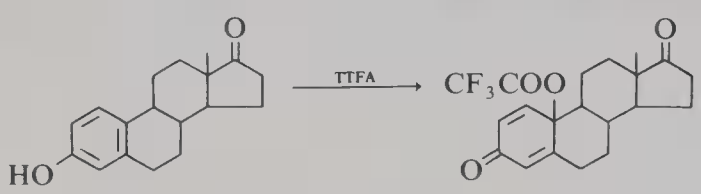
(59)

out in exactly the same way but the filtrate is passed through a short column of alumina prior to evaporation, then the products are **125** and **126**, i.e., the "expected" products of oxidative rearrangement. Note that oxidative rearrangement of the acetyl group also occurs in the formation of **123** and **124**. Finally, in a reaction reminiscent of the TTFA-induced oxidation of **20** and **65b**, 2,6-disubstituted phenols are smoothly converted into 2,6-disubstituted *p*-benzoquinones on treatment with TTN in methanol [Eq. (60)].[166]

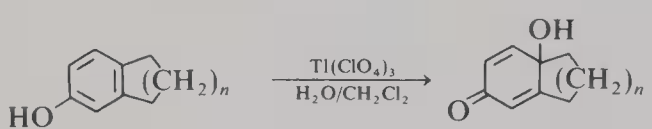


72%–83% (60)

A much more unusual and synthetically more significant reaction is the direct oxidation of 4-substituted phenols to 4,4-disubstituted cyclohexa-2,5-dienones. Use of thallium(III) for this type of reaction was first reported in 1963 by Hecker and Lattrell, who succeeded in isolating quinol ethers and acetates in low yields from the boron trifluoride catalyzed reactions of a number of 4-alkylphenols with thallium(III) acetate in methanol and acetic acid, respectively.[169] Further isolated examples have been reported subsequently[170,171] [Eq. (61) and (62)], but the first detailed study of this type of reaction appeared only in 1976.[166] TTN

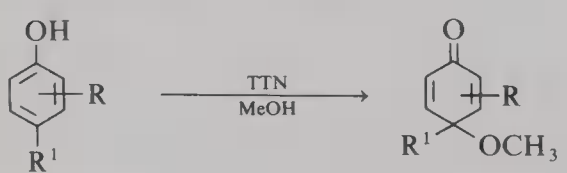


75% (61)



$n = 1$ or 2, 80% (62)

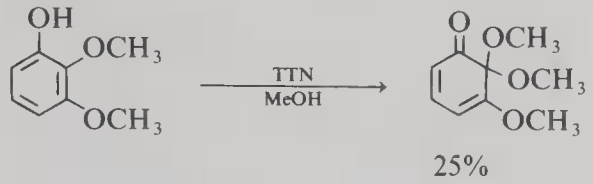
in TMOF/methanol or in methanol alone was found to be an excellent reagent for the conversion of 4-methoxy- and 4-alkylphenols in almost quantitative yield to 4,4-dimethoxy- and 4-alkyl-4-methoxycyclohexa-2,5-dienones, respectively [Eq. (63)]. Simple 4-alkoxyphenols



R^1 = alkyl, alkoxy **127** (63)

are also converted to **127** ($R^1 = OCH_3$) in generally excellent yield under the same conditions, but with more highly substituted aromatic substrates mixed acetals and hemiacetals can be obtained. Alcohol solvents other than methanol can be used for the preparation of mixed acetals and hemiacetals, but yields are generally only moderate. A few 6,6-dimethoxycyclohexa-2,4-dienones have been prepared in an analogous manner [Eq. (64)], but these products are very unstable and rapidly dimerize.

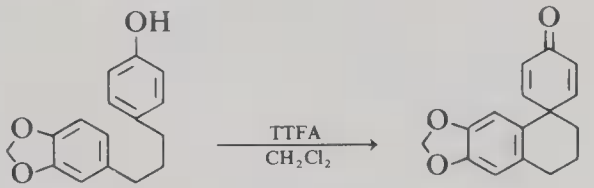
Quinone monoacetals are valuable synthetic intermediates, but prior to the thallium-induced oxidation procedure, which is now quite widely used,[172–180] there were few satisfac-



25% (64)

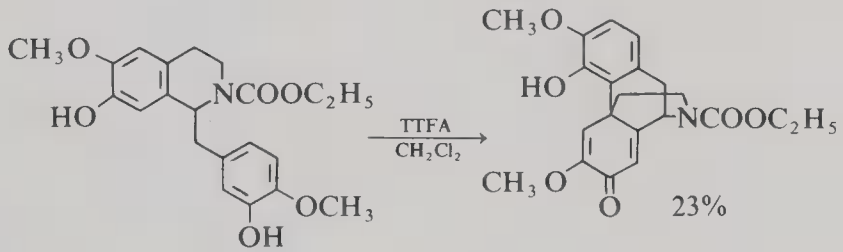
tory methods for their preparation. Analagous oxidations of phenols have been effected by various other oxidants such as silver(I), copper(II), manganese(III), cerium(IV), and DDQ, but in general yields are low. Büchi has reported on a comparative study of the oxidation of ten *p*-alkoxyphenols with iron(III) chloride, DDQ, and TTN, and in the majority of cases TTN was as good as, or better than, either of the other oxidants.[181] He also pointed out that the yields of acid sensitive products could be improved substantially if powdered potassium bicarbonate were added to the reaction mixture.

In all of the above reactions the reactive intermediate, the nature of which is unknown, is trapped intermolecularly. Intramolecular capture is, however, also possible in what appear to be closely related reactions. Thus, Schwartz showed that oxidation of **128** with TTFA in methylene chloride gave the spirocyclic ketone **129** in excellent yield [Eq. (65)].[182,183] The

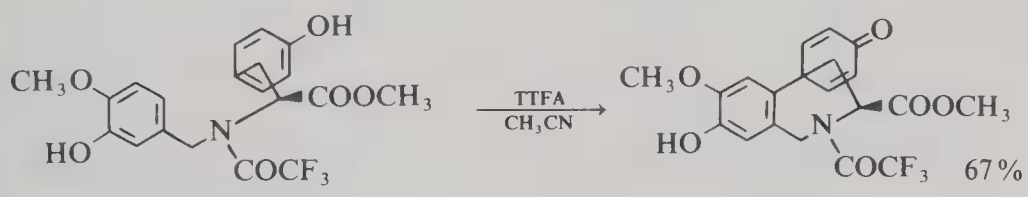


128 **129** 88% (65)

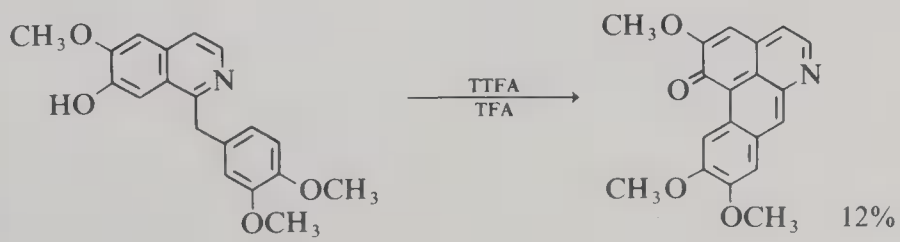
utility of TTFA in the oxidative cyclization of such 1,3-diarylpropanes has been further demonstrated by Ronlan *et al.*; they used acetonitrile as solvent, obtained yields of 80%–100% of the spirocyclic cyclohexadienones, and found the TTFA method to be superior to anodic oxidation.[184] Other examples of applications to natural product chemistry/synthesis are summarized in Eqs. (66)–(68),[185–188] and while in some cases the



(66)

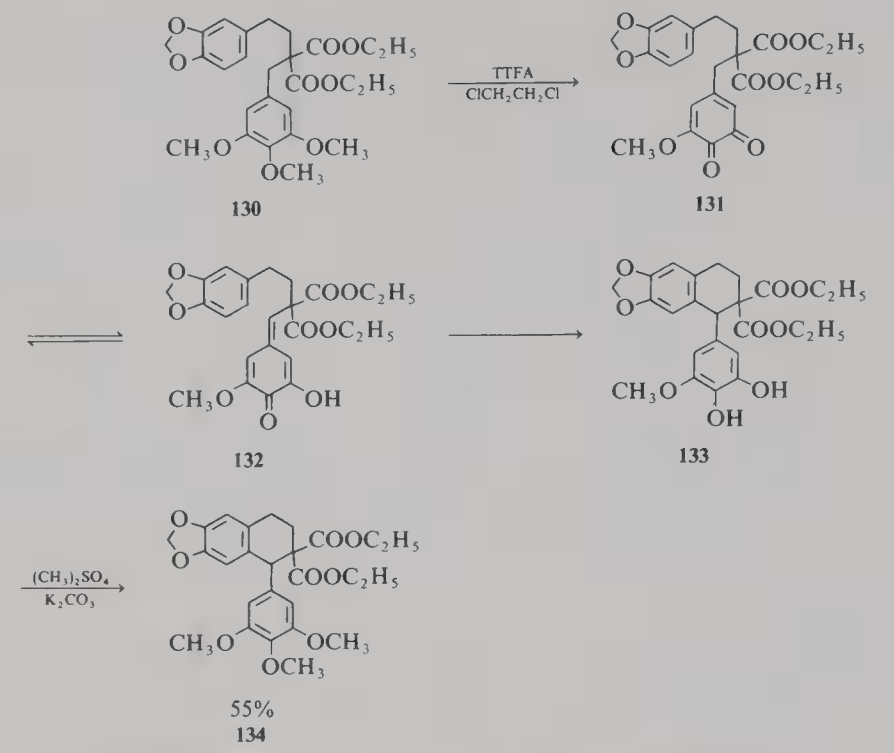


(67)



(68)

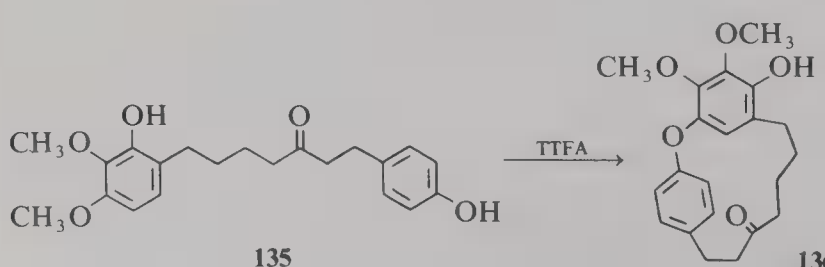
SCHEME 16



130 131 132 133 134

yields are low, they are generally considerably better than those obtained using alternative oxidation procedures. Reactions of this type could become of considerable importance in natural product chemistry, especially if care is taken to devise the optimum reaction conditions and to utilize the best thallium(III) salt. It is interesting to note, for example, that TTFA was the reagent used in all of the above intramolecular cyclohexadienone syntheses; apparently no attempt was made in any case to examine the possible efficacy of TTN in such oxidations.

Finally, there are three reports of TTFA oxidations of phenols which apparently result in different types of intramolecular ring closure. During studies of synthetic routes to podophyllin lignan lactones the phenol **130** was oxidized with TTFA in either 1,2-dichloroethane or methylene chloride. This produced a deep red solution which was reduced with bisulfite; the product after extraction was methylated and was found to be **134** (Scheme 16).[189] There is good evidence that this reaction proceeds by an initial oxidative demethylation to give the *o*-benzoquinone **131**[190]; the latter is in prototropic equilibrium with the quinone methide **132**, and intramolecular electrophilic aromatic substitution of the methylenedioxyaryl ring would give the catechol **133**. Remarkably, under the same conditions but in the absence of boron trifluoride etherate, only the catechol **133** is obtained (66%). In another unusual reaction, the 1,7-diarylheptanoid **135** was oxidized with TTFA to the 14-oxa-[7,1]-metaparacyclophane (**136**) [Eq. (69)] and TTFA was reported to give the



135 136 (69)

cleanest reaction of the various one- and two-electron oxidants examined.[191] Compound **136** was the first example of its type to be prepared synthetically, and this general approach may prove to be valuable for the synthesis of naturally occurring *m,m*-bridged biaryls. Clearly, however, much more detailed studies of these and related reactions will be necessary before any attempt can be made to define the full utility of the reactions.

3. EXPERIMENTAL CONSIDERATIONS AND PROCEDURES

The two most important thallium(III) salts used as oxidants in organic synthesis, thallium(III) trifluoroacetate[192] and nitrate,[193] are commercially available.*

Thallium(III) trifluoroacetate and nitrate are highly toxic, but do not present the explosive hazard associated with thallium(III) perchlorate. They may be safely handled using prudent laboratory procedures.[193] Rubber gloves and laboratory coats should be worn and reactions should be carried out in an efficient hood. Thallium wastes should be collected and disposed of separately.† For information on an antidote for thallium poisoning see Ref. 194.

2,2′-Dibromo-4,4′,5,5′-tetramethoxybiphenyl.[195] 4-Bromoveratrole (4.34 g, 0.02 mol) was added in one portion to TTFA (5.5 g, 0.01 mol) in trifluoroacetic acid (TFA) (25 ml) at room temperature. The solution immediately turned deep red in color and became warm, and a colorless solid precipitated within a few minutes. The mixture was stirred for 10 min, then poured into water and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was passed through a short column of alumina using petroleum ether (bp 40–60°C)/$CHCl_3$ (1:1) as eluent to remove highly colored polymeric materials. Evaporation of the eluent under reduced pressure followed by crystallization of the residual solid thus obtained from petroleum ether (bp 100–120°C)/toluene gave pure 2,2′-dibromo-4,4′,5,5′-tetramethoxybiphenyl (3.48 g) as colorless needles, mp 159–160°C (lit,[196] mp 157–159°C). Concentration of the mother liquors gave 4-bromoveratrole (0.35 g, 8% recovery). The yield of biaryl based on 92% conversion of the starting material is 88%.

*(±)-3-Methoxy-N-Acetylnornantenine (**23**) and (±)-6a,7-Dehydro-3-methoxy-N-acetylnornantenine.*[197] A solution of TTFA (280 mg, 0.52 mmol) in TFA (120 ml) was cooled to 0°C and a solution of 1-(3′,4′-methylenedioxybenzyl)-2-acetyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (200 mg, 0.5 mmol) in CH_2Cl_2 (5 ml) and $BF_3 \cdot Et_2O$ (1 ml) was added quickly. The reaction mixture was stirred at 0°C for 3 h; the solvent was then removed under reduced pressure, water was added to the residue, and the mixture was basified with diluted NH_4OH solution. Extraction with $CHCl_3$ until no color was apparent in the extract, followed by drying over K_2CO_3 and evaporation, gave an oily residue which was purified by preparative TLC (benzene/Me_2CO 8:1) to give pure **23**, 81 mg (40%), R_f 0.39, mp 175–177°C (lit,[198] mp 174–175°C) and (±)-6a,7-dehydro-3-methoxy-*N*-acetylnornantenine, 62 mg (31%), R_f 0.50, mp 235°C; uvλ_{max}(EtOH) (log ε) 206(4.31), 263(4.63), 284(4.26), 324(3.89) nm; ir (KBr) 1638 cm^{-1}; NMR ($CDCl_3$) δ 8.99, 8.54, 7.91 (3 s, 3 H, 3 ArH), 6.08 (s, 2 H, OCH_2O), 4.10, 3.95, 3.90 (3 s, 9 H, 3 OCH_3), 3.23 (m. 4 H, 2 CH_2), 2.41 (s, 3 H, NAc). Analysis, calculated for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54; found: C, 66.75; H, 5.41; N, 3.33%.

*(5aR,8aS,13a,13bR)-2,3,11,12-Tetramethoxy-5,6,7,8-tetrahydrobisbenzo[a,c]cycloocteno[6,7-c]-2-tetrahydrofuranone (**37**).*[11] A solution of matairesinol dimethyl ether (0.10 g, 0.26 mmol), mp 129–130°C (lit,[199] mp 126.5–127°C) in CH_2Cl_2 (5 ml) and freshly distilled $BF_3 \cdot Et_2O$ (0.12 ml, 1.02 mmol) were added to an ice-cooled stirred suspension of thallium(III) *tris*-trifluoroacetate (0.18 g, 0.34 mmol) in CH_2Cl_2 (5 ml) under N_2. The mixture was stirred at room temperature for 40 h and then treated with an aqueous solution

* For example, from the Aldrich Chemical Co. Ltd.

† Solid wastes should be collected in an appropriate solid waste container and liquid wastes in suitably labeled bottles or cans. These wastes may be buried in deep pits after covering with sand.

of KI (0.10 g, 0.52 mmol). Stirring was continued for 30 min, the mixture was basified with Na_2CO_3, and sodium disulfite (0.20 g) was added. The mixture was filtered and the residue was washed thoroughly with $CHCl_3$. EtOAc was added to the combined filtrate and washings and the solution was washed with water, dried (brine, Na_2SO_4), and the solvents were removed. Preparative t.l.c. ($CHCl_3$:PhH,4:1) gave **37** which crystallized from $CHCl_3$ as needles (82 mg), mp 194–197°C, $[\alpha]_D$ 211.5° ($CHCl_3$); uvλ_{max} 218, 250(sh), 279, 292(sh) nm; ir ν_{max} 2950, 1780, 1720, 1600, 1500, 1450, 1250, 1150, 1120, 1000 cm^{-1}; ^1H NMR ($CDCl_3$; 60 MHz) δ 2.00–2.80 (br, 4 H, H-5,9), 3.18 (d, $J_{5a,8a}$ 13 Hz, 2 H, H-5a,8a), 3.94, 3.98 (2s, 12 H, OCH_3), 4.33 (dd, J_{obs} 11 Hz, 5 Hz, 1 H, H-8), 4.38 (t, J_{obs} 7 Hz, 1 H, H-8), 6.75–6.80 (m, 4 H, aryl-H); ^{13}C NMR ($CDCl_3$; 15 MHz) δ 32.1 (t, C-5), 34.2 (t, C-9), 46.9 (d, C-5a), 50.1 (d, C-8a), 56.0 (q, OCH_3), 70.1 (t, C-8), 111.9 (d, C-10), 112.2 (d, C-4), 114.1 (d, C-13), 114.3 (d, C-1), 131.0 (s, C-9a), 132.0 (s, C-4a), 132.5 (s, C-13a, 13b), 147.3 (s, C-2,12), 148.8 (s, C-11), 148.9 (s, C-3), 176.5 (s, C-6); MS *m/e* (70 eV) 384 ($M^{+\cdot}$), 369, 299, 285. Analysis, calculated for $C_{22}H_{24}O_6$: C, 68.7; H, 6.3; found: C, 68.4; H, 6.3%. Reaction for 18 h gave **37** in 51% yield.

General Procedure for TTFA Oxidative Cyclizations.[13] Thallium(III) trifluoroacetate (TTFA, 1.1 equiv, 0.60 g/mmol of substrate) was dissolved in TFA, 4-5 ml/mmol of substrate) and the solution diluted with CH_2Cl_2 (16–20 ml/mmol of substrate). $BF_3 \cdot Et_2O$ (0.5 ml/mmol) was added, and the temperature of the mixture was adjusted to −20°C, under a stream of nitrogen, by means of a dry ice/CCl_4 bath. A solution of the appropriate substrate (arylalkanoic acid or arylalkanol) in a minimum volume of CH_2Cl_2 and a little TFA, if needed for solubility, was added at once to the cooled and vigorously stirred mixture. After the specified period of time the reaction mixture was rapidly quenched with *t*-butyl alcohol (10 ml/mmol) and allowed to come to room temperature. The mixture was then washed with water (4 × 25 ml/mmol) followed by saturated aqueous base (25 ml/mmol of Na_2CO_3 with naphthalenylalkanoic acids; otherwise $NaHCO_3$). When arylalkanoic acids were used as substrates, unreacted starting material was often recovered by acidification of these basic extracts; otherwise, they were discarded. The remaining organic solvent layer was dried over anhydrous Na_2SO_4 and evaporated and the residue chromatographed (silica gel, preparative TLC, or column), or in some cases filtered and the product recrystallized. All reported products were isolated pure, as determined both by NMR and by TLC, unless otherwise noted.

*6,7-Dimethoxy-3,4-dihydrocoumarin (**46**).* 3-(3,4-Dimethoxyphenyl)propionic acid was oxidized by the general procedure: 1 mmol scale, 5–10 s reaction time. The crude reaction product was separated by preparative TLC (5% $Me_2CO/CHCl_3$): R_f 0.75; yield, 38%; mp (benzene/pentane) 84–86°C; ir ($CHCl_3$) 1760 cm^{-1}; NMR ($CDCl_3$) δ 6.67 (s, 1 H), 6.62 (s, 1 H), 3.80 (s, 6 H), 2.65–3.05 (m, 4 H). Analysis, calculated for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; found: C, 63.37; H, 5.66%.

*7-Methoxy-1-oxaspiro[5.4]deca-6,9-diene-2,8-dione (**47**).* Isolated in 19% yield from the above preparative TLC; R_f 0.44; mp (benzene/pentane) 86–89°C; ir ($CHCl_3$) 1792, 1781, 1688, 1652, 1626 cm^{-1}; NMR ($CDCl_3$) δ 6.87 (d d, 1 H, *J* 3, 10 Hz), 6.24 (d, 1 H, *J* 10 Hz), 5.78 (d, 1 H, *J* 3 Hz), 3.71 (s, 3 H), 2.25–3.00 (m, 4 H). Analysis, calculated for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19; found: C, 61.61; H, 5.32%.

Compound (**47**) was also isolated (40% yield) by oxidation of 3-(4-acetoxy-3-methoxyphenyl)propionic acid at room temperature: 1 mmol scale, 15–20 s reaction time.

*Reaction of 2-(4-Methoxyphenoxy)benzoic Acid (**63a**) with TTFA.*[16] A solution of TTFA (3.8 g, 6.9 mmol) in TFA (15 ml) was treated with CH_2Cl_2 (75 ml) and $BF_3 \cdot Et_2O$ (5 ml) and cooled below −25°C. To the vigorously stirred mixture was added a solution of 2-(4-methoxyphenoxy)benzoic acid (**63a**) (1.12 g, 4.6 mmol) in CH_2Cl_2 (20 ml) in one portion. The dark red mixture was stirred at −20 to −25°C for 12 min and was poured into ice water (200 ml). The organic layer was separated, washed with H_2O, and extracted with 5% $NaHCO_3$ (2 × 25 ml), dried (Na_2SO_4), and evaporated. The residue was dissolved in a little CH_2Cl_2 and applied to a column of alumina (15 g). Elution with CH_2Cl_2 (75 ml) gave, after evaporation, a nearly white solid (**64a**), mp 155–159°C, 0.56 g (53%). An analytical sample

had mp 160–162°C after recrystallization from CH_2Cl_2-petroleum ether (40–60); ^1H NMR (60 MHz, $CDCl_3$) δ 8.08 (dd, J 7.5, 2.0 Hz, 1 H), 7.85–6.95 (complex, 5 H), 6.34 (d, J 10 Hz, 2 H).

General Procedure for Oxidative Coupling of Cinnamic Acids with Thallium(III) Trifluoroacetate (TTFA).[18] The cinnamic acid (20 mmol) in CH_2Cl_2/TFA (4:1, 30–35 ml) was added all at once to a rapidly stirred solution of TTFA (10.6 g, 20 mmol) in CH_2Cl_2/TFA (4:1, 500 ml) and $BF_3 \cdot Et_2O$ (4–5 ml) at room temperature. The deep red reaction mixture was quenched *immediately** with *t*-butyl alcohol (100 ml). Water (200 ml) was added and the CH_2Cl_2 layer was separated. The remaining aqueous solution was extracted with $CHCl_3$, and the combined organic layers were washed with water (4 × 200 ml) and saturated aqueous $NaHCO_3$ (3 × 100 ml), dried over Na_2SO_4, and evaporated. The oily residue was then filtered through a short column packed with alumina (*maximum* 6–7 g) covered with silica gel (*maximum* 12–14 g), with $CHCl_3$ as eluent. The crude product was triturated with a few milliliters of warm EtOH and the resultant mixture treated dropwise with pentane until precipitation ceased. The solid thus obtained was collected by filtration and washed with cold Et_2O to give the pure (TLC) 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane-4.8-diones. Yields are based on recovered starting material.

*2,6-Bis(3,4,5-trimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-4,8-dione (**79b**).* From 3,4,5-trimethoxycinnamic acid; R_f (5% $Me_2CO/CHCl_3$) 0.56; mp 195–198°C (lit.[200] mp 195–196°C); 54% yield; ir ($CHCl_3$) 1780 cm^{-1}; NMR ($CDCl_3$) δ 6.51 (br s, 4 H), 5.87 (br s, 2 H), 3.85 (s, 12 H), 3.82 (s, 6 H), 3.57 (br s, 2 H).

*Octaethyloxophlorin (**88**).*[21] Treatment of the magnesium or zinc porphyrins (**87a**, **87b**) with thallium trifluoroacetate gives high yields of the oxophlorin (**88**). Typically, zinc octaethylporphyrin (**87b**; 415 mg) in dry THF (30 ml) and CH_2Cl_2 (100 ml) was treated with a solution of TTFA (480 mg, 1.25 equiv.) in THF (20 ml) and the mixture stirred at room temperature for 1 min. Water (0.25 ml) in THF (10 ml) was then added (solution turned from purple to red) and the solution was stirred for a further 10 min. After brief treatment with sulfur dioxide [Tl(III) salts → Tl(I) salts] the mixture was stirred for 5 min with concentrated HCl (2 ml) and then the products were extracted into $CHCl_3$ which was dried (Na_2SO_4) and evaporated to dryness. Chromatography on Brockmann grade III alumina in CH_2Cl_2 gave octaethyloxophlorin (**88**, 302 mg; 79%) after crystallization from CH_2Cl_2/MeOH, mp 254–256°C, (lit.[201] mp 255°C). Analysis, calculated for $C_{36}H_{46}N_4O$: C, 78.50; H, 8.42; N, 10.17; found: C, 78.54; H, 8.30; N, 10.23%.

General Procedure for the Oxidation of Olefins with TTN-Methanol[29] (Scheme 7). Thallium(III) nitrate trihydrate (4.4 g, 0.01 mol) was dissolved in MeOH (50 ml) and the olefin (0.01 mol) was added. The reaction mixture was stirred at room temperature or heated until a starch–iodide test indicated complete reduction of Tl(III) to Tl(I) (with cyclic olefins and styrenes, reaction was complete within a few minutes). The reaction mixture was then filtered, and an alcoholic solution containing 2,4-dinitrophenylhydrazine (0.01 mol) was added to the filtrate. The resulting mixture was evaporated to one-third of its volume and, after addition of water (10 ml), heated on a steam bath for 10 min. After cooling to 0°C, the 2,4-dinitrophenylhydrazone of the carbonyl compound was collected by filtration.

On a preparative scale, the reaction mixture was filtered from precipitated thallium(I) nitrate, the filtrate evaporated to a small volume, and the resulting mixture of the carbonyl compound and its acetal (or ketal) heated on a steam bath for 30 min with an excess of 5% sulfuric acid. The free carbonyl compound was isolated by Et_2O extraction followed by final distillation or crystallization.

(+)-(1S,5S)-Bicyclo[3.2.1]-2-octanone[39] *[see Eq. (14)].* Triphenylmethylphosphonium bromide[202] (17.9 g, 0.05 mol) in dry dimethyl sulfoxide (50 ml) was added under nitrogen to sodium hydride (1.2 g, 0.05 mmol) in dimethyl sulfoxide[203] (25 ml). To this was added a solution of (+)-2-norbornanone (2.8 g, 25 mmol, 96% optically pure) in dimethyl

* It is of utmost importance that the rapid addition of *t*-butyl alcohol take place less than 1 s after addition of the substrate.

sulfoxide (20 ml). The mixture was heated at 50°C for 3 h and was then poured into water (120 ml) and extracted with redistilled pentane (4 × 5 ml). The combined organic phases were washed with 50% aqueous dimethyl sulfoxide (30 ml) and then with brine (3 × 30 ml), dried ($MgSO_4$), and concentrated carefully to 20 ml. Two severe fractional distillations yielded (+)-(1S,4R)-2-methylenenorbornane (1.15 g): bp 122°C (760 Torr):$[\alpha]_D^{25}$ +97.4° (*c* 1.7 in MeOH) (lit.[204] bp [of (±)] 123°C (755 Torr)].

Thallium trinitrate trihydrate (3.7 g, 8.3 mmol) in MeOH (20 ml) was added with stirring at −10°C to (+)-(1*S*,4*R*)-2-methylenenorbornane (900 mg, 8.3 mmol) dissolved in MeOH (25 ml). After being stirred at −10°C for 30 min the mixture was filtered and concentrated. Et_2O (50 ml) was added and then 2 *N* HCl (50 ml), the resulting mixture was shaken well, and the phases were separated. The aqueous solution was reextracted with Et_2O (3 × 50 ml) and the combined Et_2O layers were dried ($MgSO_4$) and evaporated. The oil obtained was adsorbed onto a silica column (15 × 2.5 cm), washed with benzene, and eluted with Et_2O–benzene (1:6). The remaining trace impurities were removed by treatment with charcoal followed by steam distillation and sublimation to give (+)-(1*S*,5*S*)-bicyclo[3.2.1]-2-octanone, mp 120–123°C, $[\alpha]_D^{25}$ +142.9° (*c* 2.6), which extrapolates to +149° for the pure enantiomer (lit.[205] $[\alpha]_D^{25}$ +130°).

1-Ethyl-2-benzosuberone[48,206] *[see Eq. (18)].* To a solution of TTN.$3H_2O$ (4.5 g, 0.01 mol) in MeOH (40 ml) was added, in one portion with stirring, 1-propylidenetetralin (1.72 g, 0.01 mol). After 1 min, the reaction mixture was diluted with $CHCl_3$ (30 ml) and filtered. The filtrate was neutralized with aqueous $NaHCO_3$, washed with water, dried (anhydrous $MgSO_4$), and concentrated under reduced pressure to give a crude product which was distilled (bp 84–86°C/0.01 mm Hg) to yield 1-ethyl-2-benzosuberone (1.8 g, 96%); NMR ($CDCl_3$) δ 0.89 (t, *J* 7 Hz, 3 H), 1.47–2.27 (m, 4 H), 2.27–2.68 (m, 2 H), 2.68–3.07 (m, 2 H), 3.68 (t, *J* 7 Hz, 1 H), 7.14 (s, 4 H). Analysis calculated for $C_{13}H_{16}O$: C, 82.93; H, 8.56; found: C, 82.75; H, 8.50%.

2′-Benzyloxy-7-hydroxy-4′-methoxyisoflavone[96] *[see Eq. (25)].* Thallium(III) nitrate (1.12 g), 2-benzyloxy-2′,4′-bis(methoxymethoxy)-4-methoxychalcone (1.32 g), and MeOH (150 ml) were stirred for 30 min, 3 *N* HCl (10 ml) was added, and the mixture refluxed for 5 h[207] and filtered hot. The product crystallized as *needles* (800 mg, 75%), mp 226–228°C, MS *m/e* 374 (41%, M^+). Analysis calculated for $C_{23}H_{18}O_5$: C, 73.8; H, 4.9; found: C, 73.6; H, 5.0%.

Reaction of Chalcones with TTN in Methanol. General Procedure.[100] A solution of the chalcone (0.01 mol) in MeOH (25 ml) was added to a solution of TTN · $3H_2O$ (5.0 g, 0.011 mol) in MeOH (50 ml) containing 70% $HClO_4$ (5 ml), and the reaction mixture was stirred at room temperature for 4–25 h. A small amount of sodium bisulfite was then added to ensure complete reduction of Tl(III), and the mixture was cooled and filtered through a sintered-glass filter to remove $TlNO_3$. The filtrate was diluted with water (100 ml) and extracted with $CHCl_3$ (3 × 50 ml). The combined extracts were washed with saturated $NaHCO_3$ (50 ml) and water (50 ml) and dried (Na_2SO_4). Evaporation under reduced pressure then gave the crude product, which was examined by NMR. In chalcones where the migratory aptitude (MA) of the Ar ring is high, 3,3-dimethoxy-1,2-diarylpropan-1-ones (keto acetals) are the only products, and they may be recovered in good yield by recrystallization from an appropriate solvent (for details see Ref. 100). In chalcones where the MA of the Ar ring is only moderate or poor, however, the crude reaction products are a mixture of the keto acetal and methyl 2,3-diaryl-3-methoxypropanoates (esters); the former could often be obtained pure from the mixture in moderate yield by recrystallization, usually from MeOH.

Reaction of Chalcones with TTN in Trimethyl Orthoformate (TMOF) (Scheme 8). General Procedure.[100] A solution of TTN · $3H_2O$ (5.5 g, 0.011 mol) in TMOF (25 ml) was added to a solution or slurry of the chalcone (0.01 mol) in TMOF (35 ml), and the mixture was stirred at room temperature for 4–25 h [until the disappearance of Tl(III), as monitored by starch–iodide paper] and then worked up as described above except that Et_2O rather than $CHCl_3$ was used in the extraction.

Reaction of Chalcone Ketals with TTN in TMOF. General Procedure.[100] Chalcone

ketals were prepared *in situ* by stirring the chalcone (0.01 mol) with 2–6 g of Dowex 50W-X4 cation-exchange resin in TMOF (35 ml) at room temperature. After ketal formation was complete (15–24 h, as determined by TLC monitoring using $CHCl_3$ and silica gel plates), the reaction mixture was filtered into a solution of TTN · $3H_2O$ (5.0 g, 0.011 mol) in TMOF (20 ml). After the oxidative rearrangement was complete [6–24 h, as determined by the disappearance of Tl(III)], a small amount of sodium bisulfite was added, followed by Et_2O (200–300 ml), and the reaction mixture was chilled and filtered to remove $TlNO_3$. It was then worked up as described above. The methyl 2,3-diaryl-3-methoxypropanoates, which were obtained crude (90%–98% purity by NMR) in almost quantitative yield, were recrystallized from MeOH for analysis.

General Procedure for the Preparation of Aryl Malonaldehydic Acid Dimethyl Acetals[208] *[Eq. (32)].* The appropriate methyl cinnamate (0.01 mol) was dissolved in a solution of TTN (4.5 g, 0.01 mol) in trimethyl orthoformate (25 ml); for examples not incorporating a nuclear alkyl or alkoxy group, use of 5.6 g (0.0125 mol) of TTN was found to lead to more rapid, specific conversions. The resulting solution was either stirred at room temperature or heated under reflux with stirring for 4–73 h, and then cooled to room temperature, partitioned between Et_2O and saturated aqueous NaCl solution, and washed with saturated aqueous $NaHCO_3$ solution, and saturated NaCl solution. The Et_2O layer was separated, dried ($MgSO_4$), filtered, and evaporated to dryness to yield the crude product. Crystallization or distillation provided the pure material.

General Procedure for the Oxidation of Acetophenones with $Tl(NO_3)_3$ TTN[103] *[see Eq. (34)].* The acetophenone (0.01 mol) was added to a solution of TTN (0.01 mol) in MeOH (25 ml) containing 70% $HClO_4$ (5 ml), and the mixture was stirred at room temperature for the appropriate period. The thallium(I) nitrate which precipitated was removed by filtration; the filtrate was diluted with water, extracted with $CHCl_3$ (2×25 ml), dried (Na_2SO_4), concentrated, and chromatographed on acid-washed alumina using benzene as eluent. The product obtained on concentration of the eluate was distilled to give the pure methyl arylacetate. Where mixtures of products were obtained (as shown by either NMR or GLPC), the mixture obtained after chromatography was heated under reflux with 2 *N* NaOH solution for 2 h. Decantation of the aqueous phase followed by acidification with concentrated HCl gave the crude arylacetic acid as a colorless solid which was purified by crystallization from EtOH or water.

General Procedure for the Preparation of α-Nitrato Ketones[122] *(Scheme 11).* A solution of the ketone (10 mmol) in MeCN (5 ml) was added in one portion to a solution of TTN (20 mmol) in MeCN (25 ml), and the mixture was heated at 60–80°C for 12 h. It was then cooled and the precipitated thallium(I) nitrate was collected by filtration and washed well with Et_2O (3×100 ml). The filtrate was washed with water (2×150 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude α-nitrato ketone; yields were determined by NMR.

No attempt was made to purify liquid α-nitrato ketones as these are known to be thermally unstable. Solid products were recrystallized from aqueous MeOH for microanalysis.

A-Nor-2α-methoxycarbonyl-3-androsten-17β-yl Acetate[130] *[see Eq. (40)].* $Tl(NO_3)_3$ (1.57 g) was dissolved in a mixture of $HC(OCH_3)_3$–MeOH (13:10 ml) and the resulting solution left under stirring at 0°C for 30 min. After this time, a cold (0°C) solution of 17-acetoxytestosterone (0.98 g) in $HC(OCH_3)_3$–MeOH (20:15 ml) was quickly added to the $Tl(NO_3)_3$ solution. After some minutes a white precipitate appeared. After 30 min, the reaction mixture was neutralized by adding a solution of saturated Na_2CO_3, filtered, and extracted with Et_2O. The crude reaction mixture was chromatographed on a silica gel column. Elution with 9:1 hexane–Et_2O gave the title compound (75% yield), plates from hexane with mp 120–123°C, $[\alpha]_D$ +123°. ir($CHCl_3$) ν_{max} 1730 cm^{-1}; NMR($CDCl_3$) δ 0.81 (s, 3 H), 0.98 (s, 3 H), 2.0 (s, 3 H), 3.68 (s, 3 H), 4.60 (m, 1 H), 5.18 (br s, 1 H), $W_{1/2}$ 5 Hz); MS *m/e* 360 (parent peak).

General Procedure for the Oxidation of Diarylacetylenes with TTN-Glyme-Perchloric Acid[137] *[see Eq. (41)].* A solution of the diarylacetylene (0.01 mol) in glyme (20 ml) was

added to a solution of TTN (8.9 g, 0.02 mol) in water (10 ml) containing 70% $HClO_4$ (5 ml), and the reaction mixture was heated gently under reflux for 2–7 h. After cooling, thallium(I) nitrate was removed by filtration and the filtrate diluted with water (100 ml). The mixture was extracted with $CHCl_3$ (2 × 25 ml), the extracts were dried (Na_2SO_4) and concentrated, and the crude product was freed from traces of inorganic thallium salts by passage through a short column of acid-washed alumina (2 × 10 cm) using benzene–$CHCl_3$ (1:1) as eluent. Evaporation of the eluate gave the crude benzil, which was purified by crystallization or distillation.

General Procedure for the Oxidative Rearrangement of Alkylarylacetylenes with TTN-CH_3OH [Eq. (44)].[137] The alkyne (0.01 mol) was added to a stirred solution of TTN (4.88 g, 0.011 mol) in MeOH (25 ml), and the mixture was heated under reflux for 2 h. Thallium(I) nitrate was removed from the cooled reaction mixture by filtration, and the filtrate was extracted with Et_2O or $CHCl_3$. The extracts were washed with water and 5% aqueous $NaHCO_3$ solution and dried (Na_2SO_4). The solution was then filtered through a short column of Florisil (10 g) using $CHCl_3$ as eluent; evaporation of the eluate gave the methyl α-alkylarylacetates, which, in every case, were shown to be pure at this stage by GLPC.

Conversion of 5-Pyrazolones into 2-Alkynoic Esters by Treatment with TTN[138] *[Eq. (45)].* A solution of thallium(III) nitrate (0.021 mol) in MeOH (25 ml) was added to a suspension or solution of the 5-pyrazolone (0.010 mol) in MeOH (25 ml), and the reaction mixture was stirred for 15 min at room temperature and then for an additional 15 min at reflux (water bath). The cooled reaction mixture was filtered to remove precipitated thallium(I) nitrate and the filtrate diluted with water and extracted with $CHCl_3$. The extracts were washed with water, dried over anhydrous Na_2SO_4, filtered through a short column of Florisil, and evaporated to give the pure (GLPC) 2-alkynoic esters.

General Procedure for the Conversion of Oximes into Aldehydes and Ketones by Treatment with Thallium(III) Nitrate (TTN)[145] *(Scheme 15).* A solution of TTN in MeOH was added to a stirred solution of an equimolar amount of the oxime in MeOH at room temperature. Reaction was rapid and nonexothermic, and was complete within a few minutes. The precipitated thallium(I) nitrate was removed by filtration, and the filtrate was shaken with dilute H_2SO_4 for a few minutes and then extracted with Et_2O or $CHCl_3$. The extract was dried, concentrated, and filtered through a short column of alumina or silica, using benzene or $CHCl_3$ as eluent, Evaporation of the solvent followed by distillation or crystallization gave the pure aldehyde or ketone.

Cyclohexanone[210] *(See Scheme 15).* Cyclohexanone oxime (1.13 g, 0.01 mol) was dissolved in the minimum amount of glyme (5 ml), and the solution acidified with two drops of 70% aqueous $HClO_4$ in water (15 ml). TTN (4.5 g, 0.01 mol) was added to the solution and after about 30 s thallium(I) nitrate had separated as a colorless solid. The reaction mixture was stirred at room temperature for 1 h, but there was no further visible reaction. The inorganic salt was removed by filtration and the filtrate extracted with $CHCl_3$. The combined extracts were washed as described above, dried, and the solvent removed to yield a pale yellow liquid which was pure by GLPC and had a retention time identical to that of cyclohexanone. Distillation gave pure cyclohexanone (0.91 g, 92%).

9-Methyl-5(10)-octalin-1,6-dione-1-ethylene Thioacetal[159] *[Eq. (54)].* Thallium(III) nitrate trihydrate (0.27 g) in MeOH (2 ml) was rapidly added to 9-methyl-5(10)-octalin-1,6-dione-1,6-bisethylene thioacetal (0.20 g) dissolved in MeOH (8 ml) and THF (2 ml). A white precipitate formed immediately and after 5 min CH_2Cl_2 (10 ml) was added and the precipitate was filtered. The solvents were removed from the filtrate *in vacuo* and the residue dissolved in $CHCl_3$, washed with H_2O, dried ($MgSO_4$), and the solvents evaporated to give the product (0.15 g), mp 113–114°C (Et_2O), ir(Nujol) ν_{max} 1660(C=O), 1615(C=C) cm^{-1}; ^1H NMR($CDCl_3$) δ 1.47 (s, 3 H, CH_3), 3.24 (s, 4 H), (SCH_2CH_2S), 5.78 (d, J 1.6 Hz, 1 H, C=CH) ppm; ^{13}C NMR($CDCl_3$) δ 22.2 (q, CH_3), 24.3(t), 30.8(t), 31.3(t), 34.4(t), 39.0(t), 40.3(t, SCH_2), 40.6 (t, CH_2S), 45.6 (s, C-9), 79.7 (s, C-1), 126.0 (d, C-5), 116.2 (s, C-10),

198.7 (s, C-6) ppm. Analysis, calculated for $C_{13}H_{18}S_2O$: C, 61.4; H, 7.1; S, 25.2; found: C, 61.0; H, 7.0; S, 24.9%.

General Procedure for the Oxidation of Hydroquinones and 2,6-Dialkylphenols with TTN[166] *[Eq. (60)].* A solution of the hydroquinone (5 mmol) in MeOH (10 ml) was added dropwise to an ice-cold solution of TTN (5 mmol) in MeOH (15 ml). After addition had been completed the reaction mixture was stirred for a further 10 min, the thallium(I) nitrate which had precipitated was removed by filtration, and the filtrate was partitioned between CH_2Cl_2 and saturated aqueous NaCl solution. The organic layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. The crude *p*-benzoquinone thus obtained was purified by chromatography on silica gel or neutral alumina using benzene or benzene–CH_2Cl_2 as eluent.

Oxidation of 2,6-dialkylphenols to *p*-benzoquinones was carried out in exactly the same manner except that the reaction was performed at room temperature and 10 mmol of TTN was used.

General Method for the Preparation of 4,4-Dialkoxy- and 4-Alkyl-4-alkoxycyclohexa-2,5-dienones Using TTN in Alcohols[166] *[See Eq. (63)].* A solution of TTN (5 mmol) in the appropriate alcohol (15 ml) was added to a stirred, cooled (−20°C) solution of the phenol (5 mmol) in the same alcohol (15 ml) and the reaction mixture allowed to warm to room temperature. Petroleum ether (60 ml, bp 60–80°C) was then added, the thallium(I) nitrate which precipitated was removed by filtration, and the filtrate was passed down a short column of basic alumina (8 × 1 in) using either petroleum ether or CH_2Cl_2 as eluent. Evaporation of the eluate gave the product, which, in almost all cases, was chromatographically and spectroscopically pure as isolated. Most of the compounds could be crystallized from either MeOH or petroleum ether, preferably at −70°C, but only with attendant losses in material of up to 75%.

*Oxidation of (***128***) with Thallium(III) Trifluoroacetate.*[183] To a slurry of 272 mg (0.501 mmol) of TTFA (Ventron Corp., Alfa Products; used without purification, but weighed and transferred in a dry box under nitrogen) in anhydrous CH_2Cl_2 (100 ml) was added monophenol (**128**) (128 mg, 0.500 mmol), and the mixture was stirred under nitrogen at room temperature in the dark for 3 h. The resulting pale yellow solution was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and was passed through a column of silica gel, eluting with $CHCl_3$; evaporation of the eluate afforded 112 mg (88%) of dienone (**129**) as a yellow solid, homogeneous to TLC ($CHCl_3$). Recrystallization from MeOH gave **129** as white crystals, mp 171°C; ir ($CHCl_3$) 6.04, 6.17, 6.68, 6.78, 8.11, 9.63, 10.66, 11.41, 11.65 μm; NMR ($CDCl_3$) δ 1.97 (m, 4 H), 2.82 (m, 2 H), 5.85 (s, 2 H), 6.23 (d, 2 H, *J* 10 Hz), 6.40 (s, 1 H), 6.60 (s, 1 H), 6.97 (d, 2 H, *J* 10 Hz). Analysis, calculated for $C_{16}H_{14}O_3$: C, 75.59; H, 5.51; found: C, 75.26; H, 5.42%.

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ketals with TTN in trimethyl orthoformate (Ref. 100/1980), the procedure for the preparation of α-nitrato ketones (Ref. 122/1978), and the procedures for the oxidation of hydroquinones and 2,6-dialkyl-phenols with TTN, also the preparation of 4,4-dialkoxy- and 4-alkyl-4-alkoxycyclohexa-2,5-dienones using TTN in alcohols (Ref. 166/1976). The preparation of A-nor-2α-methoxycarbonyl-3-androsten-17β-yl acetate was reprinted from Ref. 130 by permission from the Società Chimica Italiana. We thank the Royal Society of Chemistry for allowing us to reprint the preparation of 2′-benzyloxy-7-hydroxy-4′-methoxyisoflavone from Ref. 96, and Verlag Chemie for their permission to copy the method for conversion of 5-pyrazolones into 2-alkynoic esters by treatment with TTN (Ref. 138). Finally, we are grateful to Pergamon Press for permitting us to reprint the preparations of octaethyloxophlorin (**88**) (Ref. 21) and 1-ethyl-2-benzosuberone (Ref. 48).

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14

Oxidations With Lead Tetraacetate

Mihailo Lj. Mihailović, Živorad Čeković, and Ljubinka Lorenc

1. INTRODUCTION

Lead tetraacetate (LTA), $Pb(OAc)_4$, is one of the most versatile oxidants in organic chemistry. Depending on the reaction conditions and nature of the substrate, it can be used for selective and partial oxidations of various reactive groupings, but also—and this is of primary importance—for the functionalization of nonactivated carbon atoms. The versatility of LTA originates from its properties: it can act as a radical and/or ionic oxidant and participate in processes involving substitution, elimination, addition, or fragmentation reactions, depending on the functionality and experimental conditions.

The manifold applications of LTA during the last few decades have been, naturally, reflected in the publication of numerous papers and review articles. The general scope of LTA as an oxidant has been reviewed by Rubottom,[1a] Butler,[1b] Rotermund,[2] and Criegee,[3] while Fieser and Fieser[4] have discussed useful synthetic applications of this reagent. Other published reviews are more specific and deal with LTA oxidations of hydroxylic compounds, including intramolecular oxidative cyclization of alcohols to tetrahydrofuran derivatives,[5–9] glycol cleavage, and oxidations of sugars[10,11] and phenols[12]; oxidative transformations of olefins[13] and decarboxylation of acids[14] by LTA and their synthetic value have been discussed in detail, and the reactions of LTA with organic nitrogen compounds in general,[15] and particularly with azomethines,[16] oximes,[17] hydrazones,[18] as well as oxidative cyclizations of hydrazone-type derivatives[19] have also been surveyed.

LTA is commercially available or can be readily prepared in the laboratory from red lead oxide (Pb_3O_4), acetic acid, and acetic anhydride.[20–23] Pure LTA is colorless and crystallizes in the monoclinic form from acetic acid.[3] It is very hygroscopic, reacting rapidly with water to give brown lead dioxide (PbO_2); it decomposes upon heating over 140°C (completely at about 175°C),[24] and loses gradually its oxidizing activity when exposed to sunlight.[25] Therefore, it is best stored under 10°C in the dark in the presence of about 10%

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of dry acetic acid. However, for some reactions it is necessary to remove acetic acid by drying the reagent *in vacuo* over potassium hydroxide and phosphorous pentoxide for several days. Depending upon the starting material, functionality, and desired reaction course, oxidation with LTA can be carried out in different types of solvents, such as acetic acid, benzene, chloroform, methylene chloride, carbon tetrachloride, chlorobenzene, nitrobenzene, acetonitrile, dimethyl sulfoxide, and others, while alcohols and water cannot be used (because of alcoholysis and hydrolysis), except in some special cases. The purity of LTA can be determined iodometrically, whereas the concentration of the reagent in solution in the course of reaction can be monitored spectrometrically, by potassium iodide–starch testing paper or by spot test with leucomalachite green.

LTA shows no "ester-type" carbonyl groups in its IR spectrum, suggesting that each oxygen of the four acetoxy groups is equivalent and that these acetate groups are ionically associated around the lead(IV) atom, forming, in the solid state, a distorted cubic structure.[26]

2. HYDROCARBONS

2.1. Saturated Hydrocarbons

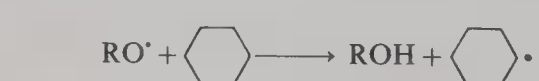
The resistance of saturated hydrocarbons towards LTA attack very often allows their use as solvents in LTA oxidations, the nonactivated carbon–hydrogen groups being almost unreactive in straight-chain or branched acyclic hydrocarbons.[27] However, if reaction with alkanes proceeds, it usually results in substitution by an acetoxy group, dehydrogenation, or skeletal rearrangement. Cyclohexane was thus converted to cyclohexyl acetate in low yield by prolonged treatment with LTA under irradiation conditions (20–25°C) or at higher temperature (80°C).[28] However, induced oxidation of cyclohexane by using short-chain alcohols and LTA affords cyclohexyl acetate in higher yield.[29]

2.1.1. Mechanism

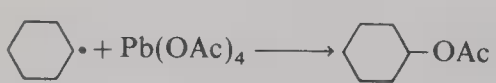
The acetoxylation of saturated hydrocarbons by LTA in the presence of short-chain alcohols is considered to proceed via alkoxy radicals as transient intermediates, which abstract a hydrogen atom from cyclohexane [Eqs. (1)–(4)].[29]

$$R-OH + Pb(OAc)_4 \longrightarrow RO-Pb(OAc)_3 \tag{1}$$

$$RO-Pb(OAc)_3 \longrightarrow RO^{\bullet} + {}^{\bullet}Pb(OAc)_3 \tag{2}$$



$$RO^{\bullet} + \bigcirc \longrightarrow ROH + \bigcirc^{\bullet} \tag{3}$$



$$\bigcirc^{\bullet} + Pb(OAc)_4 \longrightarrow \bigcirc\!\!-OAc \tag{4}$$

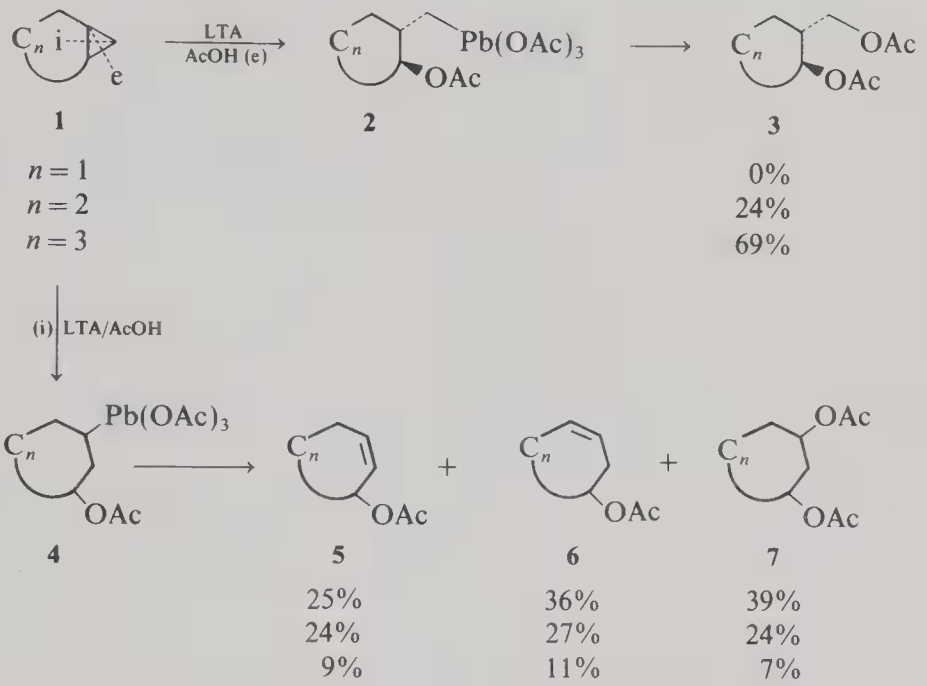
2.1.2. Scope and Limitations

Lead tetra(trifluoroacetate) is a more powerful oxidizing agent for nonactivated C–H groups. Thus, in the reaction with *n*-heptane, a mixture of isomeric *n*-heptyl trifluoroacetates was obtained in over 45% yield.[30]

Saturated hydrocarbons possessing a cyclopropane ring undergo ring cleavage in the reaction with LTA. In bicyclic hydrocarbons of the [n.1.0] type 1 the facility of cyclopropane C–C bond cleavage increases with increasing strain of the system. There are

two ways for cyclopropane ring opening, internal (i) and external (e), and it was found that internal bond cleavage increases with decreasing ring size.[31–33]

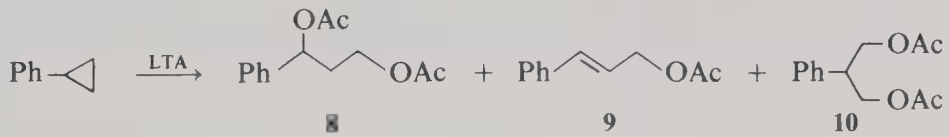
External bond cleavage of the cyclopropane ring (e) occurs by electrophilic attack of the lead salt on the strained ring with formation of an organo-lead intermediate of type **2**, which is subsequently solvolyzed to *trans*-2-acetoxymethylcycloalkyl acetate **3**.[31] On the other hand, internal bond cleavage (i) involves organo-lead species **4**, which upon solvolysis involving the corresponding carbenium ions, afford unsaturated acetates **5** and **6** and a mixture of *cis*- and *trans*-1,3-diacetates **7**.[31]



1	2	3
$n=1$		0%
$n=2$		24%
$n=3$		69%

4	5	6	7
	25%	36%	39%
	24%	27%	24%
	9%	11%	7%

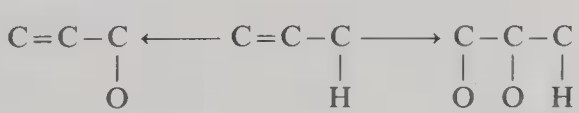
Aryl substituted cyclopropanes are also cleaved by LTA, yielding 1,3-diacetates **8** and **10** and unsaturated monoacetates **9**.[34–36] On the basis of kinetic evidence, these cleavage reactions were considered as over-all second-order reactions proceeding via a concerted mechanism, in which the cyclopropane ring coordinates with lead(IV) before C–C bond breaking.[34]



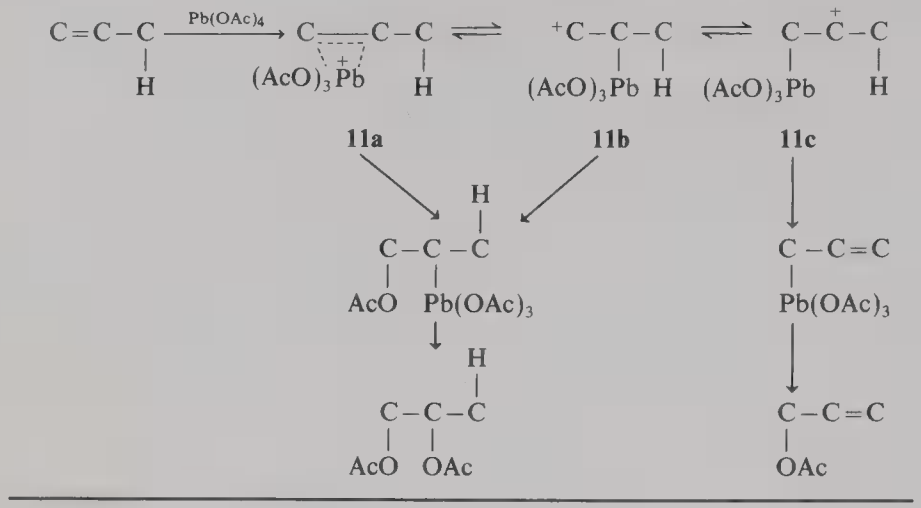
8	9	10
63%	32%	5%

2.2. Unsaturated Hydrocarbons

As an electrophilic and radicophilic oxidizing agent, LTA reacts with olefins in two major ways: addition of an oxygen function to the double bond or substitution of hydrogen at the allylic position.[37] In addition to these two general types of LTA oxidations of olefins, depending on the structure of the substrates, other reactions, such as skeletal rearrangement, double bond migration, and C–C bond cleavage, can occur leading to complex mixtures of products.[13]



SCHEME 1

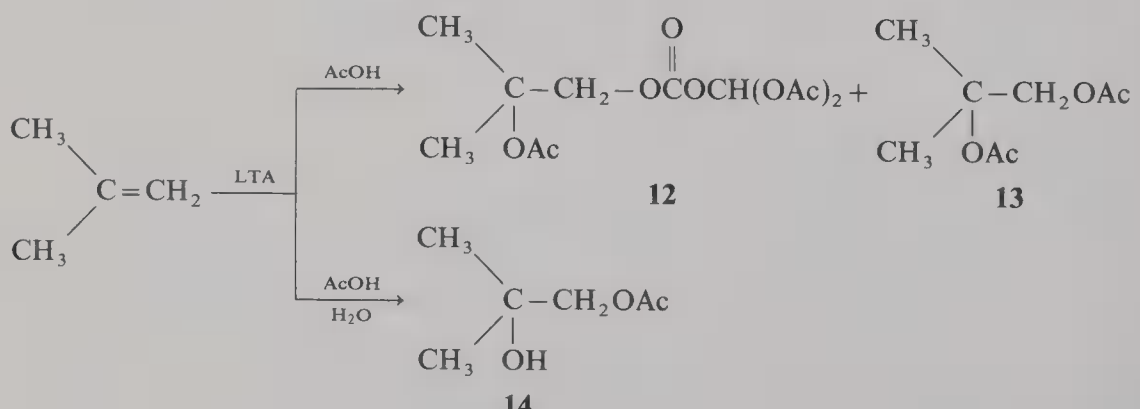


2.2.1. Mechanism

The initial step in the LTA oxidation of olefins probably involves electrophilic addition of $^{+}Pb(OAc)_3$ with formation of an intermediate **11a**, indicated by the isotopic distribution observed in the LTA oxidation of ^{13}C-cyclohexene.[37,38] Nonstereoselective addition of acetoxy groups and the allylic rearrangement support the carbenium ionic structures **11b** and **11c** (Scheme 1).

2.2.2. Scope and Limitations

2.2.2a. Acyclic Olefins. Oxidations of acyclic olefins with LTA have not been extensively investigated. In the reaction of LTA with mono- and disubstituted acyclic olefins three competitive reactions, namely, 1,2-acetoxylation, allylic substitution, and allylic migration, can occur, and complex mixtures of products, without much synthetic value, are usually obtained.[27,39,40] Isobutylene reacts readily with LTA in acetic acid affording the glyoxylic acid derivative **12** as a principal product, along with a small amount of the 1,2-diacetoxy compound **13**. However, by using acetic acid containing water, the major product was the monoacetate of isobutylene glycol **14**.[39] The formation of the diol monoacetate **14** probably involves attack of HO^{-} on the intermediate **11**, this being supported by the fact that the use



of methanol as nucleophile in the LTA oxidation of alkenes results in the formation of mono- and dimethyl ethers **15** and **16**.[40]

The LTA oxidation of styrene and derivatives involves several competing reactions,

$$C_6H_{13}-CH=CH_2 \xrightarrow[CH_3OH]{LTA} C_6H_{13}-C(OCH_3)-CH_2-OCH_3 + C_6H_{13}-C(OCH_3)-CH_2OAc$$

15 52% **16** 12%

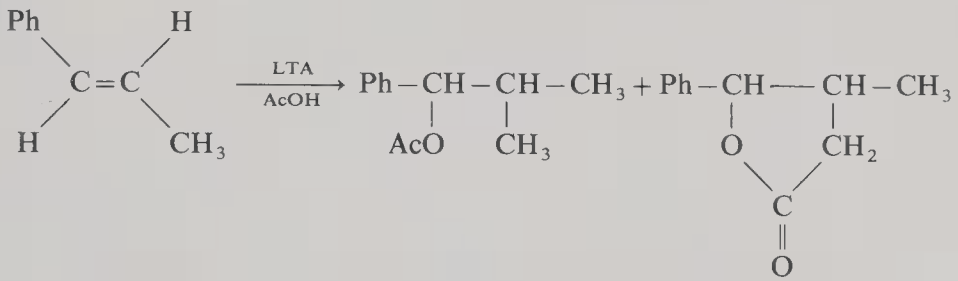
$$+ C_6H_{13}-C(=O)-CH_3$$

23%

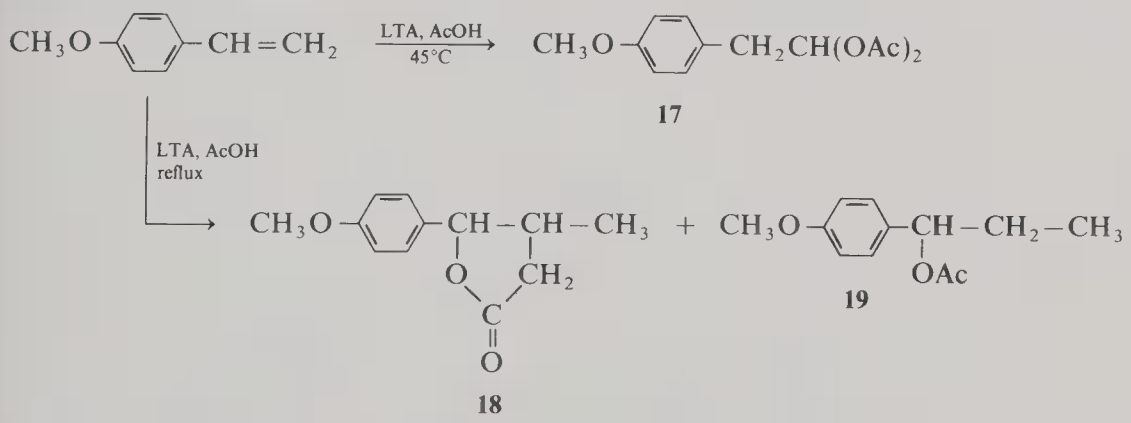
depending on substrate and reaction conditions. Thus, styrene and 1,1-diphenylethylene react with LTA in boiling benzene to give, unexpectedly, products resulting from the addition of a methyl and an acetoxy group to the double bond,[41] while styrene and (*E*)-β-methylstyrene in

$$Ph-CH=CH_2 \xrightarrow[C_6H_6]{LTA} Ph-CH(OAc)-CH_2-CH_3$$

$$Ph_2C=CH_2 \xrightarrow[C_6H_6]{LTA} Ph_2C(OAc)-CH_2-CH_3$$



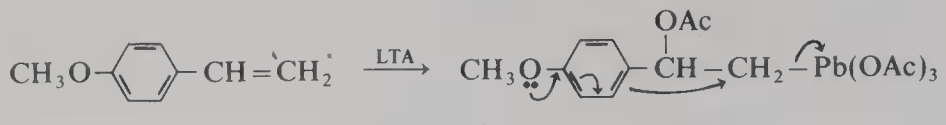
acetic acid give a methyl acetate adduct and a γ-lactone as main reaction products.[41a] The LTA reaction of *p*-methoxy styrene in acetic acid at room temperature affords in high yield the 1,1-diacetate **17**, while at reflux temperature the γ-lactone **18** and the acetoxymethyl compound **19** are obtained as major products.[42,43]



17

18 **19**

The proposed mechanism of the geminal diacetoxylation (to **17**) at the terminal olefinic carbon involves 1,2-migration of the aryl group in the organo-lead species **20**, resulting in the formation of a cyclopropane intermediate **21**,[43] whereby this 1,2-aryl shift was confirmed by using as substrate *p*-methoxystyrene-1-^{14}C.[43] 1,2-Migration of the *p*-methoxyphenyl group occurs also in the LTA oxidation of *p*-methoxy-1-methylstyrene and 1,1-di-*p*-methoxyphenylethylene.[44]



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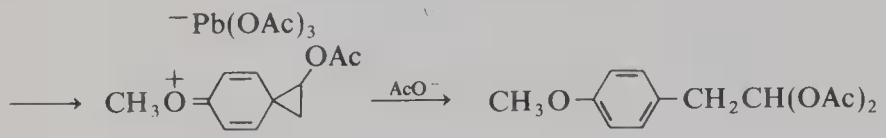
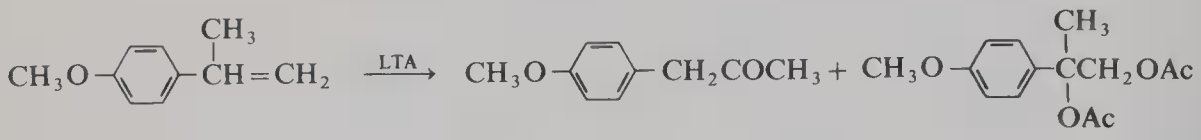
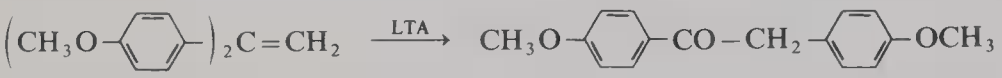
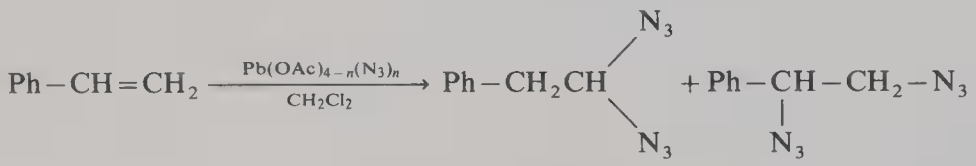


21 **17**

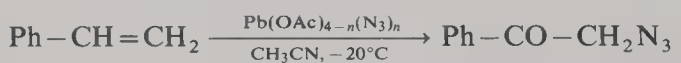




The reaction of styrene derivatives and other olefins with $Pb(OAc)_{4-n}(N_3)_n$ often proceeds through a similar pathway, to give *gem*-diazido, *gem*-acetoxyazido, *vic*-diazido, and/or *vic*-acetoxyazido compounds.[45]

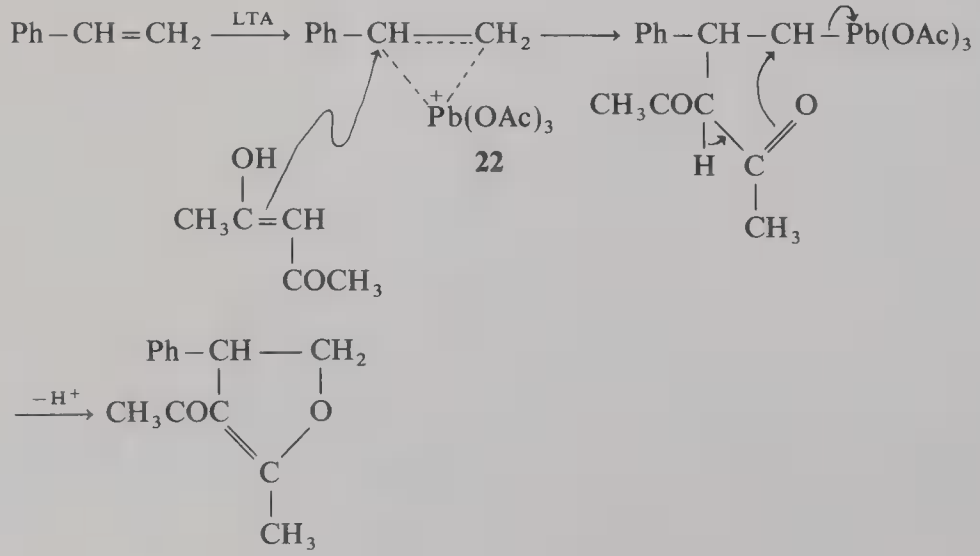


39% 15%



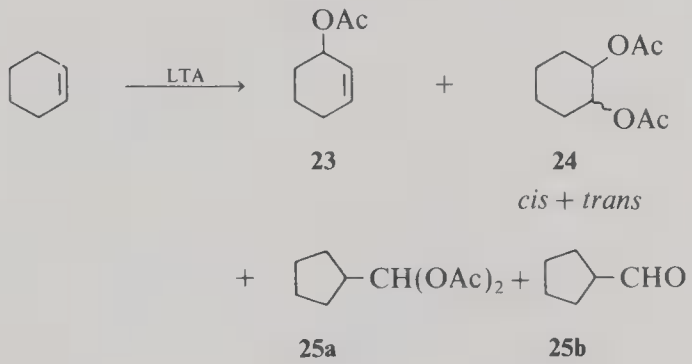
60%

Interesting reaction products have been obtained by treatment of styrene derivatives with LTA in the presence of some nucleophiles. Thus, a dihydrofuran derivative is formed in the reaction of styrene with LTA in the presence of acetylacetone.[46] Closing of the dihydrofuran ring in this reaction involves electrophilic addition of lead(IV) onto the olefinic



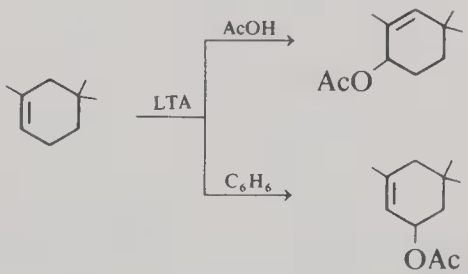
double bond to give a three-centered cyclic organo-lead intermediate **22**, which then undergoes nucleophilic attack by the enol form of the β-diketone with C–C bond formation, followed by cyclization.[46]

2.2.2b. Cyclic Olefins. LTA oxidations of cyclic olefins have been much more investigated than those of acyclic systems. As pointed out above, several types of reactions, such as acetoxylation, allylic oxidation, skeletal rearrangement, and other transformations, can occur in olefinic systems, depending on the ring size (for cyclic alkenes), structure, solvent, and reaction conditions.[2,13,47] Thus, in the LTA oxidation of cyclohexene, which has been studied in detail by several groups,[38,47–50] the major products were 3-acetoxycyclohexene, **23**, *cis*- and *trans*-1,2-diacetoxycyclohexane, **24**, and pinacolic-type five-membered ring contraction compounds **25a** and **25b**, the relative yields depending somewhat on the solvent used (acetic acid or benzene).

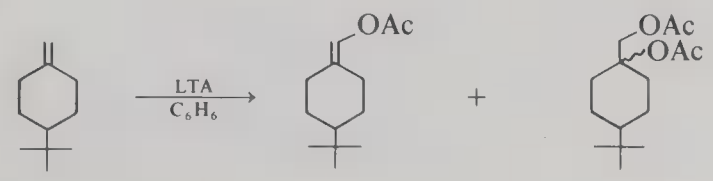


3-Acetoxycycloalkenes and/or cycloalkane 1,2-diacetates were obtained in the LTA oxidation of cyclopentene,[51] cycloheptene,[52] and cyclooctene,[52] and, in the latter case, an appreciable amount of products resulting from transannular rearrangement, i.e., 5-acetoxycyclooctene and 1,4-diacetoxycyclooctane, was also formed.[52]

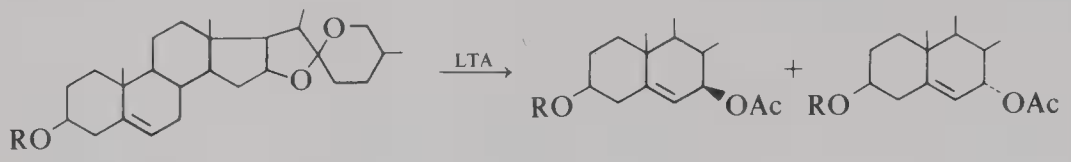
In the reaction of LTA with methylcyclohexene,[38] di- and trialkyl substituted cyclohexenes, such as 1-*p*-menthene,[38,53,54] 3-*p*-menthene,[55] and 2,4,4-trimethylcyclohexene,[56] rearranged and unrearranged allylic acetates, along with 1,2-diacetoxy derivatives were usually obtained, whereby allylic rearrangement is more favored in acetic acid than in benzene (as solvent).[56]



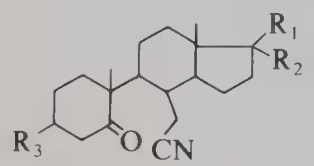
Cyclohexane derivatives having an exocyclic double bond, such as 1-methylene-4-*t*-butylcyclohexane, react with LTA to give a mixture of enol-acetate and vicinal diacetoxy compounds.[57,58]



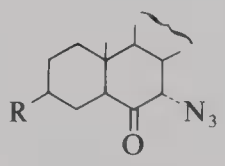
2.2.2c. Polycyclic Olefins and Terpenes. Oxidation of Δ^5-steroidal olefins with LTA in benzene or acetic acid proceeds without allylic rearrangement and results in nonstereospecific allylic acetoxylation at position C(7).[59]



By using $Pb(OAc)_{4-n}(N_3)_n$, Δ^5-steroids undergo cleavage of the C(5)–C(6) bond to give 5,6-seco-6-cyano-5-ketones, **26a**, in 20%–74% yield,[46,60a] whereas Δ^6- and other steroidal alkenes unsubstituted at the double bond afford with this reagent α-azidoketones **26b** in 45%–80% yield.[46,60b]

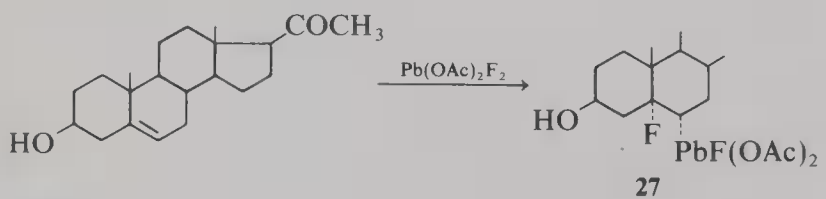


26a

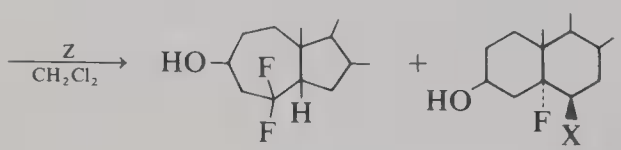


26b

The intervention of organo-lead intermediates in the LTA oxidation of olefins is strongly supported by the isolation of an α-fluoroorgano-lead compound **27** in the reaction of pregnenolone with $Pb(OAc)_2F_2$.[61] This solid gave rearranged and solvolytic products upon reaction with iodine, methyl iodide, bromine, or benzyl bromide in methylene chloride solution.



27

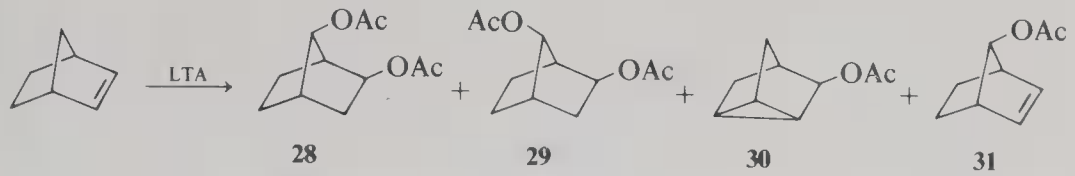


X = I or Br Z = I_2, CH_3I, Br_2, or $C_6H_5CH_2Br$

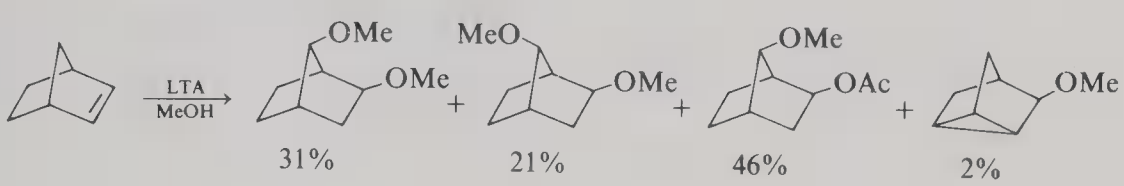
The reaction of norbornene with LTA in various solvents was investigated by several groups.[62–64] In all cases the 2,7-disubstituted norbornanes **28** and **29** were the major products, accompanied by 3-nortricyclyl **30** and norbornenyl derivatives **31**. The product ratio varied somewhat with solvent, and in methanol methoxy substituted compounds were also obtained.[62,64]

The mechanistic aspects of this reaction were extensively discussed, and the results rationalized in terms of electrophilic attack of a lead(IV) species, followed by rearrangement involving nonclassical norbornyl carbonium ion intermediates **32**.[63–65]

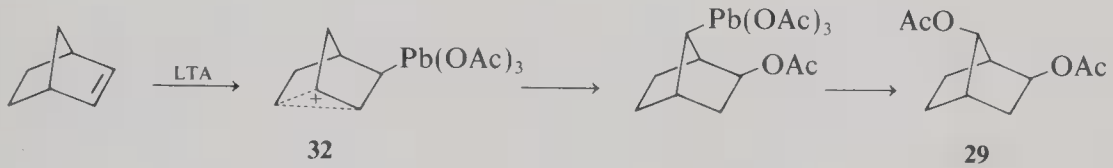
A different ratio of products was obtained in the reaction of LTA with 2-methylnorbornene (total yield about 35%), where 3-methyl-3-nortricyclyl acetate was the principal product, and no diacetoxy compounds were obtained.[65] The isomeric 2-methylenenorbornane was converted into allylic acetoxylated products in 27% yield, the ratio of 3-*exo*-



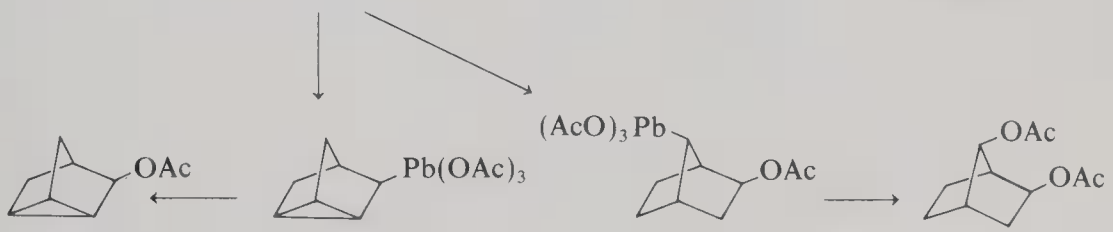
	28	29	30	31
in AcOH:	59%	27%	11%	1%
in C_6H_6:	55%	6%	21%	8%



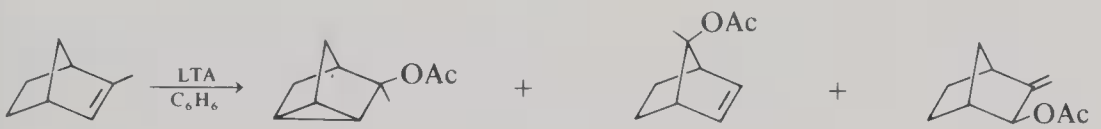
31% 21% 46% 2%



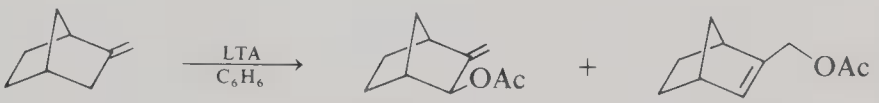
32 **29**



30 **28**



56% 35% 9%

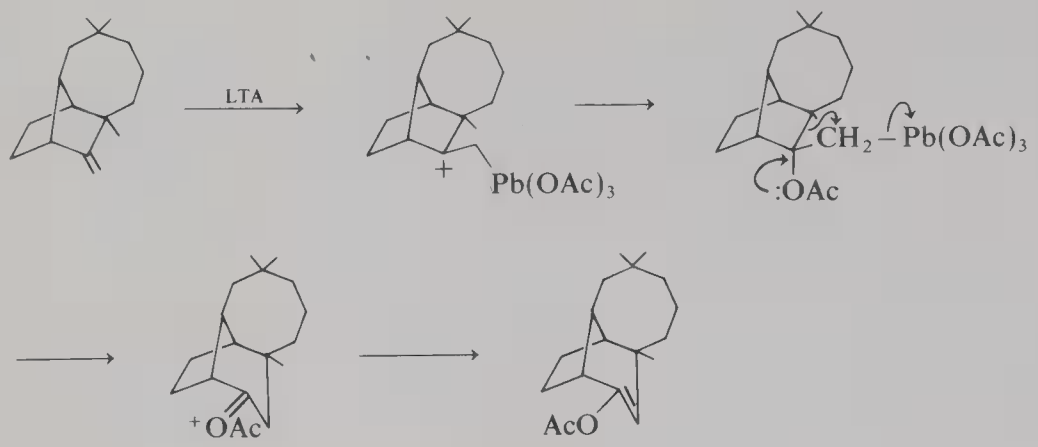


acetoxy-2-methylenenorbornane to 2-acetoxymethyl-2-norbornene being 93:7.[65] No products of skeletal rearrangement were observed.[65]

In compounds where formation of allylic systems via deprotonation in the first organolead intermediate is precluded, skeletal rearrangement takes place. Thus, camphene[66,67] and longifolene[68] react with LTA and undergo ring enlargment to give enol-acetates, such as **33** from longifolene, as final products, in 50–85% yield.

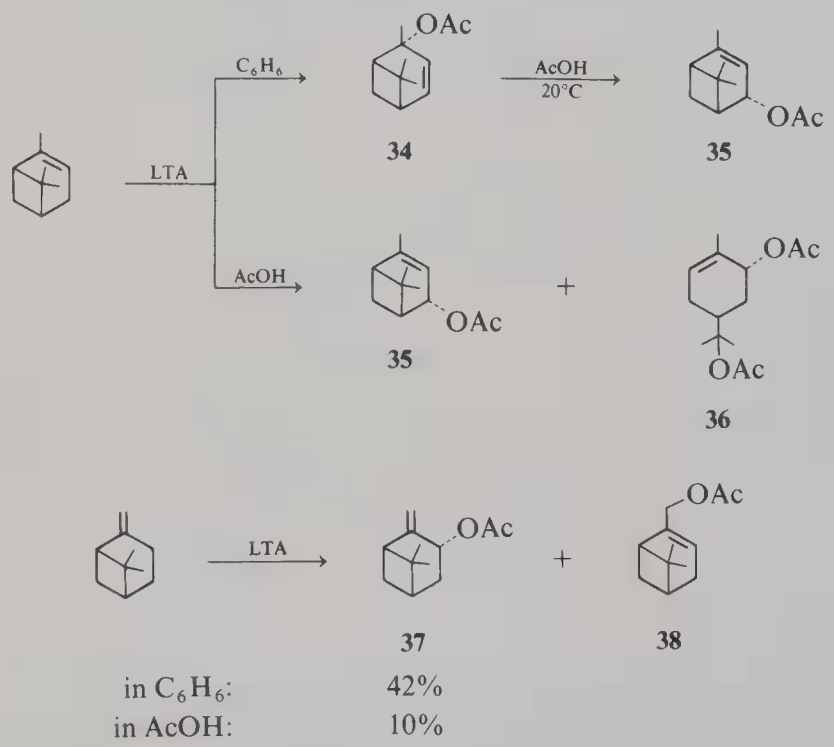
The oxidation of α-pinene with LTA in benzene gave as primary product *cis*-2-acetoxypin-3-ene, **34**, which in the presence of acetic acid underwent rapid allylic rearrangement to *trans*-verbenyl acetate **35**.[69] However, in acetic acid as solvent the products of the LTA reaction were verbenyl acetate, **35**, sobrerol diacetate, **36**, and verbenone.[2,47,70] The formation of the diacetoxy compound **36** is best explained in terms of carbenium ion intermediates, involving a Wagner–Meerwein-type rearrangement.

The isomeric β-pinene reacts with LTA similarly to 2-methylenenorbornane, affording



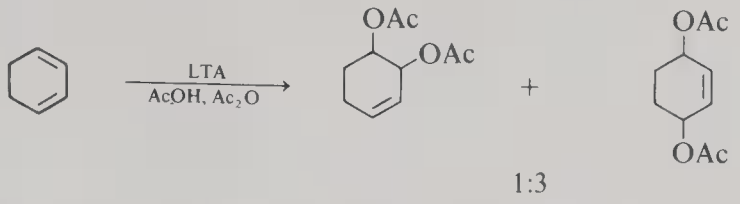
33

trans-pinocarvyl acetate **37** as the product of simple allylic acetoxylation and myrtenyl acetate **38** as the product of allylic rearrangement.[71] In benzene as a solvent acetoxylation without migration of the double bond is the preferred reaction,[71,72] whereas in acetic acid myrtenyl acetate **38**, along with a complex mixture of acetoxylated products and products of skeletal rearrangement, is predominant.[73] LTA oxidations of 3-carene[74] and 4-carene[75] in benzene or acetic acid gave complex mixtures of acetoxylated products and products of cyclopropane ring cleavage.

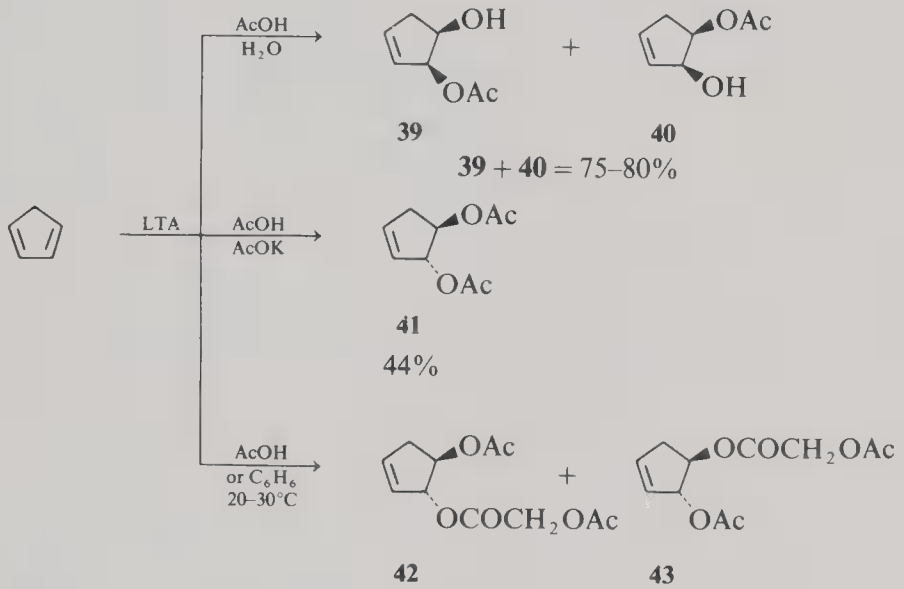


2.2.2d. Dienes and Polyenes. Conjugated dienes with LTA afford generally products of 1,2- and 1,4-diacetoxylation.[37,76–79] Thus, cyclohexa-1,3-diene reacts with LTA in acetic acid containing 3% of acetic anhydride to give a mixture of 1,2- and 1,4-diacetoxycyclohexenes in 42% yield.[77,78] Isoprene behaves similarly[77] but 1,3-butadiene, under the same conditions, affords only the 1,2-diacetoxy derivative along with products of addition of a methyl and an acetoxy group,[77] as observed in the LTA reaction of styrene.

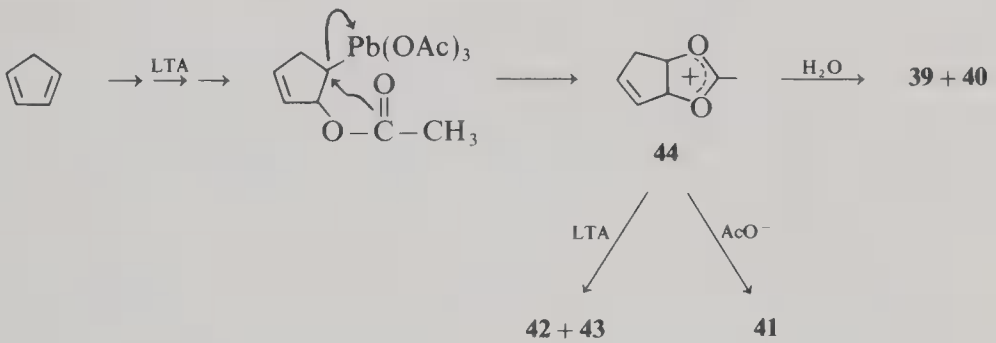
The distribution and stereochemistry of the products in the LTA oxidation of cyclopentadiene depend on the reaction conditions and nature of the solvent used. In wet acetic acid



at room temperature a mixture of monoacetates of *cis*-cyclopentene-1,2-diol, **39** and **40**, was obtained, while in glacial acetic acid containing potassium acetate *trans*-1,2-diacetoxycyclopentene, **41**, was formed.[79] In addition, the formation of mixed esters of cyclopentene-1,2-diol with acetic acid and acetylglycolic acid, **42** and **43** (and of products of

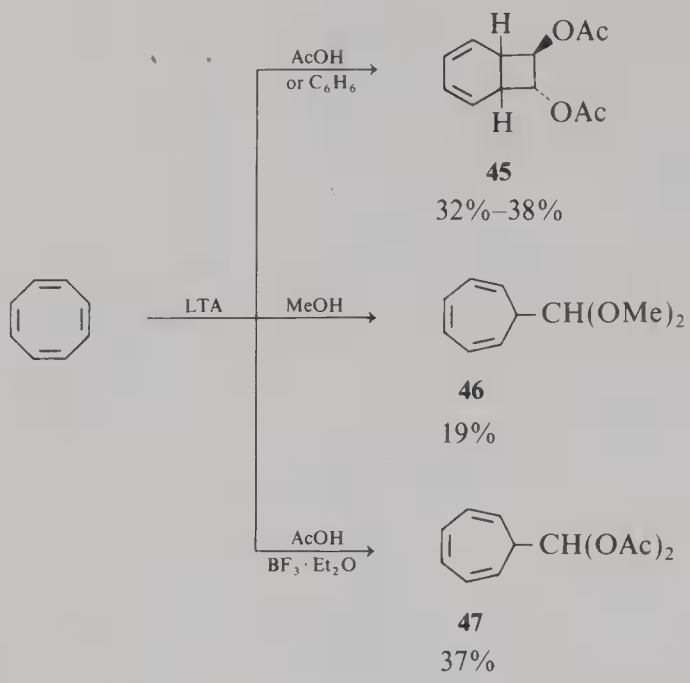


1,4-diacetoxylation), has also been reported.[37,76] It was suggested[2,13,79] that formation of all three types of reaction products may involve the same intermediate dioxolonium cation **44**, which, depending upon the experimental conditions, can react with water or acetate anion as nucleophiles or can be further oxidized by LTA (upon loss of a proton).

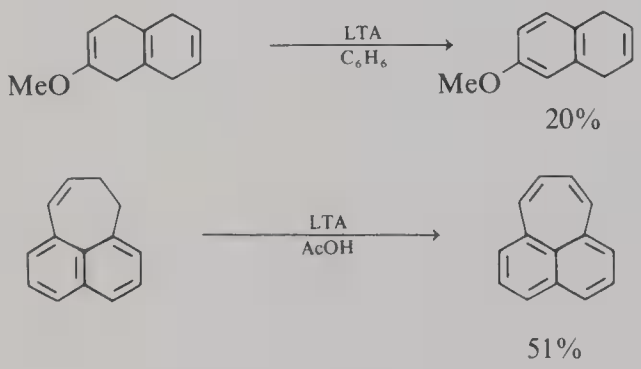


In the LTA oxidation of cyclooctatetraene two types of ring contracted products can be obtained. In acetic acid or benzene bicyclo[4.2.0]octa-2,4-diene-7,8-diol diacetate **45** is the main product. In methanol the reaction leads to the dimethyl acetal of 2,4,6-cycloheptatriene-1-carboxaldehyde, **46**, whereas in acetic acid in the presence of boron trifluoride etherate the corresponding diacetoxy acetal **47** is formed.[80]

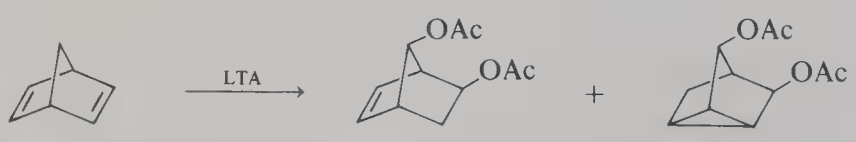
Steroids and other polycyclic structures containing a 1,3-cyclohexadiene system undergo dehydrogenation upon treatment with LTA in chloroform–acetic acid or in benzene, the driving force for this reaction being either relief of steric strain or/and aromatic stabilization



of the reaction products.[81–84] Dehydrogenation of other polycyclic conjugated polyenes by means of LTA to the corresponding condensed aromatic systems has also been successfully achieved.[84a]

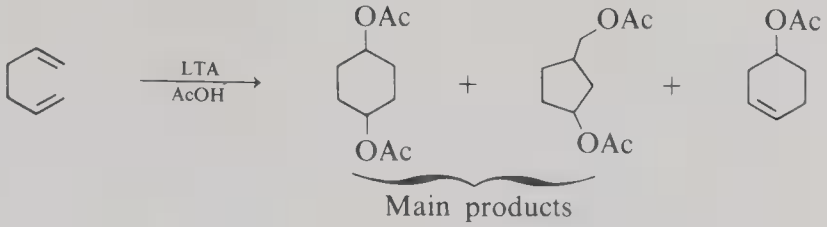


Nonconjugated bicyclic dienes such as dicyclopentadiene and norbornadiene react with LTA to give the corresponding 2,7-diacetoxy derivatives.[62] The formation of 2,7-diacetoxynorbornene **48** and diacetoxynortricyclane **49** from norbornadiene, in a remarkably solvent dependent ratio, is in agreement with the behavior of norbornene towards LTA.[62]

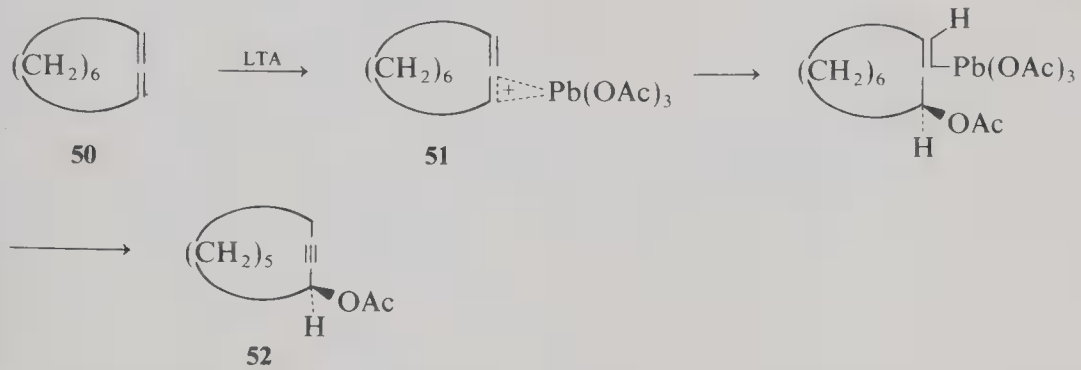


in AcOH:	25%	65%
in C_6H_6:	75–80%	10–15%

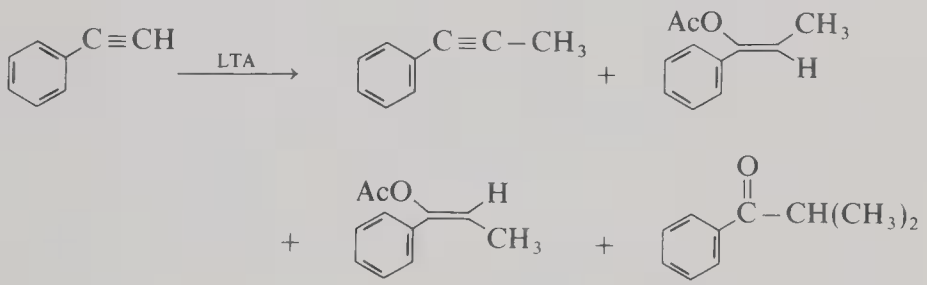
The nonconjugated diene, 1,5-hexadiene, upon treatment with LTA in acetic acid undergoes cyclooxidation with formation of acetoxylated cyclohexane, cyclohexene, and methylcyclopentane derivatives.[85]



2.2.2e. Allenes and Acetylenes. Optically active allenes react with LTA in acetic acid affording optically active α-acetoxy acetylenes,[86,87] as illustrated by the conversion of (−)-1,2-cyclononadiene **50** to (+)-3-acetoxycyclononyne **52**. The optical activity of the products indicates that the acetate anion attacks a three-membered cyclic plumbonium cationic intermediate **51** at the allylic position, thus preventing the development of a carbenium ion species.[87] In an earlier work it was claimed that the LTA reaction of 1-phenyl-1,2-butadiene results mainly in the addition of two acetoxy groups to one of the double bonds.[88]



Acetylenes react with LTA more slowly than olefins. By oxidation of dialkyl-acetylenes complex mixtures are usually obtained, containing products of α-substitution and of di- and tetraacetoxylation of the triple bond.[89,90] However, phenylbenzylacetylene underwent benzylic substitution in 61% yield.[90] In the reaction of phenylacetylene with LTA, methylphenylacetylene was the major product, along with minor products arising from addition of a methyl and an acetoxy group to the triple bond and from ketone formation.[91] LTA oxidation of β-acetylenic alcohols involves di- or tetraacetoxylation of the triple bond without reaction of the hydroxyl group.[90b]

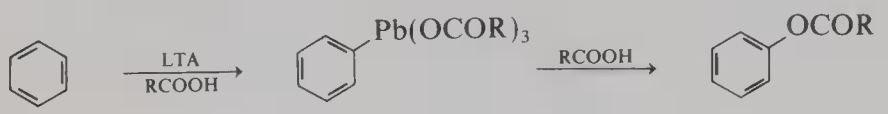


2.3. Aromatic Hydrocarbons

LTA can react with aromatic hydrocarbons in two ways: on the aromatic nucleus and at the benzylic position of side chains. In the first case the LTA reaction results in substitution of aromatic hydrogens by acetoxy or methyl groups, in the addition of two acetoxy groups, in dimerization and/or oxidation to quinones, whereas in the second case benzylic acetates are produced.

2.3.1. Mechanism

It was postulated that substitution of hydrogen on the aromatic ring involves an electrophilic attack of $^{+}Pb(OAc)_3$ species to give aryl-lead tricarboxylate, **53**, which in a subsequent reaction with acid yields the corresponding esters, e.g., **54**.[92,93] In this way substituted benzene derivatives give mixtures of *ortho*-, *meta*-, and *para*-substituted aryl esters, the ratio of isomers being dependent on the directing effects of the substituents, although usually *ortho*- and *para*-substitution predominates.[92–94]



53 **54**

$R = CH_3, CF_3$

On the basis of steady-state kinetic evidence it was proposed that benzylic acetoxylation involves acetoxy and benzyl radicals as intermediates [Eqs. (5)–(8)],[95] the free radical course also being supported by demonstrating that these reactions were inhibited by oxygen[95] and catalyzed by *t*-butyl alcohol.[29] Electron-donating groups attached to the aromatic ring were found to favor, while electron withdrawing substituents retarded, acetoxylation of benzylic carbon in the LTA reaction.[96]

$$Pb(OAc)_4 \longrightarrow {}^{\bullet}Pb(OAc)_3 + CH_3^{\bullet} + CO_2 \qquad (5)$$

$$C_6H_5CH_3 + CH_3^{\bullet} \longrightarrow C_6H_5CH_2^{\bullet} + CH_4 \qquad (6)$$

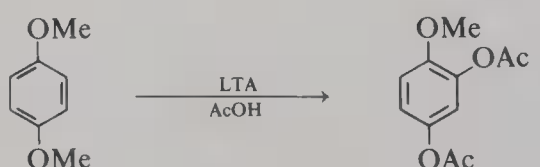
$$C_6H_5CH_2^{\bullet} + Pb(OAc)_4 \longrightarrow C_6H_5CH_2OAc + {}^{\bullet}Pb(OAc)_3 \qquad (7)$$

or

$$C_6H_5CH_2^{\bullet} + {}^{\bullet}Pb(OAc)_3 \longrightarrow C_6H_5CH_2OAc + Pb(OAc)_2 \qquad (8)$$

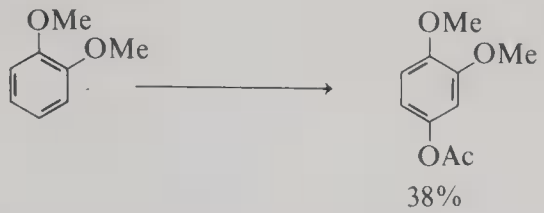
2.3.2. Scope and Limitations

2.3.2a. Aromatic Rings. Benzene itself is rather stable towards LTA at reflux and is often used as solvent in LTA reactions. Oxidation of benzene in acetic acid at elevated temperature gives benzyl acetate, which arises from toluene produced by methylation of benzene.[97] However, benzene can readily be oxidized by lead tetra(trifluoroacetate) (LTFA) to give the corresponding trifluoroacetoxy derivative in about 45% yield.[30] The oxidation of benzenoid compounds by LTA or LTFA in trifluoroacetic acid at room temperature usually



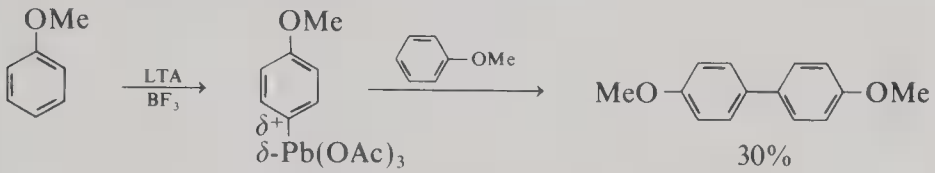
58%

affords the corresponding aryl trifluoroacetate esters as main reaction products, along with dimerization products and diarylmethane derivatives, while at higher temperature products of methylation of the aromatic ring are also obtained.[92–94,98,99] Mono- and polymethoxybenzene derivatives are oxidized by LTA in acetic acid to acetoxylated products, in up to 60% yield.[100–102]



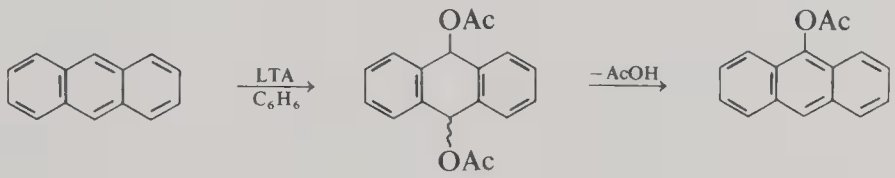
38%

The reaction of aromatic compounds with LTA catalyzed by boron trifluoride gave mixtures of dimerization and acetoxylation products, with the former predominating.[98,103] It was suggested that an ionic mechanism operates in this dimerization process, and that no free radical intermediates are involved.[103]

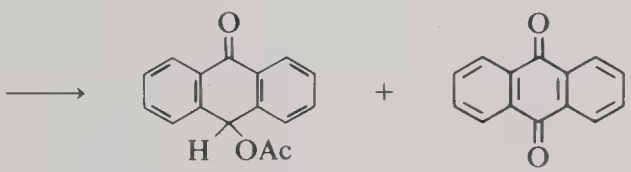


30%

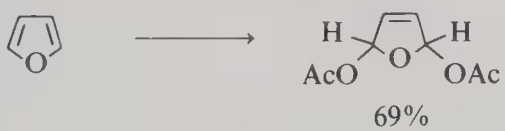
The oxidation of anthracene with LTA in benzene and other nonprotic solvents gave a mixture of *cis*- and *trans*-9,10-diacetoxy-9,10-dihydroanthracene in approximately equal amounts.[104] However, by using acetic acid as solvent, this product loses acetic acid and yields 9-acetoxyanthracene, which can undergo further oxidation to 10-acetoxy-9-oxo-9,10-dihydroanthracene and anthraquinone.[105] The LTA oxidation of anthracene in benzene containing methanol gave *cis–trans* mixtures of 9,10-dimethoxy-9,10-dihydroanthracene and 9-acetoxy-10-methoxy-9,10-dihydroanthracene, in which the *trans*-isomers predominated.[104] LTA in acetic acid converted 1,2-benzanthracene and benzpyrene into their acetoxy derivatives, in yields of 52%[106] and 85%,[107] respectively.



cis + *trans*

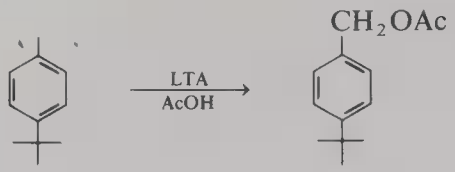


In the LTA oxidation of α-unsubstituted furans diacetoxylation occurs, affording 2,5-diacetoxy-2,5-dihydrofurans (usually as two stereoisomers),[108,109] while substitution in the α-position(s) of the starting furans, in dependence on the number and nature of the substituent groups, may or may not prevent LTA acetoxylation.[110,111]



69%

2.2.3b. Benzylic Groups. Aromatic compounds possessing a C–H group at the benzylic position can readily be oxidized by LTA to the corresponding benzyl acetates, in synthetically valuable yields. Acetoxylation of benzylic carbon by LTA is performed preferably in refluxing acetic acid. Benzylic acetoxylation can be accompanied by methylation of the aromatic ring, followed sometimes by acetoxylation of the methyl group introduced in this way.[95]



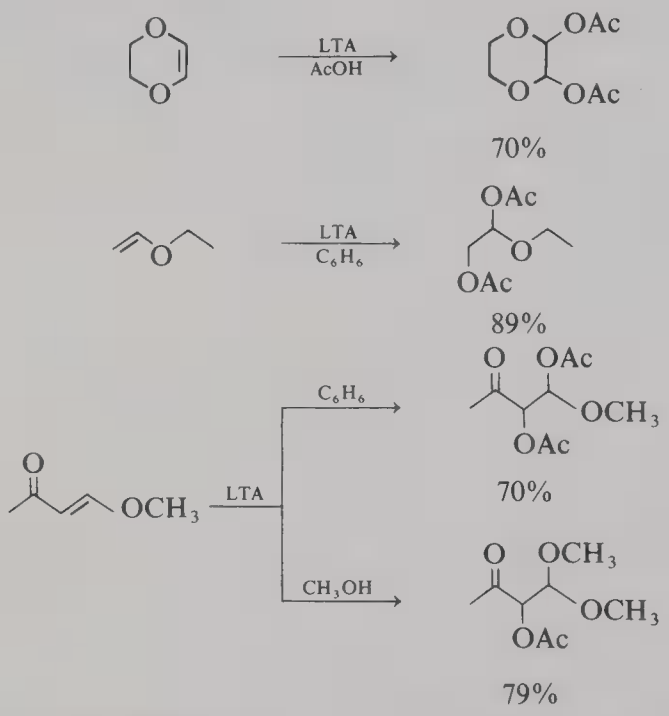
55%

Geminal diacetoxylation of the benzylic CH_2 group, in some cases, can occur to a considerable extent, while products of dimerization of the intermediary benzylic radical have not been detected.

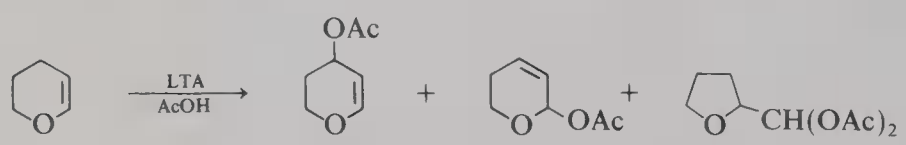
Some examples of LTA benzylic acetoxylation are given in Table I.

2.4. Vinyl Ethers and Enamines

The olefinic double bond in vinyl ethers devoid of hydrogen at the allylic position is diacetoxylated by treatment with LTA, affording 1,2-diacetoxy compounds.[125,126] However,



vinyl ethers possessing an adjacent C–H group give a mixture of isomeric allylic acetates, accompanied in some cases by products of skeletal rearrangement.[126,127]

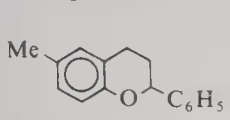
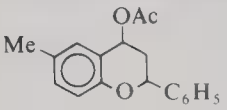
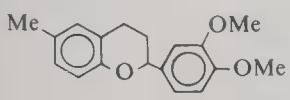
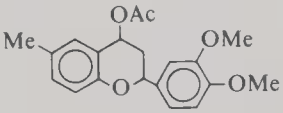
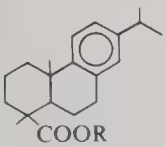
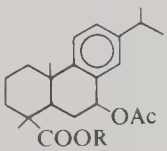
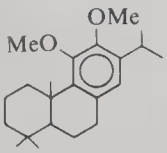
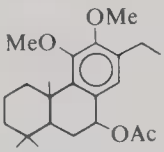
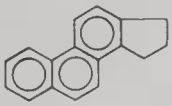
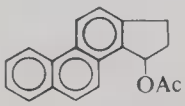
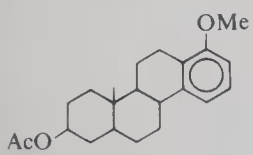
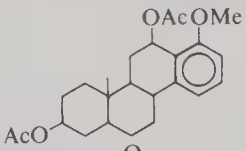
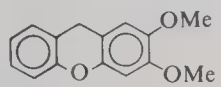
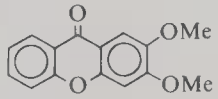
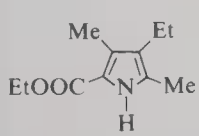
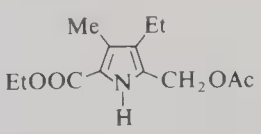


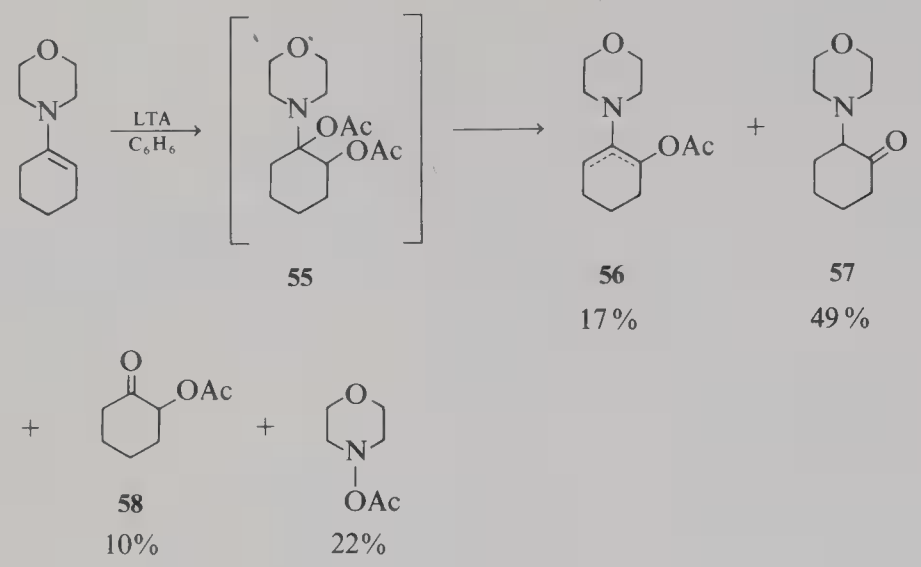
18% 13% 23%

Other, structurally different, vinyl ethers were also oxidized with LTA and the corresponding 1,2-diacetoxy compounds or allylic acetates were obtained.[107,128,129]

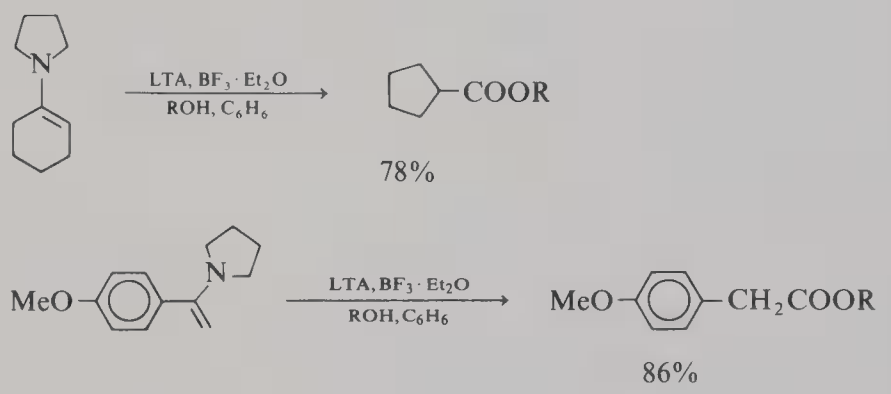
By treatment of the enamine shown below with LTA in benzene, a mixture of ketonic and/or acetoxylated products was obtained.[130] It was suggested that the first step in this oxidation is the addition of two acetoxy groups onto the double bond of the enamine,

TABLE I. Benzylic Acetoxylation with LTA

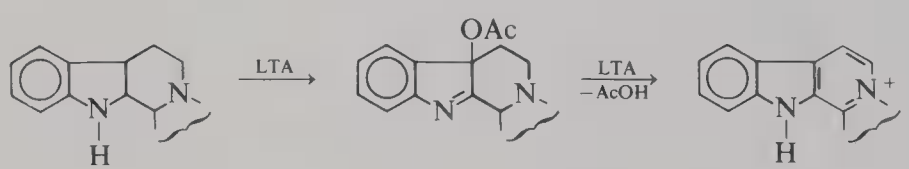
Aromatic compound	Product	Yield (%)	Reference
Toluene	Benzyl acetate	10–38	27, 96
p-Xylene	*p*-Methylbenzyl acetate	47	96
Ethylbenzene	α-Phenylethyl acetate	32	27, 95
p-Methoxytoluene	*p*-Methoxybenzyl acetate	60	96, 112
p-Nitrotoluene	*p*-Nitrobenzyl acetate	7	96
Diphenylmethane	Benzhydryl acetate	71	27
Phenyl-*p*-methoxyphenyl-methane	*p*-Methoxybenzhydryl acetate	80	113
Tetralin	1-Acetoxytetralin	37	37
6-Methoxytetralin	1-Acetoxy-6-methoxytetralin	62	114
9,10-Dimethylanthracene	9,10-Bis(acetoxymethyl)anthracene	50	115
Acenaphthene	1-Acetoxyacenaphthene	80	116
			117
			118
		45	119
		27	120
		13	121
		60–80	122
		75	123
			124



resulting in the formation of a 1,2-diacetoxy intermediate **55**, which is further converted to monoacetate esters (**56** and **58**), some of which (i.e., **56**) are finally cleaved to the α-amino-ketone **57**.[130] In the oxidation of enamines with LTA in the presence of boron trifluoride etherate and an alcohol, a Favorski-type rearrangement occurs and esters are obtained in fair yield.[131]



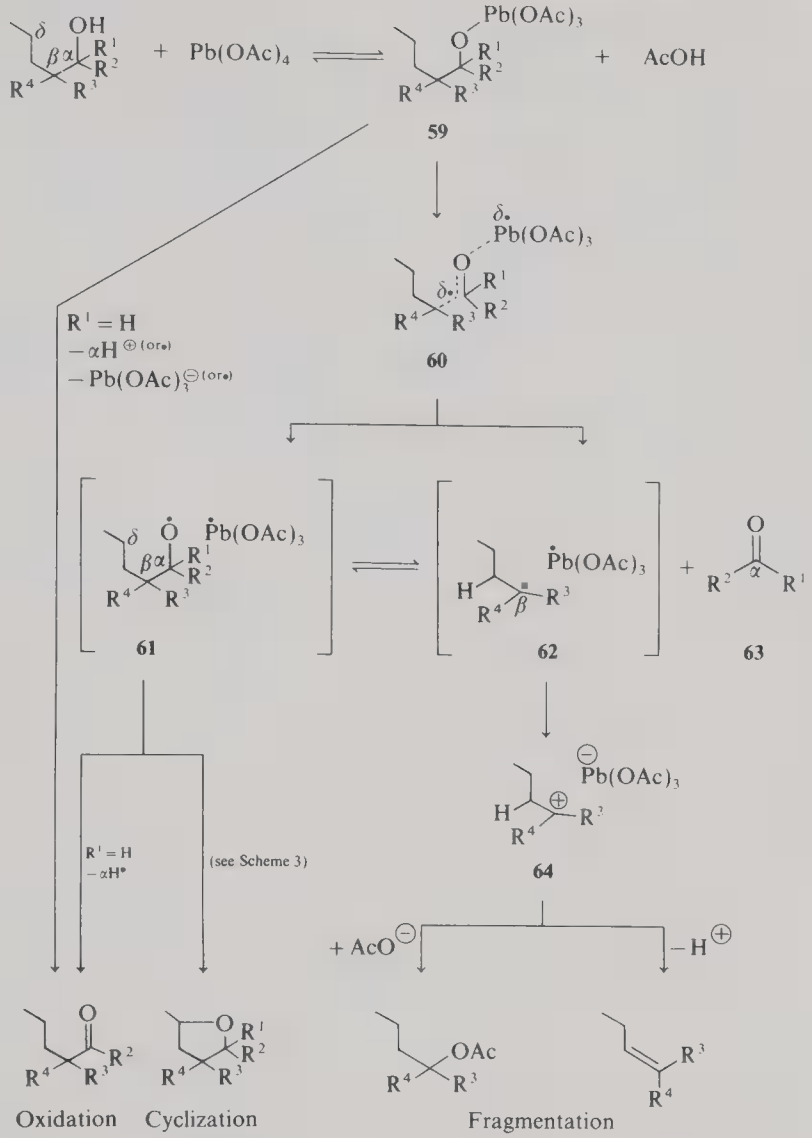
Other enamine and enamide structures were oxidized by LTA to α-acetoxylated products.[132,133] In one case this reaction was successfully applied for the aromatization of a heterocyclic systems, as shown below[134]:



3. MONOHYDROXYLIC ALCOHOLS

The oxidation of monohydroxylic alcohols with LTA can be performed in both polar and nonpolar media; depending on the polarity of the solvent and structure of the substrate, three major competing processes have been observed, namely, (a) oxidative intramolecular cyclization to cyclic ethers; (b) fragmentation of the C_α–C_β bond; (c) carbonyl compound formation. The main features of these reactions are shown in Scheme 2.

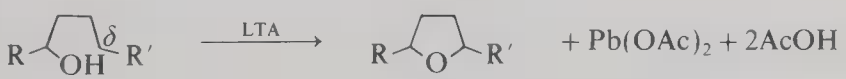
SCHEME 2



3.1. Intramolecular Cyclization to Cyclic Ethers

3.1.1. Saturated Alcohols

The LTA oxidation of saturated alcohols (possessing an appropriate carbon skeleton) in a nonpolar solvent (preferably benzene) results in the oxidative cyclization to tetrahydrofuran-type ethers, whereby a non-activated δ-carbon atom of a methyl, methylene, or methine group is functionalized by intramolecular introduction of an ether oxygen function.[135–137]



This ring closure reaction represents a convenient, efficient, and experimentally simple and mild method for the regioselective functionalization of non-activated carbon atoms, and therefore a useful one-step synthetic procedure for the preparation of cyclic ethers from

appropriate hydroxy compounds. Because of these features, it has received particular attention and has been applied successfully to the synthesis of many otherwise difficultly accessible compounds, including natural products.[138]

3.1.1a. Mechanism. Although the conversion of alcohols into cyclic ethers by means of LTA is stoichiometrically a rather simple oxidation reaction, the mechanism of this ring closure process appears to be rather complex,[5–9,135–137] involving four stages: (i) alkoxylation of lead tetraacetate by hydroxy compounds; (ii) radical cleavage of the RO–Pb bond and formation of alkoxy radical species; (iii) intramolecular hydrogen abstraction by alkoxy radicals; (iv) ring closure to cyclic ethers.

(i) Alkoxylation of lead tetraacetate. Since homolytic cleavage of an O–H bond, owing to its high bond energy (DE_{O-H} 433–439 kJ mol^{-1}), is almost impossible under normal reaction conditions, it is assumed that the first step in the LTA oxidation of alcohols consists of the reversible formation of readily cleavable derivatives, which can be formulated as alkoxy–lead(IV) acetates, **59** (See also Scheme 2). Depending on the relative concentration of reactants, the structure of starting alcohols, and the reaction conditions, it was proposed that lead(IV) alkoxides with more than one alkoxy group **59a** can be also formed.[3,139–141] However, the exact structure of these intermediates is not known, since, usually, they are too reactive to be isolated. This exchange process, which is usually fast with primary alcohols, decreases when going to secondary and particularly tertiary alcohols or secondary alcohols with a sterically hindered hydroxy group[137,142–145]; in the latter two cases this step in the LTA oxidation of alcohols may considerably prolong the reaction time.

$$\underset{}{R-OH} + Pb(OAc)_4 \rightleftharpoons \underset{\mathbf{59}}{RO-Pb(OAc)_3} \xrightleftharpoons{(n-1)\ R-OH} \underset{\mathbf{59a}}{(RO)_nPb(OAc)_{4-n}} + n\text{AcOH}$$

(ii) Alkoxy radical formation. Decomposition of lead(IV) alkoxides **59** to alkoxy radicals **61*** can be induced thermally (at temperatures around 80°C)[137–140,146–148] or photolytically (uv irradiation at room temperature or lower)[140,148,149] in a nonpolar solvent.

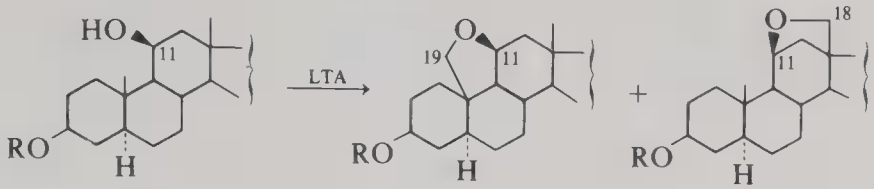
$$\underset{\mathbf{59}}{RO-Pb(OAc)_3} \xrightarrow{\triangle\ (\text{or } h\nu)} \underset{\mathbf{61}}{RO^{\bullet}} + {}^{\bullet}Pb(OAc)_3$$

This process is similar to, but energetically more favorable than, the homolytic cleavage of the ionic Pb–OAc bond in LTA,[141,150,151] which requires a temperature of about 140°C. Heterolytic decomposition of lead(IV) alkoxides into RO^+ and $Pb(OAc)_3^-$ is also known; however, it is important mainly in polar media and will be discussed later in connection with the LTA oxidation of monohydroxylic alcohols to carbonyl compounds.[152]

The intermediacy of alkoxy radicals (rather than cationic oxygen species RO^+) in the first stages of the LTA oxidation of alcohols in nonpolar solvents is substantiated by the following observations. In a number of cases, not only cyclic ethers of the starting alcohols but also isomeric and diastereomeric cyclic ethers derived from alcohols with an epimeric carbinol (α) carbon atom and/or adjacent (β) carbon atom are formed. Such products have been isolated from 11β-hydroxy steroids, **65**,[145,148,153] 4β-hydroxy steroids, **66**.[145,148] 3,5β-cyclo-6β-hydroxy steroids,[154] and also from 2-alkylcyclohexanols.[5,155,156]

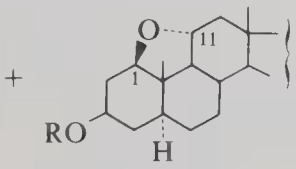
These epimerization reactions ("reversible fragmentations"), which must involve scission and recombination of the C_α–C_β bond, with temporary loss of stereochemistry at both carbons, are compatible only with alkoxy radical intermediates undergoing fragmentation to a carbon radical fragment and a carbonyl fragment **67**. In the case of heterolytic cleavage of the Pb–O bond, the resulting cationic oxygen species (RO^+) could eventually undergo β-

* Probably involving a transition state structure of type **60** (Scheme 2).



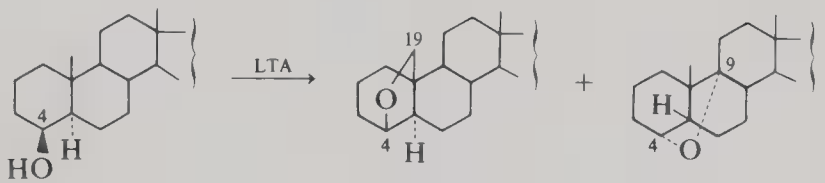
65 7.5% 4.5%

Normal products



23%

Inversion at C_{11}

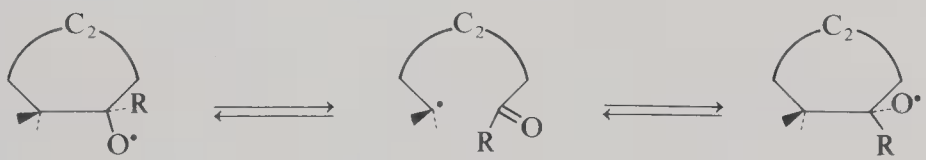


66 74% 7%

Normal product Inversion at C_4 and C_5

scission, but reattachment of the carbenium ion fragment formed in this way (corresponding to radical **67**) to the positively polarized carbon end of the carbonyl fragment is not feasible.

In addition, rearrangements observed in the LTA oxidation of triarylmethanols in benzene solution are consistent with participation of alkoxy radicals in these processes.[146,147a] Finally, alkoxy radicals generated in the LTA oxidation of alcohols were detected by ESR spectroscopy.[157]

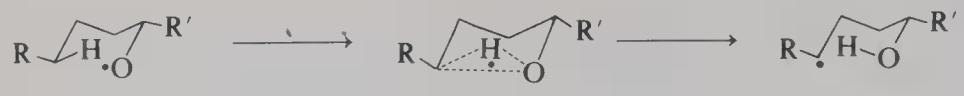


67

(iii) Intramolecular hydrogen migration. Internal hydrogen transfer is a characteristic reaction of alkoxy radicals in general, whatever their origin may be.[7,158–161] In order that in the LTA reaction intramolecular hydrogen abstraction by alkoxy radicals, resulting in final formation of cyclic ethers, proceeds in a satisfactory yield, the following requirements should be met.

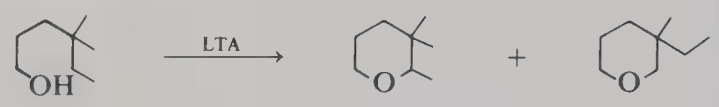
(1) The main competing reactions of alkoxy radicals **61** and their alkoxy–lead(IV) acetate precusors **59** (i.e., β-fragmentation and oxidation to carbonyl compounds, Scheme 2) must be suppressed. Usually, when intramolecular hydrogen abstraction of alkoxy radicals is feasible, these two reactions are of minor importance.

(2) The hydrogen atom to be abstracted from a constitutionally remote nonactivated carbon atom must be conformationally suitably oriented with respect to the attacking oxygen in the transition state controlling this process. From the fact that in the great majority of cases regioselective hydrogen abstraction proceeds preferentially from the δ-carbon atom, it was concluded that the most favorable transition state for intramolecular transfer corresponds to a quasi-six-membered ring, **61a**.[5–9,160,161] It can be attained with minimal

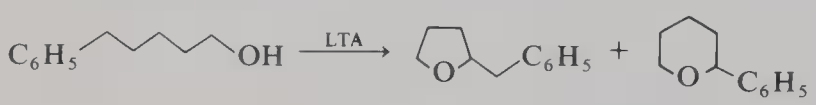


61 **61a** **68**

interactions and distortions when the intramolecular distance between the carbon attacked and the attacking oxygen radical falls in the range 2.5–2.7 Å,[7] leading to subsequent ring closure to tetrahydrofuran-type ethers. A quasi-seven-membered ring transition state resulting in 1,6-hydrogen abstraction (from the ε-carbon) leading to tetrahydropyran formation is also possible. However, it requires more activation energy. This is substantiated by the fact that the formation of six-membered cyclic ethers is not particularly favored even in the LTA oxidation of open-chained alcohols possessing structures which only permit ring closure to tetrahydropyrans or structures in which the ε-hydrogen atom is activated by benzylic or allylic interaction; in such cases six-membered cyclic ethers are also formed in rather poor yield.[162–167] On the other hand, in rigid bicyclic or polycyclic systems in which, due to



8% 3%



48% 9%

structural and stereochemical factors, the ε-carbon atom and the oxygen radical assume an optimal distance of 2.5–2.7 Å, 1,6-hydrogen migration is favored and six-membered cyclic ethers are obtained in high yield.[168,169]

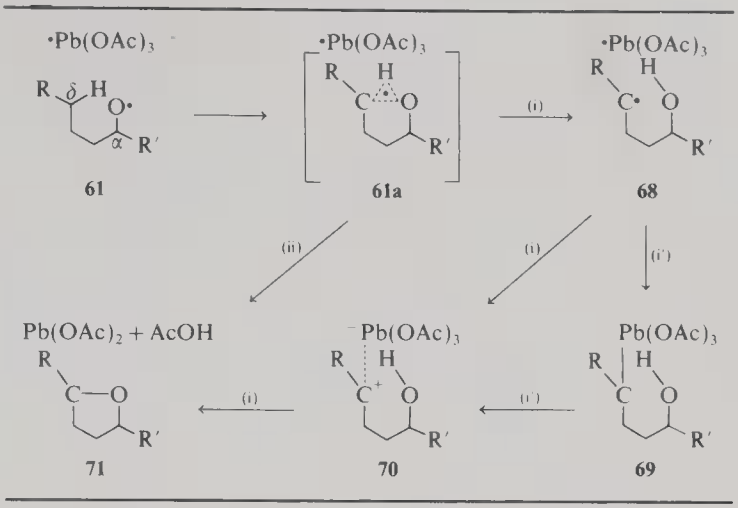
89%

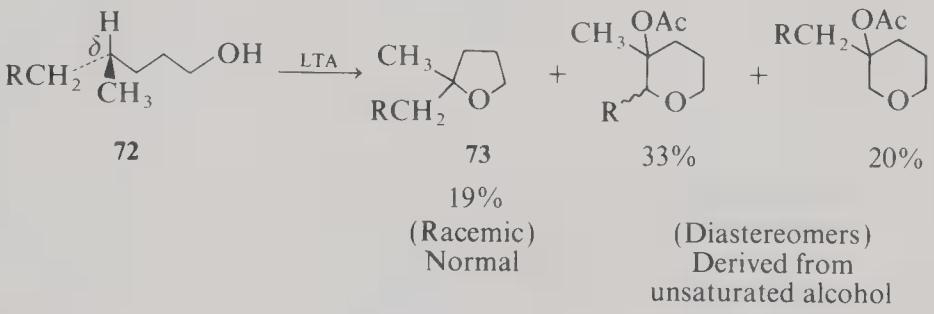
(iv) Ring closure to cyclic ethers. In the LTA oxidation of alcohols containing δ- (and/or ε-) carbon atoms, two alternatives (i) and (ii) in Scheme 3 have been envisaged[7] for the formation of cyclic ethers from alkoxy radicals **61**.

(i) One route, suggested for substrates in which one or both reacting centers are conformationally mobile, would consist in collapse of the cyclic transition state **61a** to a δ-carbon radical **68**, probably paired to a radical lead-triacetate (or similar) species. Oxidation of the δ-carbon radical **68** by one-electron transfer from carbon to lead, either directly (i) or via an organolead intermediate **69** (i'), to give the corresponding carbenium ion **70**, would lead to the cyclic ether product **71**.

Although the occurrence of δ-carbon radicals (such as **68**) has not been directly proved in the LTA oxidation of alcohols, evidence has been advanced for the intermediate production of species with radical and/or cation character on the δ-carbon atom (from which hydrogen is abstracted). Thus, in the LTA oxidation of the optically active primary alcohol (+)-(4*R*)-4,8-dimethylnonanol **72**, containing an asymmetric tertiary δ-carbon atom, among other products, a completely racemized tetrahydrofuran derivative **73** was obtained,[170] indicating that cyclization cannot have occurred directly via a cyclic transition state **61a** with a fixed geometrical arrangement of the δ-carbon, hydrogen, and oxygen.

SCHEME 3





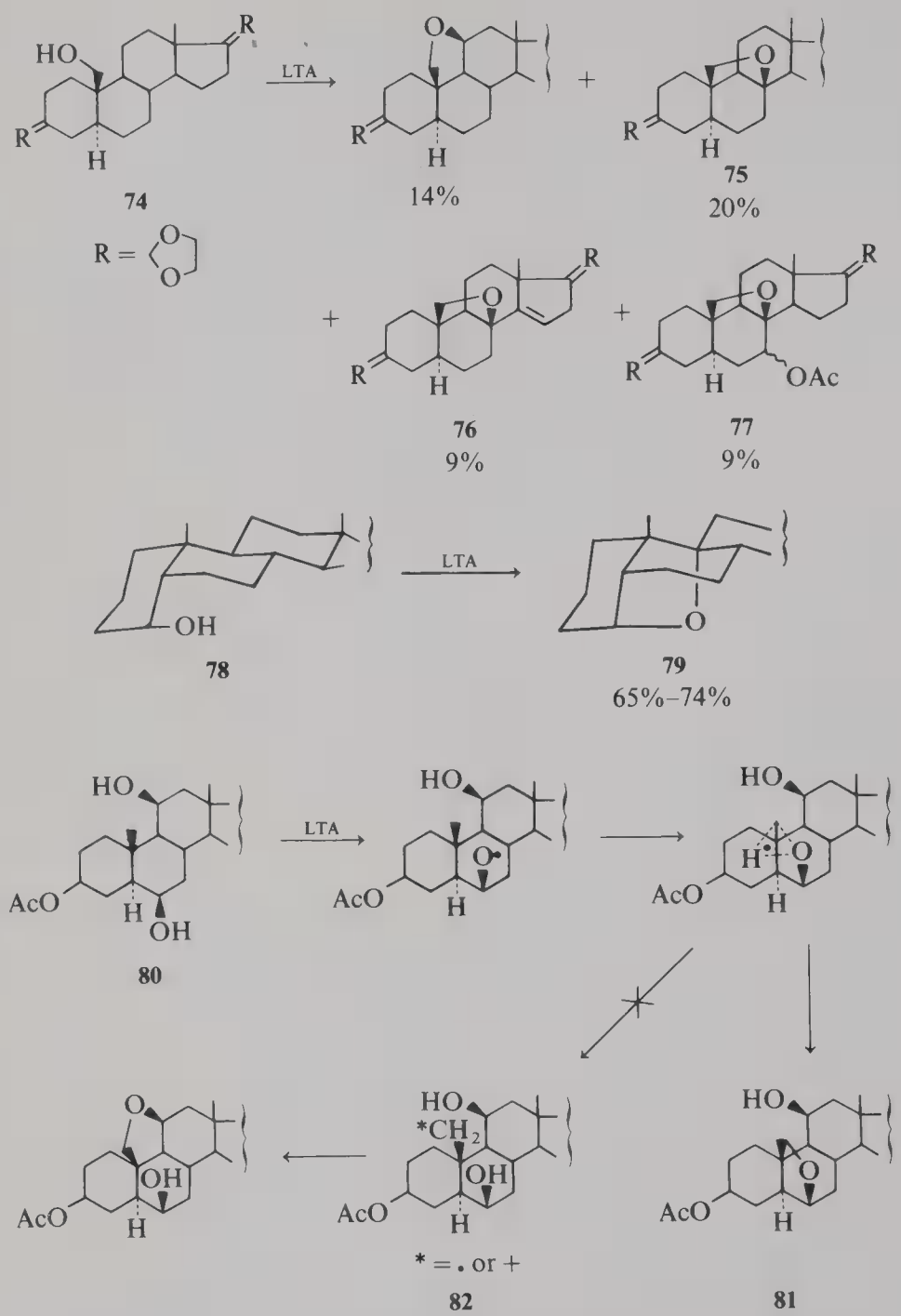
One-electron oxidation of the δ-hydroxyalkyl radical (**68**) by lead(III) or lead(IV) species to the corresponding δ-carbenium ion (**70**) is strongly supported by the results obtained in the oxidations of alcohols possessing a tertiary C_δ–H bond[171] or a neopentyl δ- or ε-carbon atom.[163,172] These substrates undergo, prior to cyclization, transformation and isomerization typical of carbenium-ion intermediates.

(ii) The alternative pathway for the formation of cyclic ethers **71** from the intermediate alkoxy radicals **61**, suggested for substrates in which the reaction centers are fixed, would consist of the removal of an electron [by lead(III) or lead(IV) species] from the developing three-electron bonding system in the cyclic transition state **61a**, resulting in oxidation of the hydrogen to a proton and the production of an internal C–O ether bond[7] (see Scheme 3, route ii).

This difference in the cyclization pathway leading to cyclic ethers is apparent by comparing, for example, the $C_{19} \rightarrow C_8$ cyclization in the 19-hydroxy steroids (such as **74**) having a conformationally mobile C–O bond, when three 8β,19-ethers **75**–**77** were obtained,[173] with $O_{4\alpha} \rightarrow C_9$ ring closure in 4α-hydroxy-5β-steroids **78** with conformationally fixed reaction centers, when only the saturated "normal" 4α,9α-ether **79** was obtained.[145]

Moreover, in the reaction with the 5α-steroidal 6β,11β-diol **80**, in which the two β-axial hydroxy groups are equidistant from the 19-methyl group, because of steric hindrance at the 11β-position, LTA attacks preferentially the 6β-hydroxy group, to give only 6β,19-cyclization product **81**, this indicating that a symmetrical species at C(19) **82** is not involved in the ether ring closure reaction.[7] Similar results were obtained with the corresponding 4β,11β-diol steroid derivative.[174]

Hypoidite lead tetraacetate reaction. By modification of the original oxidation procedure described above, lead tetraacetate is often employed in combination with iodine to produce alkoxy radicals capable of intramolecular functionalization. In this "hypoiodite lead tetraacetate reaction"[7–9,159] the reactive intermediates undergoing homolytic decomposition are alkyl hypoiodites. They have not been isolated in the pure state so far, but are formed *in situ* by exchange reaction of alcohols with acetyl hypoiodite derived from LTA and iodine



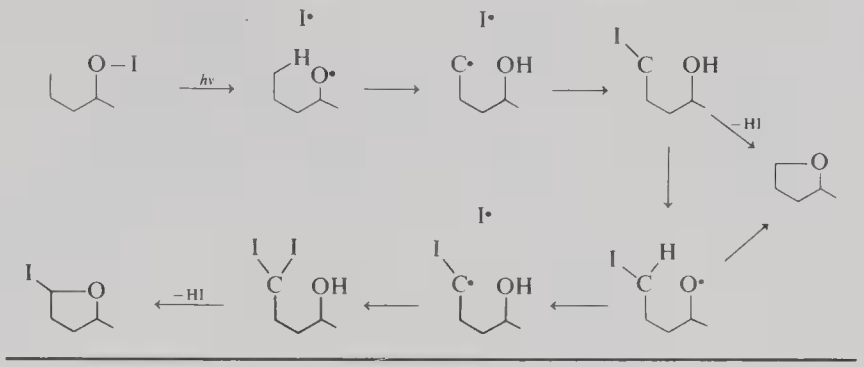
[Eqs. (9)–(11)]. Alkoxy radicals thus obtained undergo intramolecular hydrogen abstraction and an intermediate δ-alkyl radical is formed (Scheme 4).[8] Under these conditions, contrary to the LTA oxidation of alcohols, the δ-alkyl radical is intercepted by iodine before it can be oxidized by lead(III) or lead(IV) species; thus, it forms a 1,4-iodohydrin intermediate which can either undergo loss of HI to give unsubstituted five-membered cyclic ethers or can be subsequently oxidized to a δ-iodoalkoxy radical, allowing a second intramolecular hydrogen

$$Pb(OAc)_4 + I_2 \longrightarrow Pb(OAc)_2 + 2AcOI \tag{9}$$

$$AcOI + R\text{–}OH \rightleftharpoons RO\text{–}I + AcOH \tag{10}$$

$$RO\text{–}I \longrightarrow RO^{\bullet} + I^{\bullet} \tag{11}$$

SCHEME 4



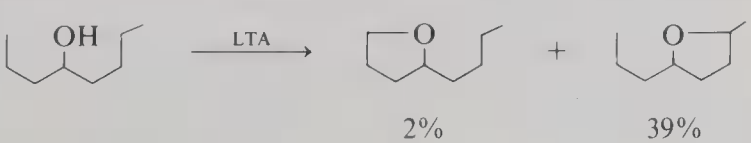
transfer and thus giving α-iodo cyclic ethers as products of double δ-carbon substitution (Scheme 4.)[7–9,159,175,176]

Intramolecular functionalization of nonactivated δ-carbon atoms by the LTA-iodine oxidation of alcohols has been successfully applied in the steroid series, but has been mainly limited to substrates possessing conformationally fixed reaction centers, i.e., the δ-(or ε-)carbon atoms and the attacking radicalic oxygen.[7–9]

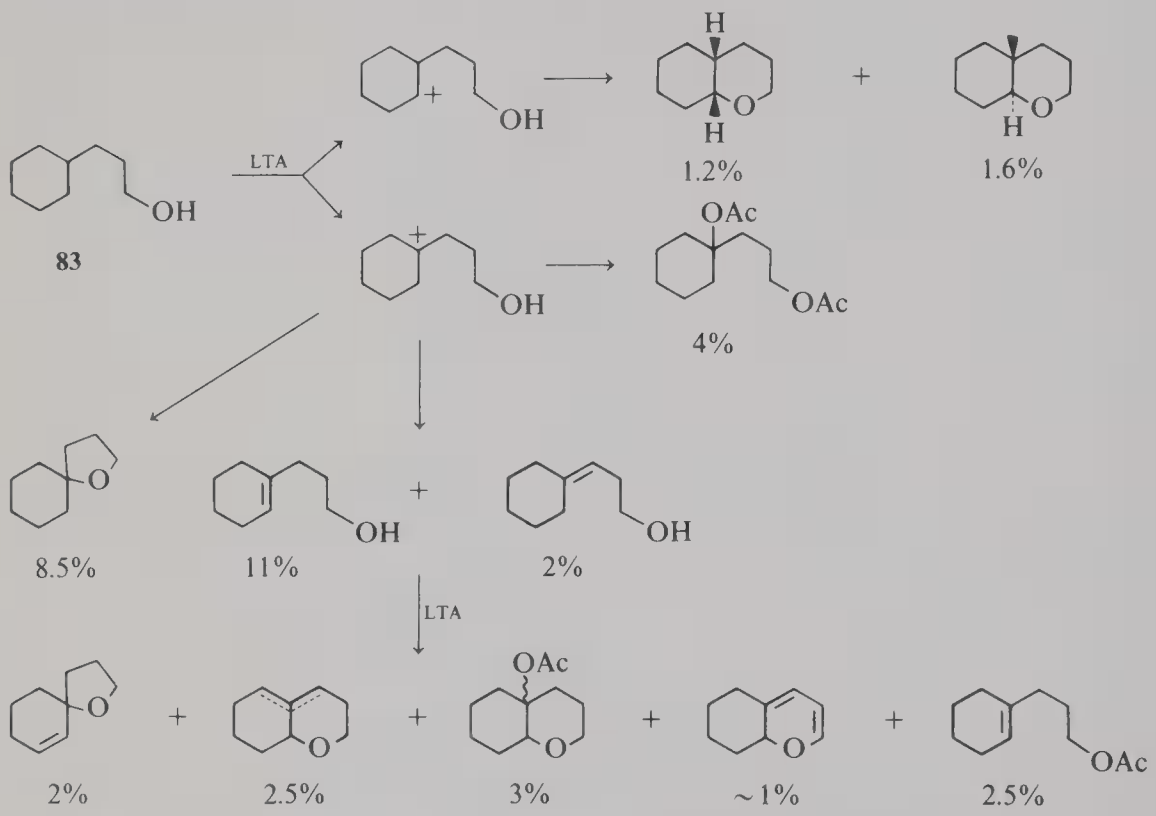
3.1.1b. Scope and Limitations. The LTA oxidation of β- and δ-unbranched primary aliphatic alcohols in nonpolar solvents leads to 2-alkyl-tetrahydrofurans in yields amounting to 45%–55%.[137,139,140,149] Secondary aliphatic alcohols containing a δ-methylene group afford 2,5-dialkyl-tetrahydrofurans in about 33%–44% yield.[135,137,139,149,177,177a] These products consist of a mixture of *cis*- and *trans*-isomers, the *cis*/*trans* ratio being about 40–45:60–55.[137,177] Tertiary aliphatic alcohols, because of unfavorable steric and electronic factors, are less suitable substrates for the preparation of tetrahydrofurans by means of the LTA reaction.[7,142,178]

In the cycloalkanol series, cyclobutanol and cyclopentanol are not converted by LTA to intramolecular ethers, since there is no structural possibility for internal homolytic 1,5-hydrogen abstraction in the corresponding cycloalkoxy radicals.[179] Cyclohexanol affords only under 1% of 1,4-epoxycyclohexane, because of the unfavorable boatlike conformation required for the quasi-six-membered cyclic transition state **61a**.[139,179] However, in larger rings, such as cycloheptanol and cyclooctanol, ring flexibility increases and the possible conformations of the six-membered cyclic transition state structures become more favorable, resulting in an appreciable increase in yield of bicyclic ethers, which amounts to 10%–15% for 1,4-epoxycycloheptane,[179,180] and over 35% for 1,4-epoxycyclooctane.[179–182] Although cyclodecanol undergoes ring closure to a considerable extent (27.5–30%), the "normal" (five-membered) 1,4-epoxycyclodecane is formed in only 2.5% yield, whereas the major cyclization products are 1,2-epoxycyclodecane (predominantly as *trans*-isomer) and the rearranged 8-ethyl-7-oxabicyclo[4.3.0]nonane (in the form of all four diastereomers).[155,179] On the other hand, cyclopentadecanol and cyclohexadecanol react normally affording bicyclic 1,4-ethers in about 45% yield.[179,183]

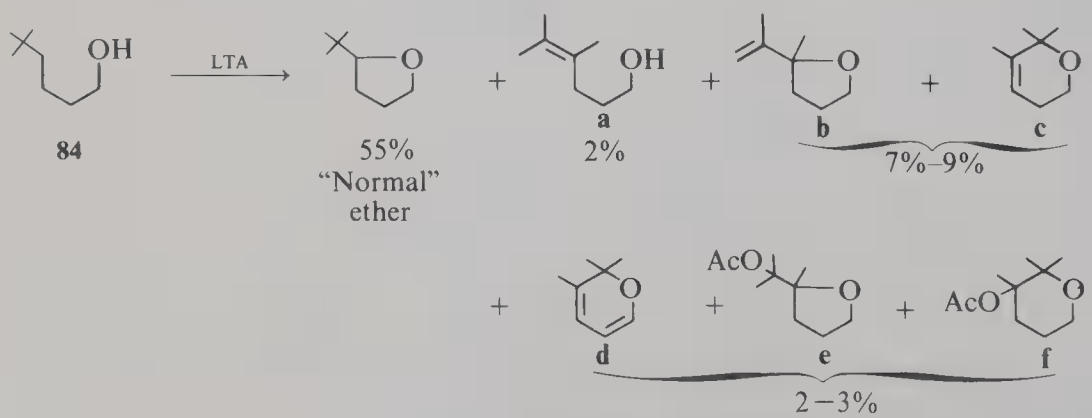
As expected, under otherwise comparable conditions, the relative susceptibility of hydrogen atoms on the nonactivated δ-carbon atoms to intramolecular abstraction by alkoxy radical decreases in the order of increasing C–H bond dissociation energies, i.e., tertiary > secondary > primary, as reflected by the yields of the respective cyclic ethers.[137,140,184–186] However, alcohols with a tertiary C_δ–H bond afford "normal" tetrahydrofuran-type ethers in reduced yields, when compared to flexible alcohols with a



(secondary) δ-methylene group, or to conformationally fixed alcohols with favorable $C_\delta \leftrightarrow O$ distance.[170,171,173, 187–189] In these reactions, other products, such as unsaturated alcohols, their acetates, five- and six-membered cyclic ethers containing a double bond or an acetoxy group (all deriving from the corresponding tertiary δ-carbenium ions) are also formed. For example, by using 3-cyclohexyl-1-propanol (**83**) as substrate, it could be shown that, together with "normal" saturated cyclic ethers, the olefinic alcohols were formed as the primary oxidation products, which upon further reaction with LTA were converted into the corresponding olefinic and acetoxylated cyclic ethers.[171]



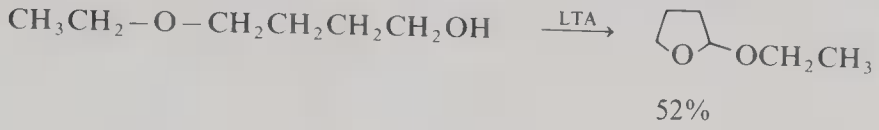
Furthermore, the LTA oxidation of alcohols possessing a neopentyl δ- or ε-carbon atom, i.e., 4,4-dimethyl-1-pentanol[163] and 5,5-dimethyl-1-hexanol **84**,[172] in addition to the "normal" ethers, gives neopentyl type rearranged products (**a–f**).



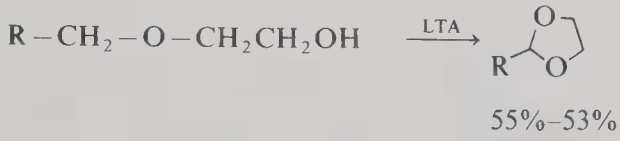
(**a–f**) = Products of 1,2-methyl migration
(Total yield 11%–14%)

Also, the structural environment of the C_δ–H and C_ε–H bonds may influence, by operation of various factors, the relative yields of the cyclic ether products in the LTA oxidation of alcohols.

Thus, an ether oxygen enhances the reactivity of an adjacent C_δ–H bond towards internal hydrogen abstraction, resulting either in shorter reaction times (but not in noticeably improved yields of cyclization products) in the case of acyclic alcohols,[190] or in preferential

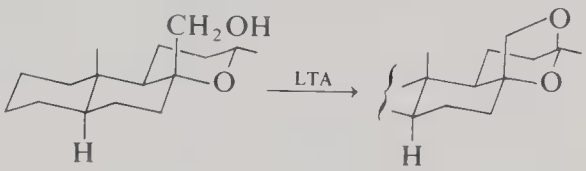


52%

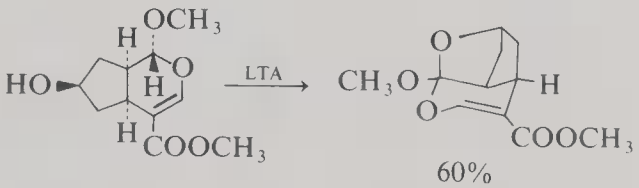


55%–53%

attack at the activated δ-position and higher yields of five-membered cyclic ethers in the case of systems possessing one or both conformationally fixed reaction centers.[191–194] However,

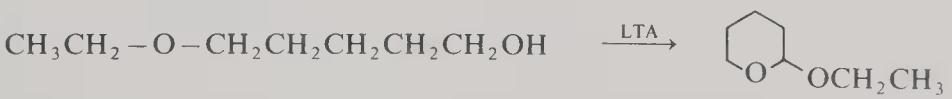


50%



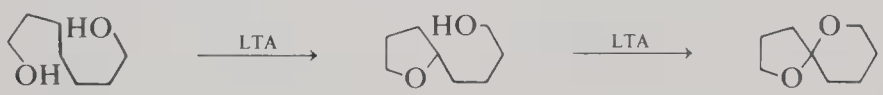
60%

when the ether oxygen is attached to an ε-carbon atom, as in the case of acyclic 1,3- and 1,5-hydroxy ethers, it exhibits a considerable activating influence on the ease of 1,6-hydrogen abstraction from the C_ε–H group, thus increasing by a factor of about 10 the yield of six-



46%

membered cyclic ethers.[190] The ring closure reaction of the diol **85** provides another example of C_ε–H bond activation by an ether oxygen group.[195]

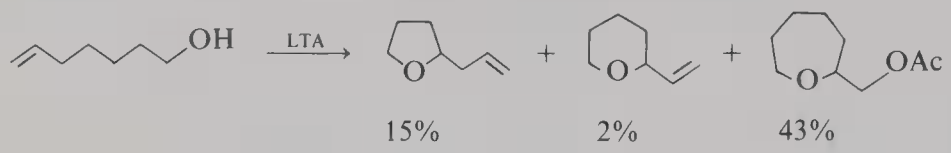


85 39%

An aromatic group adjacent to a δ-methylene group does not affect noticably the yield of tetrahydrofuran products, but when a phenyl group is attached to an ε-methylene group, the ease of six-membered cyclic ether formation is moderately enhanced.[164,166]

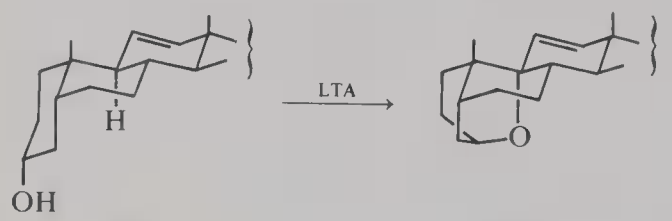
In conformationally mobile (acyclic) and semimobile (monocyclic) systems, an olefinic bond adjacent to a δ- or ε-carbon atom does not significantly activate intramolecular hydrogen abstraction, probably because in these cases the competing internal addition of the alkoxy radical to the carbon–carbon double bond is the preferred reaction.[196–198] (This reac-

tion will be discussed later; pp. 771–772.) However, when the geometrical rigidity of the substrate prevents addition of the alkoxy radical to the olefinic bond, susceptibility of the allylic ε-hydrogen atom to intramolecular 1,6-abstraction is dramatically enhanced, as can be seen by comparing yields of six-membered 3α,9α-ethers obtained from the saturated 3α-hydroxy-



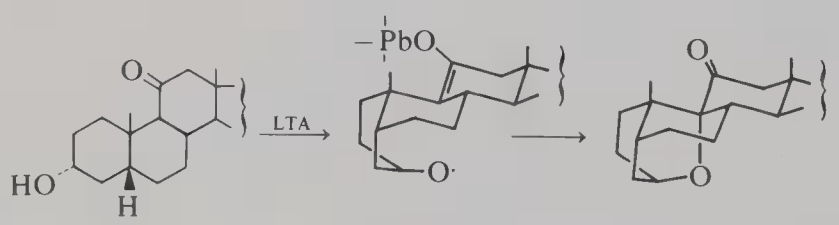
15% 2% 43%

5β-steroids (9%) and from the Δ^{11}-unsaturated analog **86** (65%).[162] Although in intermolecular hydrogen abstraction a carbonyl group deactivates the adjacent C–H bond,



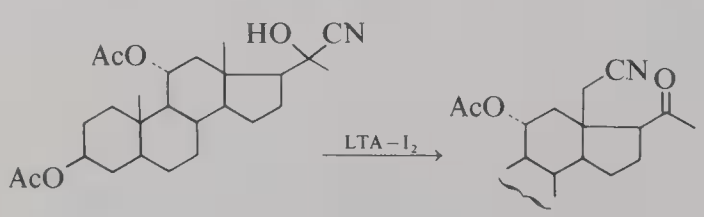
86 65%

introduction of a 11-keto group in the 3α-hydroxy-5β-steroid system (such as **87**) greatly facilitates intramolecular 1,6-cyclization.[162] This was explained by assuming that the reaction does not proceed by 1,6-hydrogen abstraction, but involves internal addition of the alkoxy radical to the double bone of the lead-enolate ester **88**.



87 **88** 45%–72%

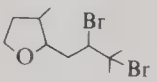
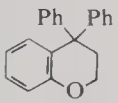
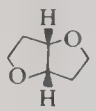
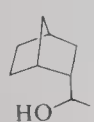
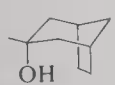
In addition to the oxidative cyclization of hydroxy steroids by means of LTA or LTA-iodine, an interesting rearrangement of 20-cyano-20-hydroxy steroids by LTA-iodine was discovered. By treatment of such cyanohydrins with LTA-iodine under irradiation conditions, migration of the cyano group to the δ-carbon radical at C(18) occurs and the corresponding 18-cyano-20-keto steroids are obtained in yields ranging from 30% to 60%.[199,200]



55–60%

Further examples of intramolecular cyclization of saturated alcohols to cyclic ethers with LTA are presented in Table II.

TABLE II. Intramolecular Cyclization of Saturated Alcohols

Alcohols	Cyclic ethers[a]	Yield (%)	References
	A. Acyclic Alcohols		
1-Butanol	Tetrahydrofuran	20	137, 140
1-Pentanol	2-Methyl-THF	43	137, 140
1-Hexanol	2-Ethyl-THF	50	137
	2-Methyl-THP	3	
(-)-2-Hexanol	*meso-cis*-2,5-Dimethyl-THF	17	137, 177
	(-)-*trans*-2,5-Dimethyl-THF	24	
3,7-Dimethyl-1-octanol	4-Methyl-5-*i*-pentyl-THF	39	201
	4-Methyl-6-*i*-butyl-THP	4	
3,7-Dimethyl-6,7-dibromo-1-octanol		15	202
Citronellol	4-Methyl-2-(2-methyl-1-propenyl)-THP	17[b]	203
5-Phenyl-1-pentanol	2-Benzyl-THF	48	164
	2-Phenyl-THP	9	
1,6-Hexanediol		15	195
1,7-Heptanediol		29	195
3,3,3-Triphenyl-1-propanol		24	147
5,5,5-Triphenyl-1-pentanol	2-(Triphenylmethyl)-THF	5	204
	2,2,3-Triphenyl-THP	59	
	B. Alicyclic, Polycyclic, and Cycloalkyl Alcohols		
2-Tetrahydrofuranethanol		45	205
		7	
endo-2-Norbornanemethanol		38	206
3,5,5-Trimethylcyclohexanol		55	207
		59	208
		51	209, 210

[a] THF, tetrahydrofuran; THP, tetrahydropyran.
[b] Special conditions.

Table continued

TABLE II. *Continued*

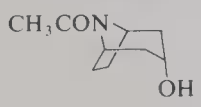
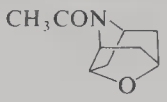
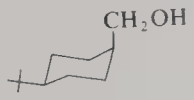
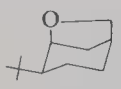
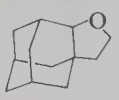
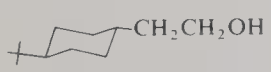
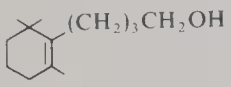
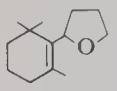
Alcohols	Cyclic ethers[a]	Yield (%)	References
		60	211
		46	212
2-Adamantanemethanol		67	213
1-Adamantanethanol		86	214, 215
		35	216
		66	217
		77	218
	C. Hydroxy Steroids		
	5α-Series		
2β-OH	2β, 19	60–75	219–223
3β-OH	3β, 19	37	224
4β-OH	4β, 19	69–74	145, 219,
	4α, 9α	12	225, 226
6β-OH	6β, 19	40–90	141, 148, 227–230
6β-OH (5αCl or Br)	6β, 19	12–53	231–233
6β-OH ($6\alpha CH_3$)	6β, 19	16–46	143, 144,
	6β, 3β	20–33	229
6β-OH (3,5-cyclo)	6β, 19	7–66	154, 234–237
7α-OH ($14\alpha CH_3$)	7α, 14α (methano)	40–80	238–241
7α-OH (B-homo)	7α, 10α	76	242
7β-OH (B-homo)	7β, 19	66	242
11α-OH	1α, 11α	50–88	145, 153, 243
11β-OH	1α, 11α	12–30	145, 148,
	11β, 18	5	153
	11β, 19	7–30	
	1β, 11α	15–42	
12α-OH	12α, 17α (methano)	50	244
19-OH	11β, 19	14	173
	8β, 19	38	

Table continued

TABLE II. *Continued*

Alcohols	Cyclic ethers[a]	Yield (%)	References
20α-OH	18, 20α	10–58	245
20α-OH (Δ^5)	18, 20α	47	245
20β-OH	18, 20β	25–32	136, 152, 245
24-OH	20, 24	8–9	187, 188
	5β-Series		
2α-OH	2α, 9α	52	246, 247
3α-OH	3α, 9α	3–71	138, 162, 248
3β-OH (5βCH_3)	3β, 5β (methano)	33–76	249–251
4α-OH	4α, 9α	85–90	145, 252
11α-OH	1α, 11α	85–87	176, 243
12α-OH	12α, 17α (methano)	50	244
19-OH	11β, 19	8	173
	8β, 19	27	
20α-OH	18, 20α	80	252
20β-OH	18, 20β	40–52	138, 253, 254

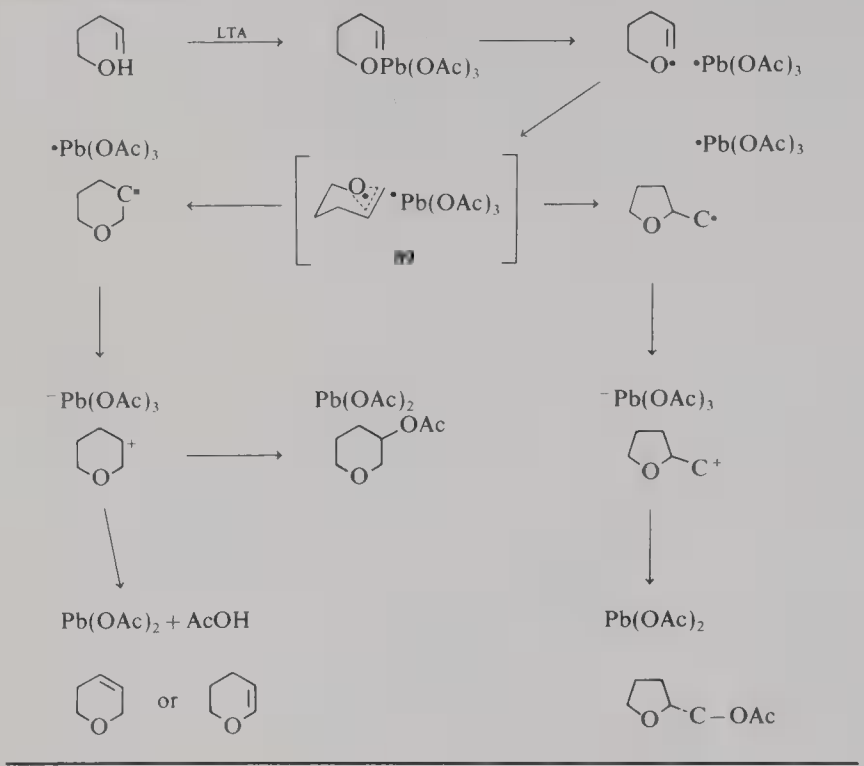
3.1.2. Unsaturated Alcohols

3.1.2a. Mechanism. As shown in Scheme 5,[170,173] the oxygen radical adds intramolecularly, probably via a π-complex of type **89**, to a sterically accessible ethylenic linkage. The carbon radicals thus formed are then converted (either directly or upon oxidation into the corresponding carbenium ions) to acetoxylated cyclic ethers, unsatured cyclic ethers, or other products. However, alternative pathways for this reaction have also been proposed.[255,256]

3.1.2b. Scope and Limitations. In unsaturated alcohols containing a double bond which is incorporated in a rigid framework, accessibility to intramolecular addition of the oxy radical is limited to the more favorably located olefinic carbon atom, so that the LTA reaction affords only one, five-membered[256–259] or six-membered,[162] cyclic ether.

On the as yet fragmentary data concerning the thermal LTA cyclization of unsaturated acyclic alcohols, in which, because of conformational flexibility, both sites of the olefinic double bond are spatially accessible to intramolecular radical addition, the following comments can be made: (1) in primary and secondary Δ^4-alkenols 1,6-addition leading to tetrahydropyran-type ethers is preferred to 1,5-cyclization, resulting in the formation of five-membered cyclic ethers[173,177a,196,198,255,260,261]; (2) in the case of Δ^5-, Δ^6- and Δ^7-alkenols, addition of the oxy radical takes place exclusively on the olefinic (trigonal) carbon which is nearer to the hydroxy oxygen, thus furnishing the cyclic ether with the smaller ring, i.e., six-membered,[197,262] seven-membered,[197] and eight-membered ring, respectively; (3) intramolecular addition to the carbon–carbon double bond to give acetoxylated or unsaturated cyclic ethers proceeds with greater ease than, and may occur to the exclusion of, intramolecular hydrogen abstraction from saturated (tetrahedral) nonactivated δ-carbon atoms leading to tetrahydrofuran formation.[197] Some typical examples are given in Table III.

SCHEME 5



3.2. β-Fragmentation

The β-fragmentation reaction, which consists of the homolytic C_α–C_β bond cleavage (Scheme 2), is a well-established mode of stabilization of alkoxy radicals in general.[5,158,264,265] Data obtained in the LTA reaction indicate that β-fragmentation cannot be suppressed in favor of intramolecular hydrogen abstraction by change of external reaction conditions,[139,148,149,191] since both processes appear to proceed through a common transition state with alkoxy radical character (Scheme 2, **60**, **61**).[7,137,179] Therefore, depending on structural features of the substrate, β-fragmentation may seriously compete with cyclic ether formation in the LTA oxidation of alcohols, particularly when complex hydroxy compounds are being oxidized.

3.2.1. Mechanism

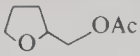
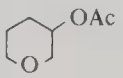
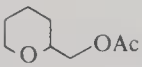
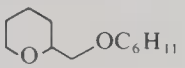
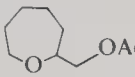
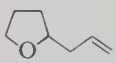
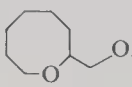
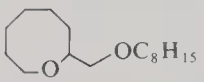
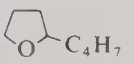
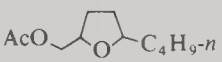
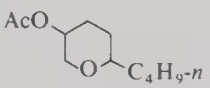
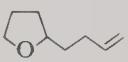
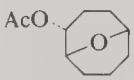
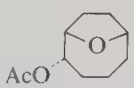
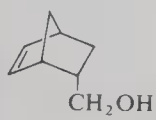
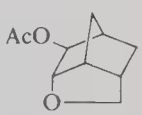
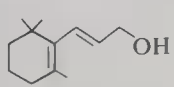
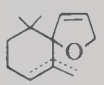
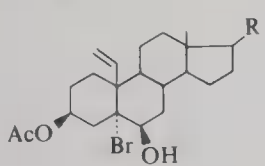
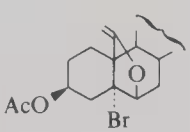
The special case of "reversible fragmentation" (β-scission–recombination process, already discussed on pp. 760–761) represents strong evidence that the initially formed β-fragment in the LTA reaction is a carbon radical **62** (Scheme 2). Usually it undergoes one-electron oxidation to the corresponding carbenium ion **64** (Scheme 2), which, in addition to normal products, i.e., olefins and acetates (see Scheme 2), might give rearranged acetates as a consequence of 1,2-hydride shift[137,179] or cyclobutyl-cyclopropylmethyl isomerization.[266]

3.2.2. Scope and Limitations

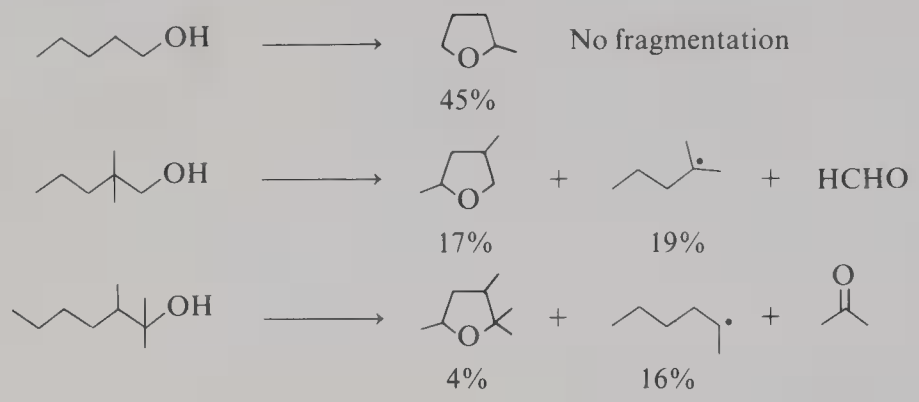
The rate of β-fragmentation of alkoxy radicals is mainly dependent on the stability of the initially formed carbon radical **62**, but it is also affected by other factors, such as stability of the carbonyl-containing fragment **63**, decrease of unfavorable steric interactions, polar and entropy effects in the transition state, etc.

Thus, in the LTA oxidation of alcohols containing saturated β- and γ-carbons, the ease

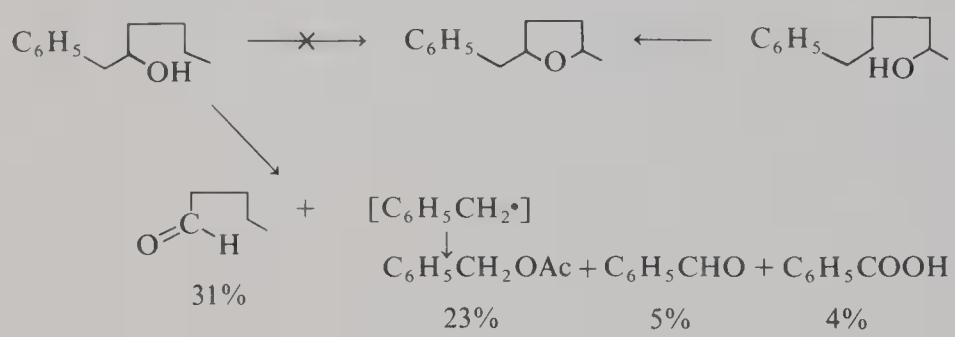
TABLE III. Intramolecular Cyclization of Unsaturated Alcohols

Alcohols	Cyclic ethers	Yield (%)	References
4-Penten-1-ol		14	255, 260
		26	
5-Hexen-1-ol		26–37	197, 262
		23	
6-Hepten-1-ol		43	197
		2.5	
		15	
7-Octen-1-ol		10	197
		11	
		15	
1-Nonen-5-ol		31	197
		34	
		2.5	
4-Cycloocten-1-ol		42	196
		28	
		30	256
		17	263
		60	259

of β-fragmentation increases and cyclic ether formation (when intramolecular hydrogen abstraction is structurally and sterically allowed) decreases with increasing stability of the alkyl-carbon radical β-fragment, which follows the well-established order $R\dot{C}H_2 < R_2\dot{C}H < R_3C^{\bullet}$,[142] whereby β-cleavage to products derived from tertiary carbon radicals is particularly favored.[267–270]



The intermediate formation of carbon radicals stabilized by an adjacent ether oxygen increases the rate of C_α–C_β bond cleavage,[191] but optimal conditions are always realized (and have been used for preparative purposes) when the LTA oxidation of alcohols affords as initial β-fragments stable benzyl radicals,[164,255] or allyl radicals.[177a,255,256] In these cases intramolecular 1,5-hydrogen abstraction from a δ-CH_2 (or δ-CH) group leading to cyclic ether, even if structurally permissible, is usually entirely suppressed; for example[166]:



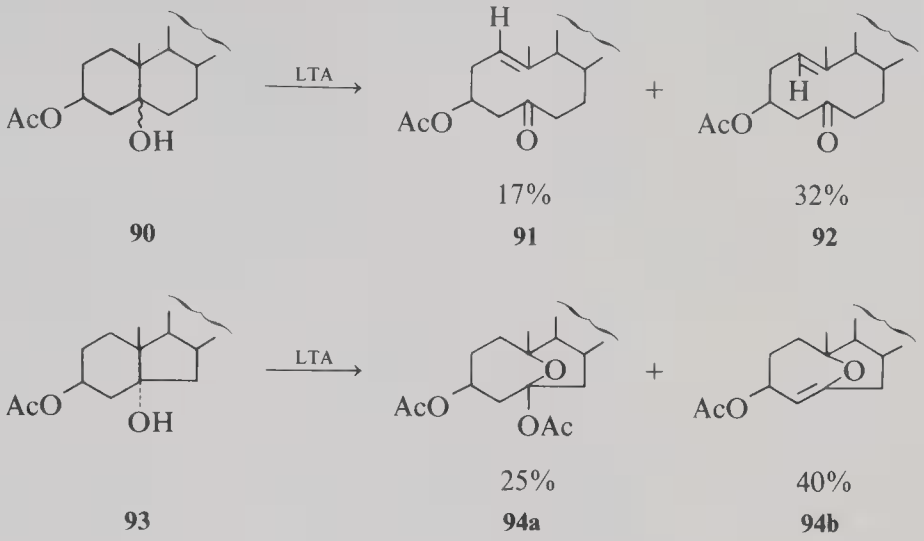
Therefore, although convenient as substrates for the preparation of fragmentation products, particularly nor-compounds in the steroid field,[173,256] homoallylic and homobenzylic alcohols cannot be used for δ-functionalization.

Another factor influencing the ease of β-fragmentation is the stability of the carbonyl fragment, which increases in the order $HCHO < R-CHO < R-CO-R'$. Therefore, the yield of β-fragmentation increases and that of intramolecular cyclization decreases when one goes from primary to secondary to tertiary alcohols.[137,142,245]

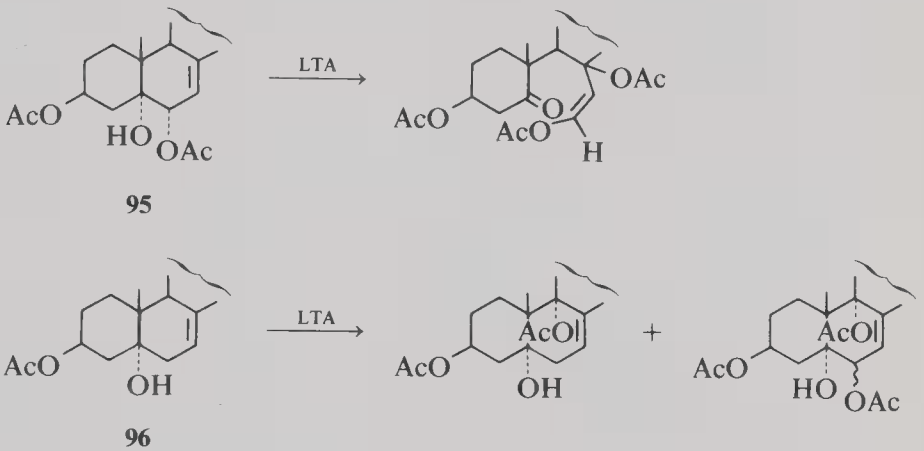
Decrease in steric crowding and steric strain may also favorably affect the rate of the β-fragmentation reaction, particularly when it involves opening of rings in bridged polycyclic alcohols,[271] or opening of cyclobutanol rings[272,273] (or cyclopropanol rings) incorporated in fused polycyclic systems. In simple secondary cycloalkanols containing four- to eight-membered rings, the amount of β-cleavage with ring opening is proportional to the total strain associated with carbocyclic rings of various size.[179]

An interesting difference was observed in the fate of medium-sized cyclic carbon radicals or cations resulting from β-fragmentation of the 5-hydroxysteroids **90** and the 5α-hydroxy-B-nor-steroid **93**, respectively. Whereas the carbon-deficient species in the ten-membered ring, resulting from fragmention of **90**, is converted by β-loss of hydrogen to the olefinic (*Z*)- and (*E*)-isomers **91** and **92** containing a 1(10)-cyclodecen-5-one system,[274,275] the nine-membered analog, generated from **93**, probably because of different conformational conditions,

undergoes recombination involving addition of the carbonyl oxygen to afford as final products the bridged 5,10-oxido-compounds **94**.[276,277]



However, in the analogous Δ^7-unsaturated 5α-hydroxy steroids **95** and **96**, C(5)–C(10) fragmentation is completely suppressed in favor of C(5)–C(6) fragmentation and allylic acetoxylation, respectively.[278]



3.3. Oxidation to Carbonyl Compounds

3.3.1. Mechanism

Another oxidation process of primary and secondary alcohols with LTA leads to the corresponding aldehydes and ketones. Possible mechanisms of their formation are outlined in Scheme 2.

3.3.2. Scope and Limitations

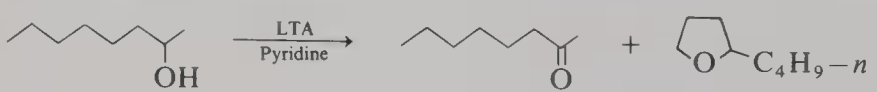
Although carbonyl compounds (and their α-acetoxylated and other derivatives) are almost always formed as by-products in the LTA oxidation of primary and secondary alcohols, their yield, when the reaction is performed in nonpolar media (such as benzene, cyclohexane, or heptane), is generaly low compared to the yields of cyclic ethers and/or β-fragmentation products.[135,137,139,245] Even when ring closure to cyclic ethers is very slow or

TABLE IV. Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds in the Presence of Pyridine

Alcohols	Carbonyl compounds	Yield (%)	Reference
1-Butanol	Butanal	70	280
1-Propanol	Propanal	87	152
2-Propanol	Acetone	93	152
Benzoin	Benzil	90	280
2-Hydroxymethyltetrahydropyran	2-Formyltetrahydropyran	80	280
2,5-Hexanediol	2,5-Hexanedione	89	280
5α-Androstane-3β,6β,17β-triol 3,17-diacetate	6-Oxo-5α-androstane-3β,17β-diol 3,17-diacetate	95	148
5α-Androstane-4β,17β-diol 17-propionate	4-Oxo-5α-androstan-17β-ol propionate	85	148
5α-Pregnane-3β,11β,20β-triol 3,20-diacetate	11-Oxo-5α-pregnane-3β,20β-diol 3,20-diacetate	54	148

not feasible and α,β-cleavage to fragmentation products is not favored, the yield of aldehydes or ketones, although somewhat higher, does not increase accordingly and rarely exceeds 15%.[137,139,152,162,163,179,191] However, the yield of carbonyl compounds is much higher when the oxidation of the carbinol function to a carbonyl group results in considerable energy gain associated with release of steric compression (examples encountered particularly in steroid and medium-sized ring hydroxy compounds)[145,155,179,248] or due to conjugation of the carbonyl group to olefinic and aromatic systems.[164,179,196]

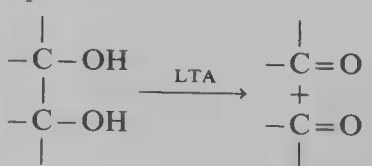
On the other hand, when the LTA reaction of alcohols is performed in benzene containing an excess of pyridine or in pyridine alone, either with heating or at room temperature, cyclization and β-fragmentation processes, even when structurally permitted, are suppressed, whereas carbonyl compounds are obtained in good and often preparatively useful yields[137,139,148,152,163,164,196,279,280] (see Table IV). This and other results have been taken as evidence that the formation of aldehydes and ketones proceeds predominantly by heterolytic decomposition of the initially produced alkoxy–lead(IV) acetate (Scheme 2, **59**) or its coordination complex with pyridine[5,6,151] (involving two-electron transfer from the alkoxy anion to lead with assisted elimination of an α-proton),[5,6,139,151] and only to a minor extent by homolytic processes.



58% 2%

4. 1,2-DIOLS AND POLYOLS

In 1931 Criegee discovered that LTA can very efficiently cleave the carbon–carbon bond of 1,2-diols to give carbonyl componds.[282]



The reaction is usually very fast, quantitative, and specific, since the carbonyl compounds formed are, in general, either unreactive towards, or react only slowly with, LTA under the

glycol cleavage reaction conditions. Because of these features, it has often been applied both to synthesis and to structure determination studies. Depending on the structure of the starting glycol, one can obtain aldehydes, ketones, dialdehydes, oxo-aldehydes, diketones, and also cyclic diketones.[3,10] The reaction can be extended to related 1,2-bifunctional compounds, such as α-hydroxy ketones, 1,2-diketones, α-hydroxy and α-keto acids, α-amino alcohols, and 1,2-diamines,[10,283] and also to polyhydroxylic compounds,[10,11] which all undergo similar cleavage to produce a variety of fragmentation products.[10,11,283–286] In addition to LTA, oxidative cleavage of 1,2-diols can be effected with other oxidative reagents, such as periodic acid, iodoso compounds, sodium bismuthate,[10] metal/peroxide, or ruthenium oxide. The latter two methods are described in Chapters 6, 8, and 16 of this book.

4.1. Mechanism

First it was assumed that the preferred mechanism of the LTA glycol cleavage involves a cyclic intermediate formed between the diol and LTA of type **97**, which is decomposed in a concerted process to the carbonyl fragments (path i, Scheme 6).[285] Since the LTA reaction can be also readily applied to *trans*-1,2-diols with *anti*-periplanar hydroxy groups, which for steric reasons cannot form lead(IV) cyclic intermediates **97**,[287] other possible mechanisms have been envisaged. Thus, an alternative cyclic pathway consists of an intramolecular proton transfer in the primarily formed monoacetoxylated LTA of type **98** (path ii).[288] Also, from the fact that the reaction can be catalyzed with bases (i.e., with acetate anion,[288] pyridine,[289] methanol,[290] or water[284]) and acids,[291] it was concluded that the carbon–carbon bond can be cleaved in noncyclic processes as well, such as **99**, involving proton transfer to an external base (path iii),[288] or **100**, involving protonated mono-alkoxy lead(IV) intermediates, which eventually break down by elimination of a proton from the free hydroxy group (path iv).

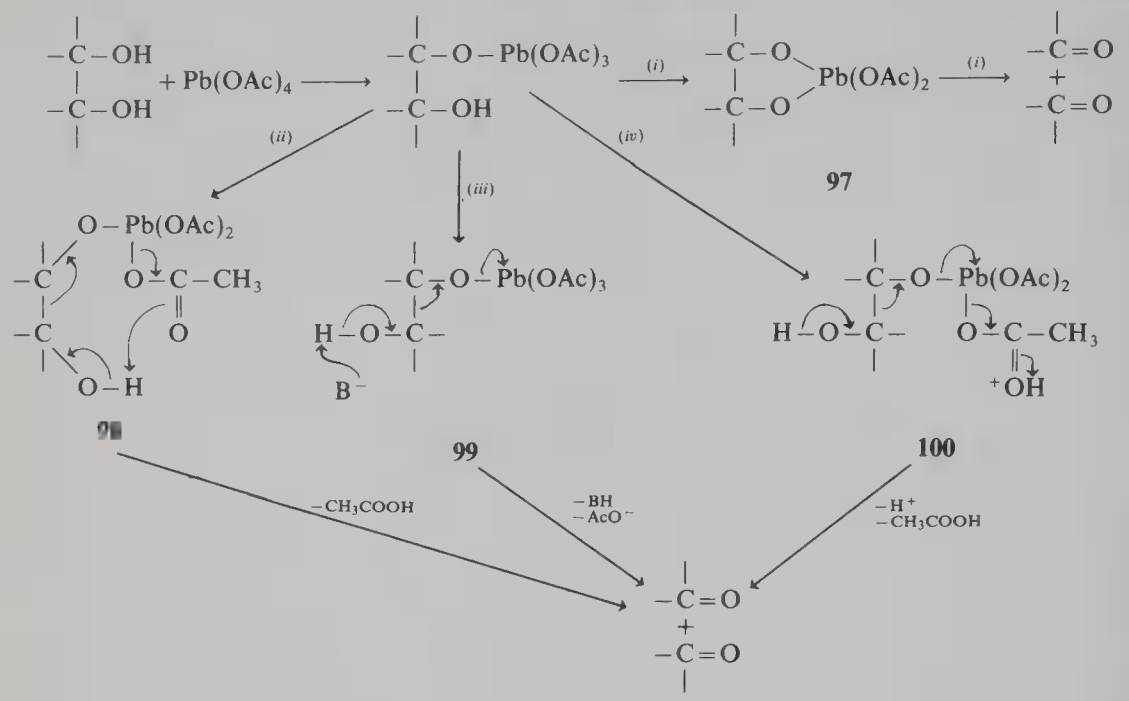
4.2. Scope and Limitations

The rate of the LTA glycol cleavage is highly dependent on the structure and stereochemistry of the substrate and reaction conditions. In general, there is correlation between the rate of oxidation and the proximity of the hydroxy groups. Thus, *cis*-diols containing small and normal rings are considerably more reactive towards LTA than the corresponding *trans*-isomers,[288,292] although exceptions are observed for some dihydrophenanthrene diols.[288,293] Some typical examples are shown in Table V.[288,292–296]

On the contrary, with cyclic 1,2-diols containing nine or more carbon atoms, the *trans*-form becomes more reactive than the *cis*-form,[297–299] presumably due to the change of dihedral angles between the hydroxylic groups.[297] In acyclic systems the "cisoid" *dl*-forms of symmetrically substituted 1,2-diols react with LTA 40–50 times faster than the corresponding "transoid" *meso*-forms.[288] The same was observed also for some hydrobenzoins.[300] The reactivity of the diols increases with the number of alkyl substituents at the carbinol carbon atoms, the main effects being steric rather than electronic. Electronic effects have been observed in the LTA oxidation of some substituted benzpinacols[301]; electron-releasing groups (Me, OMe) accelerate the reaction, while an electron-attracting group (Cl) retards it. Lack of substitution effects (a ρ of 0.02) for oxidative cleavage of a series of substituted hydrobenzoins indicates that little charge is developed on the benzylic carbon atoms in the rate-determining step.[300] (Additional examples are listed in Table VI.)

The oxidations by LTA are, in general, quantitative and fast enough to allow determination of glycols by titrimetric methods. The rate of oxidation often provides a reliable means for estimation of the stereochemical relationship of the hydroxy groups. Thus, the rates of oxidation with LTA have been used to establish the geometrical configurations of

SCHEME 6



some flavane-3,4-diols,[302] and also to determine the *cis*- to *trans*- ratio in a mixture of 3,4-dihydroxytetrahydro-2-pyrenes.[303]

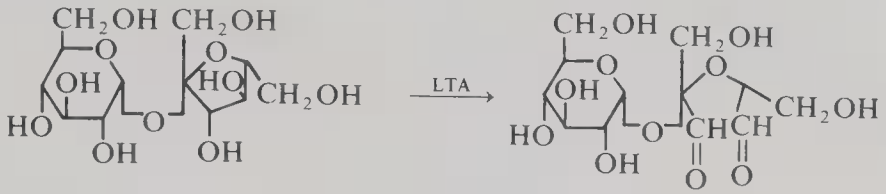
The LTA oxidation has also been widely and successfully applied to carbohydrates, and there are several exhaustive reviews summarizing this subject.[1,11,304–306] Although carbohydrates in general contain more than one glycol unit, because of structural and/or stereochemical differences, the reactivity of the individual glycol units in a sugar molecule is often not the same, thus rendering the LTA reaction a valuable tool for structure determination studies in carbohydrate chemistry.

TABLE V. Rates of Glycol Cleavage

1,2-Diol	$k_{20°}$(mol^{-1} dm^3 sec^{-1}) (in 99.5% CH_3COOH)
cis-Cyclobutane-1,2-diol	10,000
trans-Cyclobutane-1,2-diol	6.5
cis-Cyclopentane-1,2-diol	40,000
trans-Cyclopentane-1,2-diol	12.8
cis-Cyclohexane-1,2-diol	5.04
trans-Cyclohexane-1,2-diol	0.22
cis-Decaline-9,10-diol	15.0
trans-Decaline-9,10-diol	0.148
cis-Camphane-2,3-diol	25,000
trans-Camphane-2,3-diol	0.37[a]
cis-9,10-Dihydrophenanthrene-9,10-diol	10
trans-9,10-Dihydrophenanthrene-9,10-diol	157

[a] Measured at 50°C.

Monosaccharides are preferentially oxidized in their cyclic, rather than in their open-chain form[307–310]; in addition, the furanose form is more reactive than the pyranose form.[11,309]



LTA is highly selective in the oxidation of α-hydroxy hemiacetal groups. Thus, the reaction proceeds stepwise, giving first a monoformate of the corresponding lower sugar, which, after cyclization, undergoes further oxidation at the hemiacetal α-glycol group to yield a

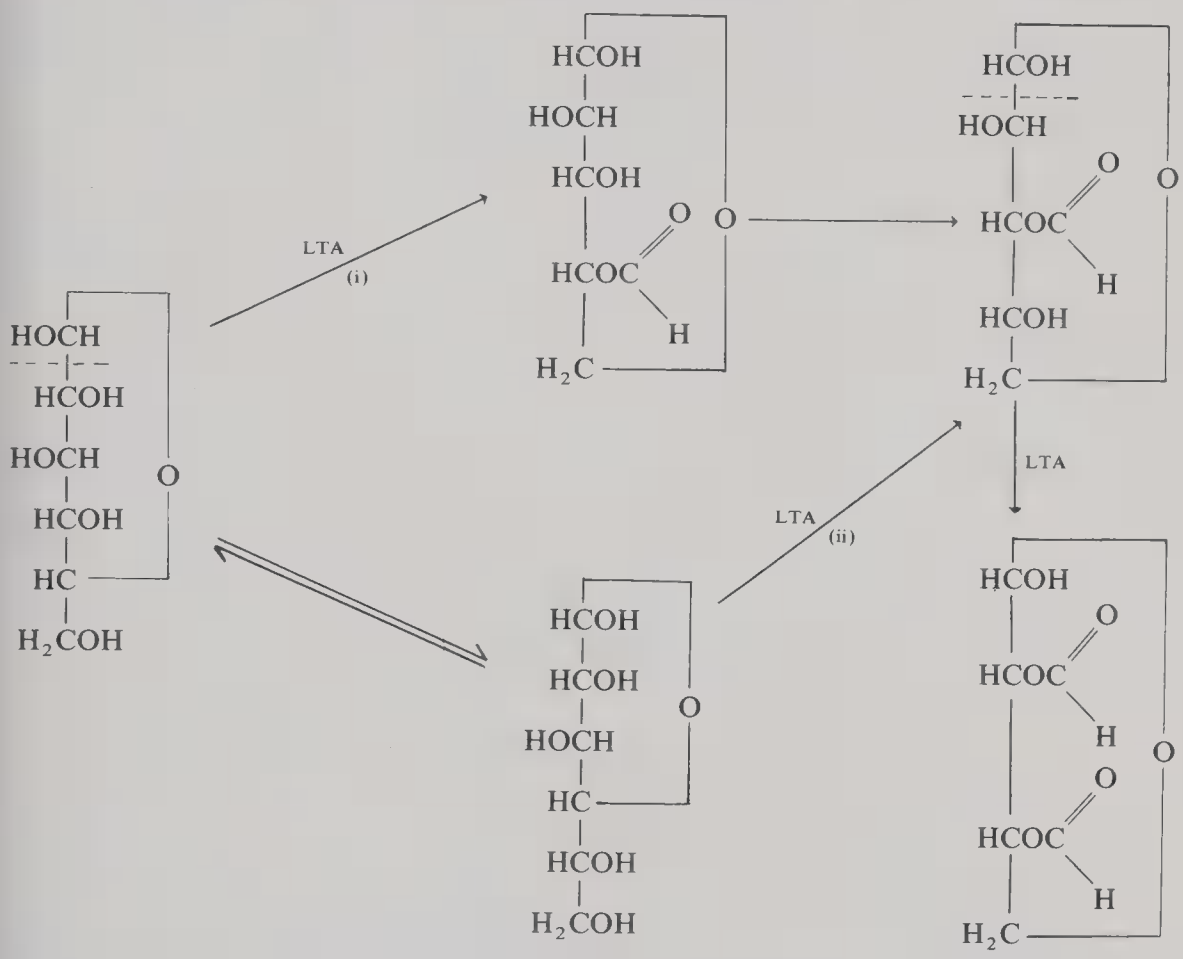


TABLE VI. 1,2-Diol and Polyol Cleavage

1,2-Diol	Carbonyl compounds	Yield (%)	Reference
	A. 1,2-Diols		
Glycol	Formaldehyde	89	278
Pinacol	Acetone	91	178
1-Hydroxymethylcyclobutan-1-ol	Cyclobutanone	90	312
cis-1,3-Cyclohexadiene-5,6-diol	*cis,cis*-2,4-Hexadienedial	96	313

Table continued

TABLE VI. *Continued*

1,2-Diol	Carbonyl compounds	Yield (%)	Reference
1,2,3-Cyclohexanetriol	Pentanedial	50	314
endo,endo-2,3-Dihydroxybicyclo-[2.2.1]heptane	1,3-Diformylcyclopentane	72	315
1,1′-Dihydroxydicyclobutyl	Cyclobutanone	85	316
2,5-Dimethylhexane-2,3-diol	3-Methylbutanal	23	317
Diethyl tartarate	Ethyl glyoxylate	54	318
cis-2-Oxahydrindane-*cis*-5,6-diol	3-Oxabicyclo[3.3.0]oct-7-en-8-carbaldehyde	92	319
cis-1,6-Dihydroxybicyclo-[4.3.0]-non-3-ene	*cis*-Cyclonon-3-ene-1,6-dione	45	320
cis-1,1,4,4-Tetramethyl-tetraline-2,3-diol	1,2-Bis[2-formylpropyl-(2)]-benzene	95	321
1,2-Dihydroacenaphthene-1,2-diol	1,8-Diformylnaphthalene	47	322
9,10-Dihydroxyoctadecanoic acid	Nonanal 8-Formyloctanoic acid	67 64	323
9,10,12-Trihydroxyoctadecanoic acid	2-Nonenal 8-Formyloctanoic acid	63 37	324
9,27-Hexatriacontadiene-18,19-diol	9-Octadecanal	30	325
cis-1,2-Diphenylcyclohexane-1,2-diol	1,4-Dibenzoylbutane	100	326
trans-1,2-Diphenylcyclohexane-1,2-diol	1,4-Dibenzoylbutane	90	326
1,2-Di-[adamantyl-(1)]ethane-1,2-diol	1-Formyladamantane	62	327
Estrane-3β,5α,10α,17β-tetrol-3,17-diacetate	3β,17β-Diacetoxy-5,10-seco-estrane-5,10-dione	55	328
3β-Methyl-A-nor-5α-cholestane-3α,5-diol	4,5-Seco-cholestane-3,5-dione	89	329
2-Hydroxymethyl-5α-cholestan-2-ol	2-Cholestanone	90	330

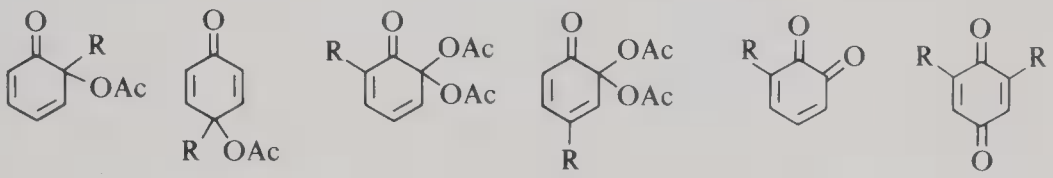
B. Polyols (Sugars)

Sugar	Carbonyl compounds	Yield (%)	Reference
L-Arabinose	L-Glycerinaldehyde	90	309
α-Methyl-1-arabinosepyranoside	L′-Methoxydiglycolic aldehyde	98	331
3-Deoxy-D-mannose	2-Deoxy-D-ribose	60	332
D-Glucose	Di-*O*-formyl-D-erithrose	89	309
D-Fructose	D-Glycerinaldehyde	89	333
L-Sorbose	L-Glycerinaldehyde	82	333
D-Mannose	D-Arabinose		309
α-Methyl-D-glucoside	Glyoxal		334
α-Methyl-D-mannopyranoside	D′-Methoxy-D-hydroxymethyl-diglycolic aldehyde	55	335
3,6-Dimethyl-D-glucose	2,5-Dimethyl-D-arabinose	100	336

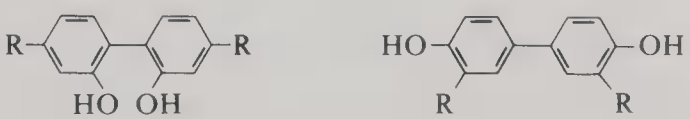
diformate of a still lower sugar. In this way D-glucose first produces mono-*O*-formyl-D-arabinose and then di-*O*-formyl-D-erythrose.[309] It is assumed that this reaction involves preferential attack of the furanose form of D-glucose (path ii), rather than of the normally predominant pyranose form (path i). By this degradation method some rare sugars can be prepared. The LTA reaction has also been applied, in a similar way, to polysaccharides.[311] A few characteristic examples of sugar degradations are presented in Table VI.

5. PHENOLS

The oxidative transformation of phenols by LTA was systematically investigated by Wessely[340–343] and reviewed by Criegee.[3] Depending on the number, position, and nature of substituents, molar ratio of the LTA, and solvent used, different types of products may be obtained.[340–352] Some illustrative examples are shown in Table VII. Thus, in acetic acid quinol acetates (**101** and **102**), *o*-quinone diacetates (**103** and **104**), and quinones (**105** and **106**) are formed, while in nonpolar solvents, such as benzene, C–C coupling leading to the dimeric products **107** and **108** becomes the more important oxidative process.[340,348]



101 **102** **103** **104** **105** **106**



107 **108**

5.1. Mechanism

It was assumed that the first step in the LTA oxidation of phenols involves reversible formation of aryloxy–lead(IV) acetates,[2,47] which decompose either homolytically leading to aryloxy radicals or heterolytically with formation of cationic aryloxy species.[47,353] Dimeric product formation and ESR spectroscopy data[349] were taken as evidence that radical species are involved in the LTA oxidation of phenols. The mechanism of formation of various types of oxidation products by homolytic cleavage of the O–Pb bond is shown in Scheme 7. However, these and other additional results (i.e., catalysis by boron trifluoride, solvent dependence, and very high reaction rate), according to some authors, speak in favor of heterolytic cleavage of the Pb–O bond.[353] Also, in order to rationalize the preferential formation of the *o*-acetoxy over *p*-acetoxy derivatives, an intramolecular pathway has been suggested.[354]

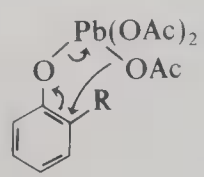
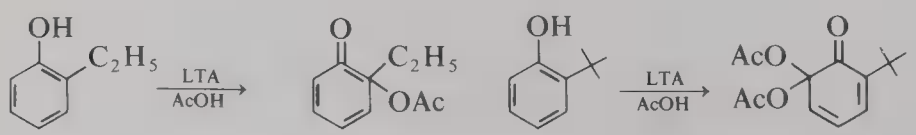


TABLE VII. Oxidation of Monohydroxylic Phenols by LTA

Phenol	Solvent	Products	Yield (%)	Reference
Phenol	AcOH	*o*-Quinone diacetate	4	359
2-Methyl	Et_2O	*o*-Quinol acetate	22	340
		Quinone	4	
4-Methyl	AcOH	*o*-Quinone diacetate	28	340
		p-Quinol acetate	14	
2-*n*-Propyl	AcOH	*o*-Quinol acetate	42	355
		o-Quinone diacetate	5	
2-*t*-Butyl	AcOH	*o*-Quinol acetate	2	355
		o-Quinone diacetate	44	
2-Allyl	AcOH	*o*-Quinol acetate	34	347
2,4-Dimethyl	AcOH	*o*-Quinol acetate	23	340
		o-Quinone diacetate	2	
2,6-Dimethyl	AcOH	*o*-Quinol acetate	95	348
	Benzene	Coupling dimers	20	348
2,4,6-Trimethyl	AcOH	*o*-Quinol acetate	42	340
	Benzene	*o*-Quinol acetate	50	348
	$CHCl_3$	*o*-Quinol acetate	92	360
2,4,6-Tri-*t*-butyl	AcOH	*o*-Quinol acetate	60	354
2,6-Dimethoxy	AcOEt	Quinone	78	361
2-Methyl-6-cyano	AcOH	Coupling dimers	100	346
2,4-Dimethyl-6-acetyl	$CHCl_3$	*o*-Quinol acetate	65	343
2-Methyl-5-bromo	Acetone	*o*-Quinol acetate	38	342
		Quinone	18	
2,4-Dimethyl-6-bromo	AcOH	*o*-Quinol acetate	62	342
		p-Quinol acetate	6	
2,6-Dimethoxy-4-carboxy	AcOEt	Quinone	57	360
2,4-Dimethyl-6-carbethoxy	AcOH	*o*-Quinol acetate	50	343
2,4-Dimethyl-6-formyl	AcOH	*o*-Quinol acetate	51	343
3-Hydroxy-17-acetyl-$\Delta^{1,3,5(10)}$-oestratriene	AcOH	*p*-Quinol acetate	25	353

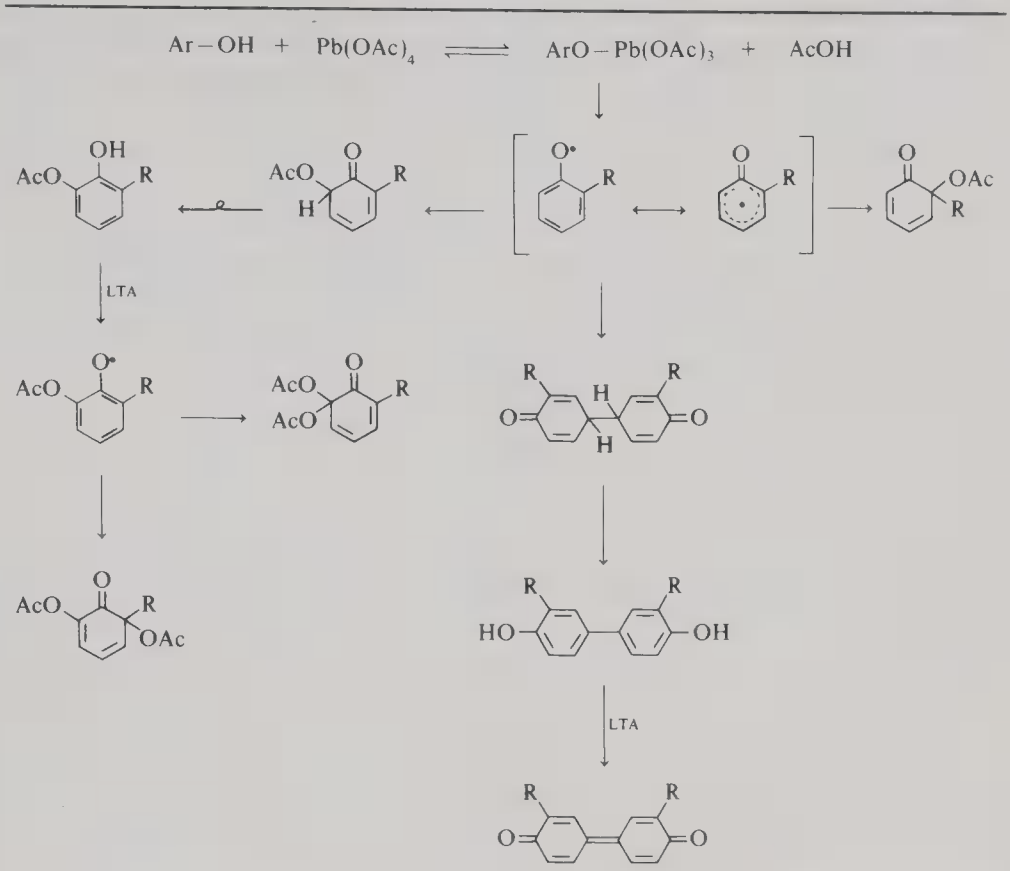
5.2. Scope and Limitations

In the LTA oxidations of *o*- and *p*-alkyl substituted phenols in acetic acid, the corresponding *o*- (**101**) and/or *p*-quinol acetates (**102**) and *o*-quinone diacetates (**103** and **104**) were obtained.[340,344,347,355] *p*-Quinone diacetates have never been isolated, probably because they are too unstable and usually undergo hydrolysis to the corresponding quinones during the work-up procedure.

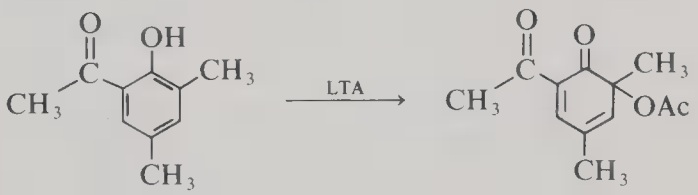


36% 44%

SCHEME 7



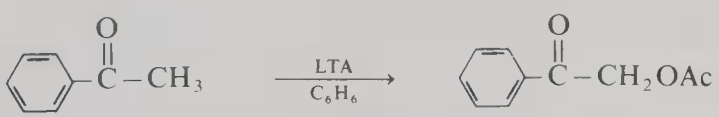
One *ortho* electron-withdrawing group favors acetoxylation at the other *o*-site with higher electron density.[356]



Dihydroxy phenols, i.e., catechol, hydroquinone, and their derivatives, are rapidly and quantitatively oxidized by LTA to the corresponding quinones.[357,358]

6. CARBONYL COMPOUNDS

Electron-withdrawing groups adjacent to the carbon–hydrogen bond enhance its reactivity towards LTA. Thus, carbonyl compounds possessing at least one α-hydrogen can readily be converted to the corresponding α-acetoxy derivatives by treatment with LTA.



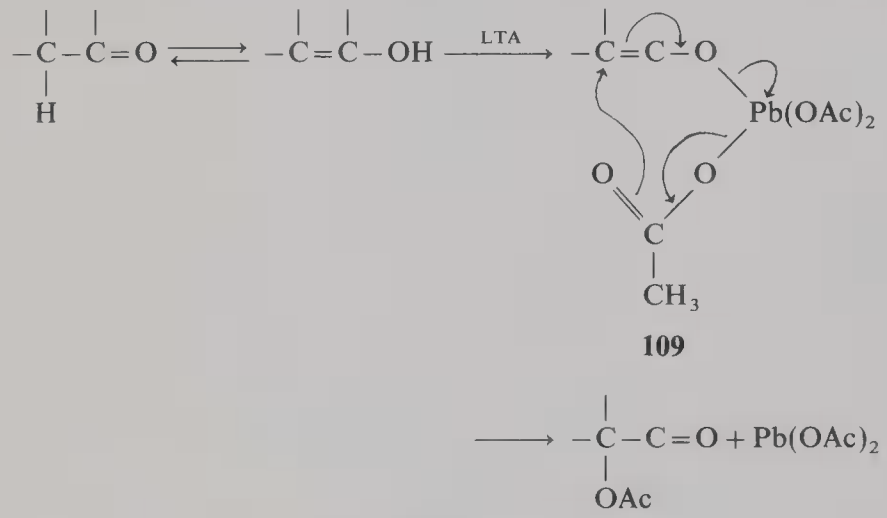
75%

The LTA α-acetoxylation reaction is usually carried out with one molar equivalent of LTA in hot acetic acid or in benzene solution at reflux. It is faster in acetic acid, but affords

better yields in benzene. In general, the reactivity of the carbonyl compounds increases in the order: acid anhydride < ester < aldehyde ~ ketone. However, the LTA acetoxylation method has been predominantly and successfully applied for the preparation of α-acetoxy ketones.

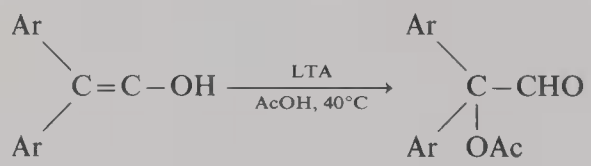
6.1. Mechanism

The rate of acetoxylation of ketones with LTA depends only on the concentration of the ketones,[362] and not on the concentration of the LTA, indicating that (similarly to the bromination of ketones)[363] enolization is the rate-determining step. For that reason it was assumed that the mechanism of α-acetoxylation of ketones consists of the formation of an enol-lead(IV) triacetate intermediate **109**, which subsequently undergoes intramolecular

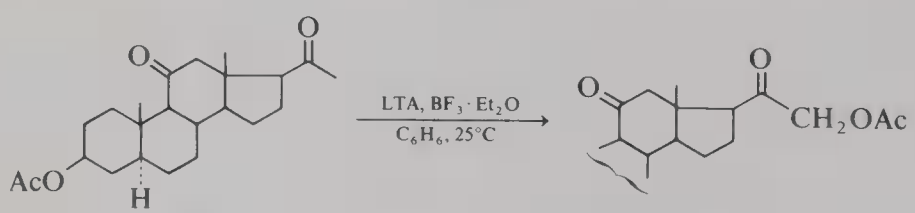


109

rearrangement and elimination of lead(II) acetate, in a process analogous to the oxidation of phenols.[2,5,354,364] This assumption was substantiated by the following observations. Carbonyl compounds which exist predominantly in the enol form are particularly reactive towards LTA, undergoing quantitative α-acetoxylation under relatively mild conditions.[3]



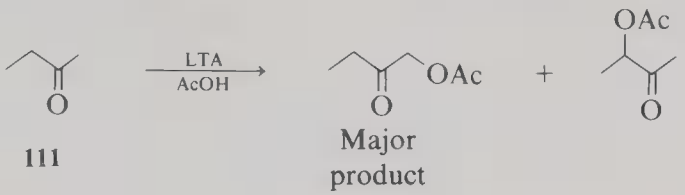
Boron trifluoride strongly accelerates the LTA oxidation of ketones.[365,366] Thus, non-catalyzed acetoxylation of the side chain in the pregnane derivative **110** requires heating with LTA in acetic acid, while in the presence of boron trifluoride the oxidation can be accomplished in benzene solution at room temperature.[366] This catalytic effect was ascribed to the



110 86%

promotion of enolization, although it could also arise from increased electrophilicity of LTA. 2-Adamantanone, which cannot enolize, was recovered unchanged when treated with LTA.[367]

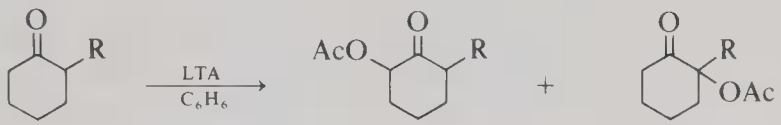
From these data it is apparent that enolic species are intermediates in this LTA oxidation reaction. However, the results obtained with some unsymmetrical methyl ketones have shown that the product ratio and enolization rate (followed by deuterium exchange) do not always agree. Namely, acetoxylation of 2-butanone (**111**) and analogous 2-ketones with LTA takes place preferentially at the methyl group, although the rate of enolization for the methylene group is faster than for the methyl group, suggesting that enolization may not be in all cases the rate-determining step in the formation of acetoxy ketones.[367]



111 Major product

6.2. Scope and Limitations

α-Acetoxylation of unsymmetrical cyclic ketones, such as 2-alkyl-cyclohexanones, proceeds preferentially at the less substituted α-carbon, which was interpreted either as the consequence of greater stability and favored formation of the enolic species containing a trisubstituted double bond (relative to the tetrasubstituted structure), or by assuming that nucleophilic attack by the acetoxy group proceeds more readily on the enolic intermediate in



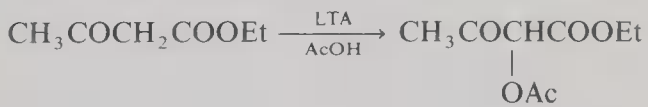
cis and *trans*

22% 11%

which the olefinic bond has less electron density. Also, from product distribution, it was concluded that of the *cis–trans* diastereomeric pairs, those epimeric products are usually formed in excess which result from axial attack of the acetoxy group on the substrate.[368]

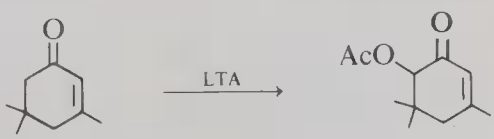
From ketones which contain two α-CH groups, it is possible to obtain diacetoxy derivatives. Geminal diacetoxy derivatives can also be formed as minor products; however, they readily hydrolyze (often under the reaction conditions used or during the work-up procedure) to give the corresponding α-diketones or keto-aldehydes.[368,369]

When two electron-withdrawing groups are attached to a methylene or methine group, such groups become particularly reactive. Thus, β-dicarbonyl compounds, β-keto-esters, malonic esters, and other compounds of similar structure, can be acetoxylated at the activated C–H bond even at room temperature.[370,371]



53%

Upon LTA oxidation of conjugated ketones, the acetoxy group is preferentially introduced at the saturated carbon adjacent to the carbonyl group.[368,369,372]



78%

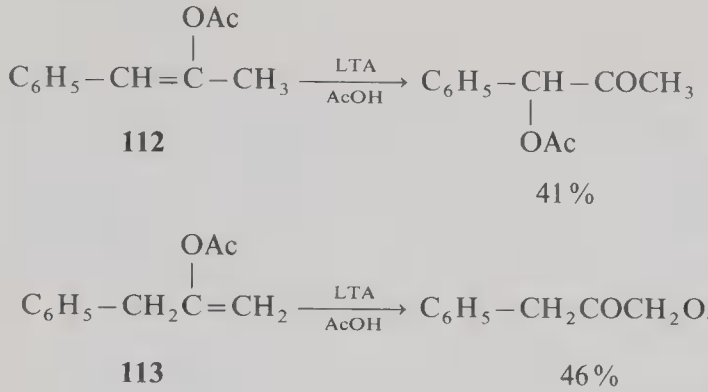
The LTA acetoxylation reaction has been applied to a variety of carbonyl compounds, particularly interesting results being achieved in the steroid series; in the latter case not only saturated and unsaturated ketones, but also epoxy-ketones[373] and steroidal lactones[374] have been successfully acetoxylated by the LTA procedure. Some typical examples of these oxidations are presented in Table VIII.

α-Acetoxy ketones have been also formed by the LTA oxidation of enol-acetates, the direction of acetoxylation depending on the position of the double bond in the parent enol-

TABLE VIII. Acetoxylation of Carbonyl Compounds by LTA

Carbonyl compound	Acetoxylated products	Yield (%)	Reference
Acetone	α-Acetoxyacetone	22	27, 370
	α,α′-Diacetoxyacetone	17	
Methyl ethyl ketone	1-Acetoxy-2-butanone	31	27, 367
Acetophenone	α-Acetoxyacetophenone	32–75	371
Butyrophenone	α-Acetoxybutyrophenone	34	375
Benzylphenyl ketone	Acetoxybenzylphenyl ketone	20–85	27, 376
α-Tetralone	2-Acetoxy-α-tetralone	14	377
Cyclopentanone	α-Acetoxycyclopentanone		377
Cyclohexanone	α-Acetoxycyclohexanone	59	368, 371
Cycloheptanone	α-Acetoxycycloheptanone	58	378
	α,α′-Diacetoxycycloheptanone	15	
2-Methylcyclohexanone	2-Methyl-6-acetoxycyclohexanone	22	368
	2-Methyl-2-acetoxycyclohexanone	11	
3,5-Dimethylcyclo-hexanone	3,5-Dimethyl-2-acetoxycyclo-hexanone	68	379
3,3,5-Trimethylcyclo-hexanone	3,3,5-Trimethyl-2-acetoxy-cyclohexanone	23	368
	3,3,5-Trimethyl-6-acetoxy-cyclohexanone	31	
Acetylacetone	3-Acetoxyacetylacetone	25	371
Ethyl acetoacetate	Ethyl α-acetoxyacetoacetate	53	370, 371
Diethyl malonate	Diethyl acetoxymalonate	79	371
Isophorone	2-Acetoxyisophorone	78	368, 372
Indan-1-one	2-Acetoxyindan-1-one	35	377
5α-Cholestan-3-one	2α-Acetoxy-5α-cholestan-3-one	51	365
5α-Cholestan-2-one	3α-Acetoxy-5α-cholestan-2-one		365
5β-Cholestan-1-one	2α-Acetoxy-5β-cholestan-1-one	28	380
Cholest-5-en-3-one	4α-Acetoxycholest-5-en-3-one	30–40	381
Cholest-4-en-3-one	2α-Acetoxycholest-4-en-3-one	10	382
17β-Acetoxyandrost-4-en-3-one	2α (and 2β), 17β-Diacetoxy-androst-4-en-3-one	42	383
Progesterone	2α-Acetoxyprogesterone	8	383
4,4-Dimethyl-5α-androstan-2-one	3α-Acetoxy-4,4-dimethyl-5α-androstan-2-one	58	384
3β-Acetoxy-5α-pregnan-20-one	3β,21-Diacetoxy-5α-pregnan-20-one	53	385
3β-Acetoxy-5α-pregnane-11,20-dione	3β,21-Diacetoxy-5α-pregnane-11,20-dione	86	366

acetate.[367] Thus, from the two isomeric enol-acetates **112** and **113**, respectively, two isomeric α-acetoxy ketones were obtained.



7. CARBOXYLIC ACIDS

LTA has been extensively used to effect oxidative decarboxylation of carboxylic acids. Applications of this reaction in organic synthesis were comprehensively reviewed in 1972.[14] Monocarboxylic acids are relatively stable towards LTA, undergoing oxidative decarboxylation only when exposed to thermal (heating) or photolytical conditions (irradiation at 300–350 nm). Most often the main reaction products are alkanes, alkenes, esters, and other products (see Scheme 8), formed in relative amounts which depend on the structure of the substrate and experimental conditions. Cupric acetate accelerates the oxidative decarboxylation of primary and secondary acids, affording alkenes in high yield. Decarboxylations performed in the presence of metallic halides give the corresponding halogenides, usually as the only reaction products.

7.1. Mechanism

It is generally accepted that decarboxylation of carboxylic acids prodeeds via a free radical chain mechanism,[386–388] outlined in Scheme 8.

There are several experimental findings supporting a free-radical chain mechanism, the most important being (i) initiation of decarboxylation by light or free radical initiators[386,387,389]; (ii) trapping of alkyl radicals by radical scavangers, such as oxygen or phenols[387,388a]; (iii) detection of both alkyl and carboxyalkyl radicals by ESR spectroscopy (in solid benzene matrix).[146,390]

Homopolar decomposition of lead(IV) carboxylates, produced in fast metathesis, leads to a transient acyloxy radical which rapidly decomposes to form an alkyl radical and carbon dioxide. In the propagation step oxidation of the alkyl radical by lead(IV) species affords the corresponding carbenium ion and lead(III) carboxylate, which by decomposition produces a new alkyl radical capable to induce further decomposition of lead(IV) carboxylates. Skeletal rearrangement typical of carbenium ions observed in some LTA oxidative decarboxylations[391] indicates that the reaction proceeds via a carbenium ion intermediate.

The rate of oxidation of alkyl radicals to carbenium ions depends on the relative stability of these species and parallels the ease of decomposition of the lead(IV) carboxylates, which increases with increasing stability of the alkyl radical in the order (as expressed in terms of the starting acid): $RCH=CHCH_2COOH > R_3CCOOH > R_2CHCOOH > RCH_2COOH > CH_3COOH$. Therefore, the structure of the radical R will greatly influence both the rate and the course of the decarboxylation reaction.

SCHEME 8

Metathesis:

$$R-COOH + Pb(OAc)_4 \longrightarrow R-COO-Pb(OAc)_3$$

Initiation:

$$R-COO-Pb(OAc)_3 \xrightarrow{\triangle \text{ or } h\nu} R-COO^{\bullet} + {}^{\bullet}Pb(OAc)_3$$

$$R-COO^{\bullet} \longrightarrow R^{\bullet} + CO_2$$

Propagation:

$$R^{\bullet} + R-COO-Pb(OAc)_3 \longrightarrow R^{+} + R-COO-\dot{P}b(OAc)_2 + AcO^{-}$$

$$R-COO-\dot{P}b(OAc)_2 \longrightarrow R^{\bullet} + Pb(OAc)_2 + CO_2$$

Termination:

$$R^{\bullet} + R-COO-\dot{P}b(OAc)_2 \longrightarrow R^{+} + R-COO-Pb(OAc) + AcO^{-}$$

or $R^{\bullet} + SH \longrightarrow RH + S^{\bullet}$ or $R-S + H^{\bullet}$ (reactions with solvent SH)

or $R^{\bullet} + R^{\bullet} \longrightarrow R-R$ (dimerization) or $R^{+} + R^{-}$ (disproportionation)

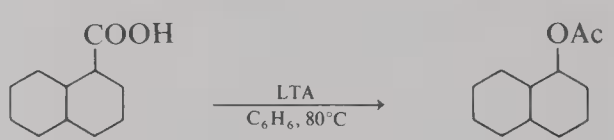
Product formation:

R^{+} —oxidative elimination→ alkenes

R^{+} —oxidative substitution→ esters

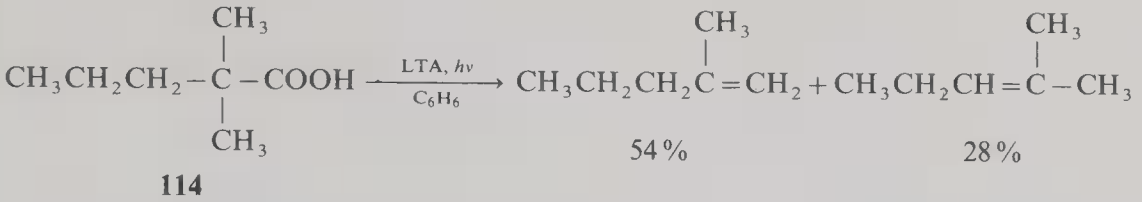
7.2. Scope and Limitations

In the oxidative decarboxylations of primary and secondary carboxylic acids a variety of products can be obtained. Since the oxidation of primary and secondary alkyl radicals by lead(IV) [or a caged lead(III) species] is an inefficient process, the main reaction products of decarboxylation of primary acids are alkanes (formed by hydrogen abstraction from the solvent) or, when the reaction is preformed in benzene solution, phenylalkanes (formed by homolytic aromatic substitution); with secondary alkyl radicals, derived from secondary carboxylic acids, in addition to alkanes, substantial amounts of the corresponding esters (i.e., products of oxidative substitution) or alkenes (products of oxidative elimination) are also formed (see Scheme 8).[387,392] On the other hand, in the case of tertiary alkyl radicals or other radicals of similar stability, both their generation [by homolysis of the respective lead(IV) carboxylates] as well as the electron transfer oxidation to the corresponding carbenium ions

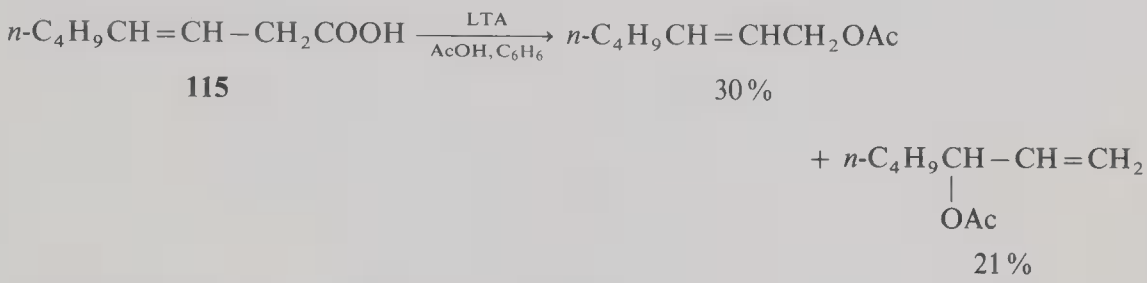


66%

are very fast processes leading to almost exclusive formation of alkenes or acetates. Usually acids which contain a tertiary alkyl group (for example, the acid **114**), upon oxidation with LTA give predominantly alkenes, whereas acids, such as **115**, which produce allylic radicals, give preferentially acetates.[387,393]



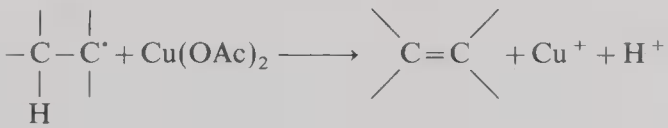
114



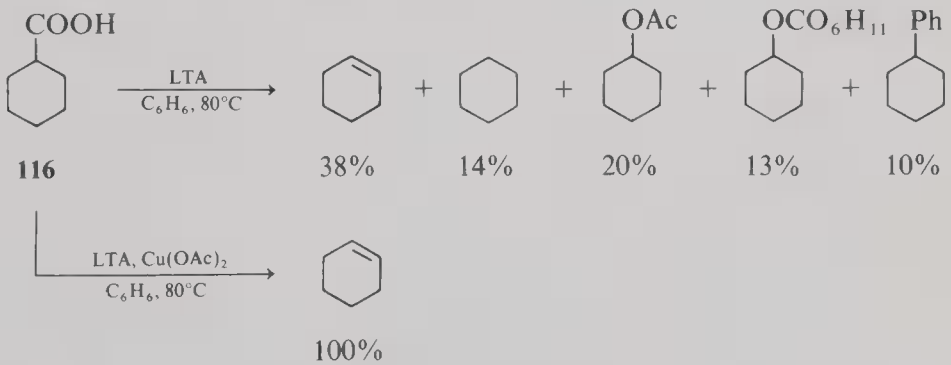
115

However, the relative proportions of alkenes to acetates may be influenced by changing experimental conditions. Thus, the yield of esters can be increased if the reaction is performed in acetic acid in the presence of a large excess of potassium acetate, while in dimethylformamide solution the yield of alkene is increased.[14]

Catalytic amounts of cupric acetate accelerate the decarboxylation of carboxylic acids; in addition, the rates of the electron transfer oxidation of primary and secondary alkyl radicals by cupric ions are [contrary to the oxidation by Pb(IV) species] very fast, approaching diffusion controlled rates.[394,395] Therefore, when a primary or secondary acid



(such as **116**) is oxidized with LTA in the presence of cupric acetate, not only the rate, but also the reaction course will be changed and olefins are formed in high (often quantitative) yield, at the expense of alkanes, esters, or other products.[386,396] On the other hand, cupric acetate has little effect on the rate of decarboxylation and product distribution in the LTA oxidation of tertiary acids, probably owing to the relatively facile oxidation of tertiary alkyl radicals to carbenium ions by lead(IV) species.[386]



116

The rate of the LTA oxidative decarboxylation of carboxylic acids is also considerably enhanced and the reaction course is again completely changed when the reaction is carried out in the presence of one molar equivalent of metal halides, such as lithium, sodium, or potassium chloride; under these conditions alkyl halides are usually the only reaction products.[397] Halodecarboxylation of acids with the LTA-LiCl reagent and formation of alkyl

$$CH_3CHCH_2COOH \xrightarrow[C_6H_6]{LTA,\,LiCl} CH_3CHCH_2-Cl \quad (99\%)$$

halides in high yield is explained by a rapid ligand-transfer oxidation of alkyl radicals by lead(IV) species containing at least one halide ligand.[398] In the case of primary and secondary acids this process outweighs by far the relatively slow electron-transfer oxidation. From the fact that in the LTA-LiCl oxidations with substrates such as **117** products characteristic

$$LiCl + R-COO-Pb(OAc)_3 \longrightarrow Cl-Pb(OAc)_3 + LiOCOR$$

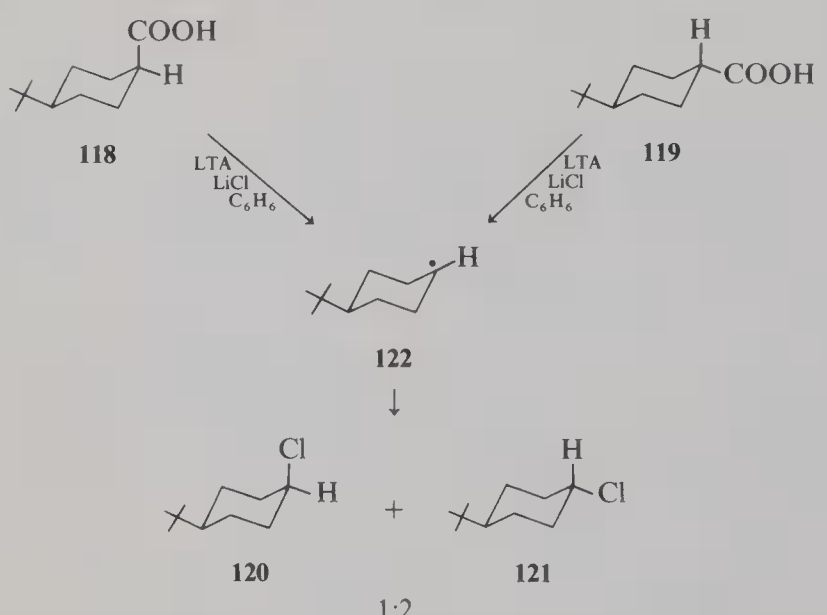
$$R^{\cdot} + Cl-Pb(OAc)_3 \longrightarrow R-Cl + {}^{\cdot}Pb(OAc)_3$$

of the rearrangement of carbenium ion intermediates have not been observed, it was concluded that the ligand transfer oxidation does not proceed via a free (or paired) carbenium ion.[14,389]

$$CH_3-C(CH_3)_2-CH_2COOH \xrightarrow[C_6H_6]{LTA,\,LiCl} CH_3-C(CH_3)_2-CH_2-Cl$$

117 92%

Halodecarboxylation of *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acid (**118** and **119**) with LTA-LiCl gave the same ratio of *cis*- and *trans*-4-*t*-butylcyclohexyl chloride (**120** and **121**), indicating, in both cases, the intermediacy of the same 4-*t*-butylcyclohexyl radical (**122**), irrespective of the stereochemistry of the starting carboxylic acid.[399,400]

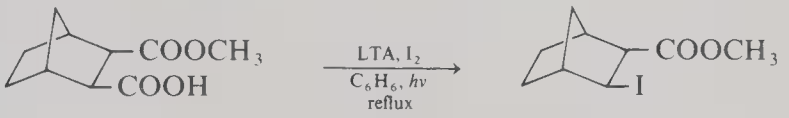


Another type of decarboxylation of carboxylic acids with LTA, known as iododecarboxylation, occurs when the LTA reaction is performed in carbon tetrachloride in the presence of one molar equivalent of iodine, and by irradiation of the reaction mixture with a tungsten lamp. This reaction represents a convenient method for the preparation of alkyl iodides from carboxylic acids[401] (similarly to the Hunsdiecker degradation), and is believed to involve the formation and subsequent decomposition of acyl hypoiodites.

$$R-COOH \xrightarrow[CCl_4, h\nu]{LTA, I_2} RCOO-Pb(OAc)_3 \xrightarrow{-{}^{\cdot}Pb(III)} R-COO^{\cdot}$$

$$\xrightarrow[-I^{\cdot}]{\dot{I}_2} R-COOI \xrightarrow{-CO_2, -I^{\cdot}} R^{\cdot} \xrightarrow{I_2 (or\ I^{\cdot})} R-I$$

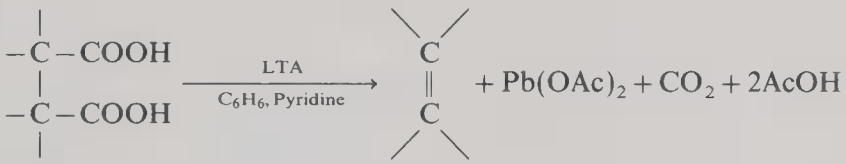
In the conversion of the ester-acid **123** to the corresponding iodo-ester **124**, the iododecarboxylation reaction with LTA-I_2 was achieved by combining photolytic and thermal conditions.[402,403]



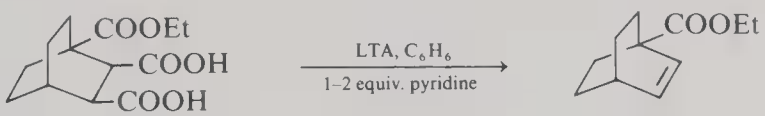
123 85%

124

1,2-Dicarboxylic acids undergo oxidative bisdecarboxylation when heated under reflux with LTA in benzene-pyridine, acetonitrile, or dimethyl sulfoxide solution, affording olefins, usually in high yield.[2,14,391,404,405] This reaction has been extensively used for the introduction of the olefinic double bond into bridged and fused polycyclic *gem*-dicarboxylic systems.[405,406,407] It is assumed that, similarly to the decarboxylation of monocarboxylic



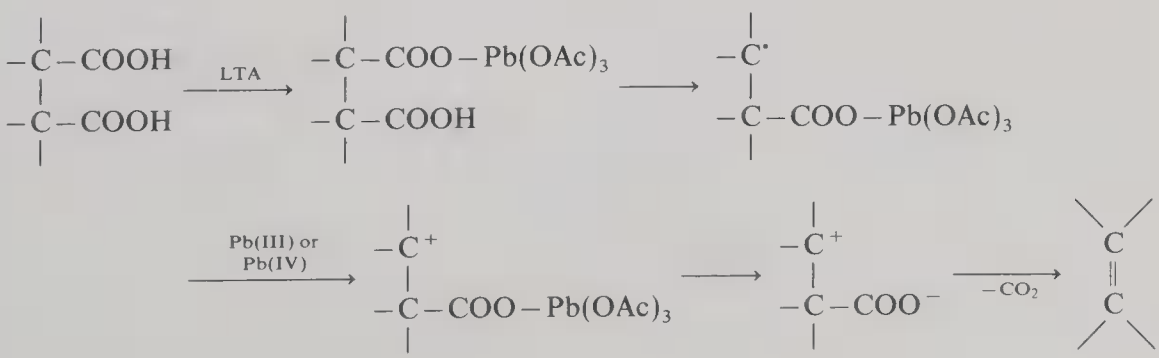
acids, bisdecarboxylation also proceeds via radical and carbenium ion intermediates.[14] Such a stepwise mechanism is supported by lack of stereospecificity in the bisdecarboxylation reac-

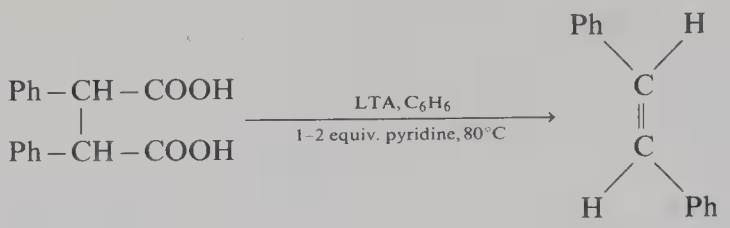


65%

20%

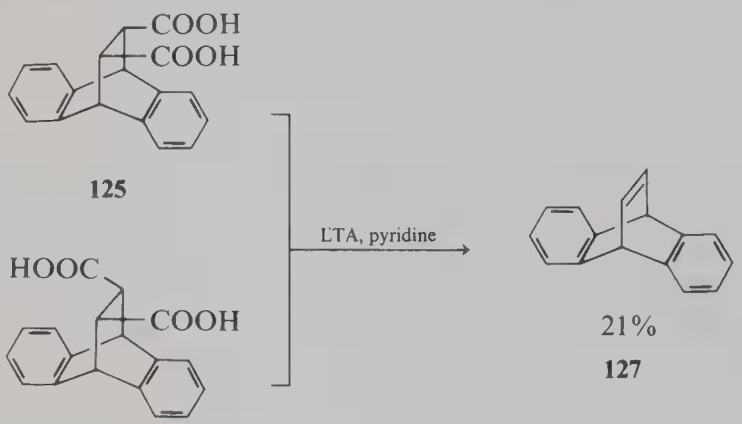
tion; thus, both racemic and *meso*-diphenylsuccinic acids yield exclusively *trans*-stilbene (without a traces of the *cis*-isomer) when treated with LTA.[391,408] Similarly, both *cis*- and





41%–44%

trans-dicarboxylic acids **125** and **126** afford the only possible unsaturated isomer (**127**) in comparable yield (ca. 21%).[14]



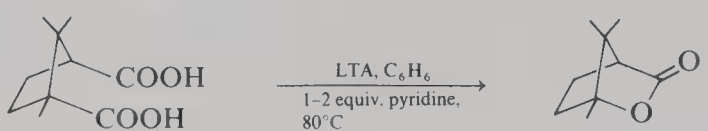
125

21%

127

126

1,3-Dicarboxylic acids react differently with LTA. Usually they undergo monodecarboxylation, yielding the corresponding γ-lactones as the main reaction products.[409]



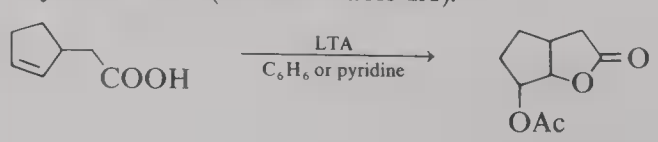
70%

1,1-Dicarboxylic acids are decarboxylated when heated with LTA in benzene solution containing two molar equivalents of pyridine. The initial products, *gem*-diacetates, are usually readily hydrolyzed (during the work-up procedure) to the corresponding ketones. By this method, disubstituted malonic acids have been successfully converted to a variety of ketones,[410–412] as for example 1,1-cyclopentanedicarboxylic acid **128** to cyclopentanone.[410] However, the yields of ketones are not always satisfactory.[14,413]

128

45%

The LTA oxidation of unsaturated carboxylic acids can lead to different types of products, depending on the relative distance and spatial orientation between the carboxyl group and the ethylenic bond. When this steric and structural relationship is favorable, acyclic and cyclic γ-olefinic monocarboxylic acids react with LTA mostly without decarboxylation but with double bond participation, to give the corresponding acyloxy monolactones, usually in good yield[13,414–416] (see also Table IX).



35%–70%

TABLE IX. Decarboxylation of Carboxylic Acids

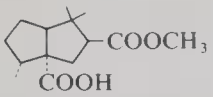
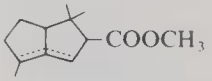
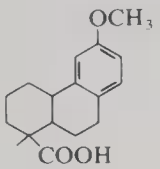
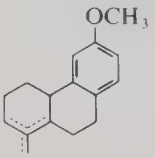
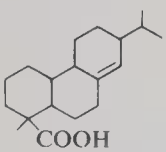
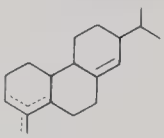
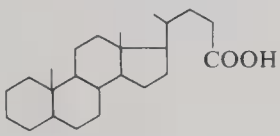
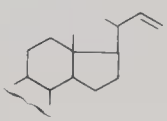
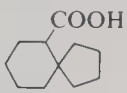
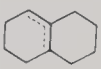
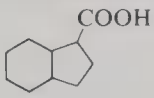
Carboxylic acid	Products	Yield (%)	Reference
A. Monocarboxylic Acids			
(a) To olefins without additives			
Trimethylacetic acid	Isobutene	48	386
	t-Butyl acetate	9	
α,α-Dimethylvaleric acid	2-Methylpent-1-ene	42	386
	2-Methylpent-2-ene	23	
		56	417
		70	418
(b) To olefins in the presence of cupric acetate			
Cyclobutanecarboxylic acid	Cyclobutene	68	396
n-Heptanoic acid	1-Hexene	72	396
Cyclohexanecarboxylic acid	Cyclohexene	100	396
Cyclohexylacetic acid	Methylenecyclohexene	84	396
Suberic acid (mono ethyl ester)	Ethyl 6-heptenoate	60	396
		76	419
		60	420
		88	421
		12	
(c) To alkyl acetates			
Vinylacetic acid	Allyl acetate	87	393
exo-Norbornane-2-carboxylic acid	*exo*-2-Norbornyl acetate	24–67	391
1-Cycloheptene-5-carboxylic acid	4-Cycloheptenyl acetate	70	422
p-Methoxyphenylacetic acid	*p*-Methoxybenzyl acetate	99	393
Triphenylacetic acid	Triphenylmethyl acetate	89–95	386, 423
		75	424

Table continued

TABLE IX. *Continued*

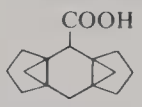
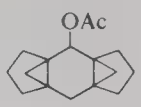
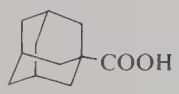
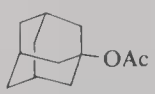
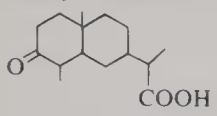
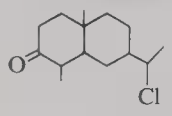
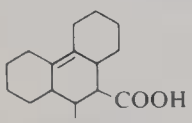
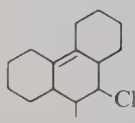
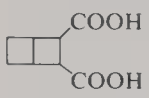
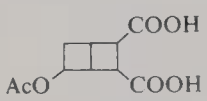
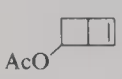
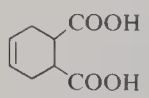
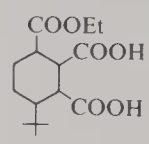
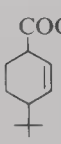
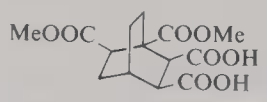
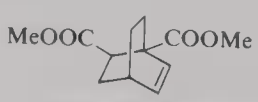
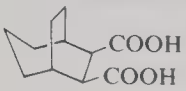
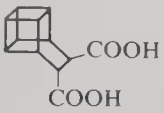
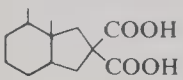
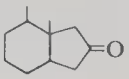
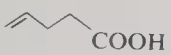
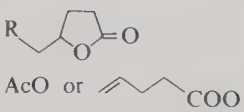
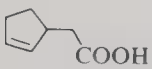
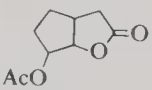
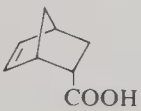
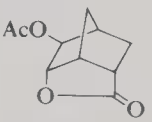
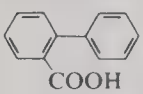
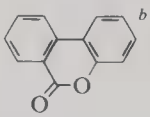
Carboxylic acid	Products	Yield (%)	Reference
		60	425
		89	426
	(d) Halodecarboxylation		
i-Butyric acid	*i*-Propyl chloride	98	397
n-Valeric acid	*n*-Butyl chloride	92	397
i-Valeric acid	*i*-Butyl chloride	99	397
Cyclobutanecarboxylic acid	Cyclobutyl chloride	98	397
β,β-Dimethylpropanoic acid	Neopentyl chloride	92	397
Cyclohexanecarboxylic acid	Cyclohexyl chloride	100	397
Phanylacetic acid	Benzyl chloride	90–95	393
		80	427
		65	428
n-Hexanoic acid	*n*-Amyl iodide	100	401, 429
12-Oxostearic acid	11-Oxoheptadecyl iodide	79	401, 429
 (*cis*- or *trans*-)		42	430
	B. Dicarboxylic Acids		
	(a) 1,2-Dicarboxylic acids		
dl-2,3-Diphenylsuccinic acid	*trans*-Stilbene	44	391
meso-2,3-Diphenylsuccinic acid	*trans*-Stilbene	41	391
		30–38	431
		40	432
		76	408
		40	433
		50	434

TABLE IX. *Continued*

Carboxylic acid	Products	Yield (%)	Reference
		33	435
		25	436
(b) *gem*-Dicarboxylic acids			
1,1-Cyclobutanecarboxylic acid	Cyclobutanone	20	14
1,1-Cyclopentanedicarboxylic acid	Cyclopentanone	45	410
1,1-Cyclohexanedicarboxylic acid	Cyclohexanone	50	410
		60	412
C. Cyclization of γ-Unsaturated and Aromatic Acids			
(a) γ-Unsaturated acids			
		75–85	416
		35–70	13, 414
		65–80	13, 414
(b) Aromatic acids			
5-Phenylvaleric acid	Tetralin[a]	42	388
Diphenyl-2-propanoic acid	9,10-Dihydrophenanthrene[a]	42	388
	 [b]	85	437, 438

[a] With decarboxylation.
[b] Without decarboxylation.

8. NITROGEN-CONTAINING COMPOUNDS

8.1. Amines

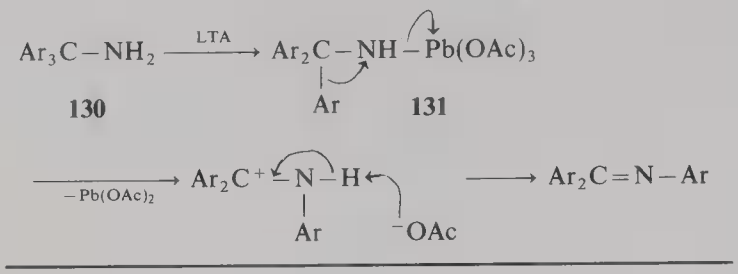
Primary alkyl- or aralkyl-amines containing an α-methylene group are dehydrogenated, upon treatment with two molar equivalents of LTA in nonpolar solvents, to the corresponding alkyl (or aryl) cyanides, in yields ranging up to 65%.[439,440] The reaction is regarded as a two-step dehydrogenation process involving initial formation of an unstable aldimine **129**, which reacts further with LTA to afford cyanide as the final product.[440] The intermediate formation of aldimines is supported by LTA dehydrogenation of independently prepared aldimines to the corresponding nitriles.[441,442]

$$R-CH_2-NH_2 \xrightarrow{LTA} R-CH_2NH-Pb(OAc)_3 \xrightarrow[-2H]{} R-CH=NH$$

129

$$\xrightarrow{LTA} R-CH=N-Pb(OAc)_3 \xrightarrow[-2H]{} R-C\equiv N$$

SCHEME 9



The LTA oxidation of 1,1-diphenylethyl- and triphenylmethylamine **130** is accompanied by rearrangement, affording ketimines.[443,444] It was suggested that migration of the aryl group from carbon to nitrogen in the intermediate **131**[443,444] occurs simultaneously with the heterolytic cleavage of the N–Pb bond, according to Scheme 9.

The LTA oxidation of primary aromatic amines leads to symmetrical azo compounds in varying yields.[445–447] Since hydrazo compounds **132** are readily dehydrogenated to the

132

35%–50%

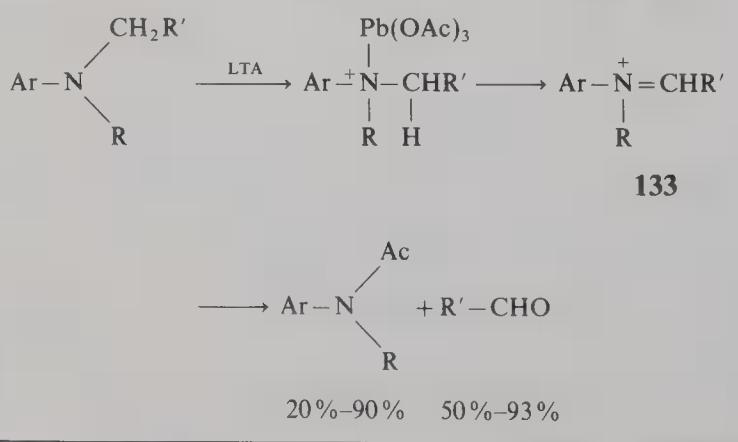
corresponding azo derivatives by means of LTA,[445,448,449] they probably appear as intermediates in these oxidations.[445–447] In addition, small amounts of quinones can be also formed, although with some aromatic amines quinones may become the major reaction products.[445]

Oxidation of aromatic 1,2-diamines, such as *o*-phenylenediamine, affords *cis*-muconitriles in fair yield.[450]

35%–50%

Tertiary aromatic amines are readily oxidized by LTA in chloroform–acetic anhydride solution to give aldehydes and *N*-acetyl-*N*-alkylamines.[451] It was suggested that the immonium ion **133** is a possible intermediate, which hydrolyzes to the final products according to Scheme 10.

SCHEME 10

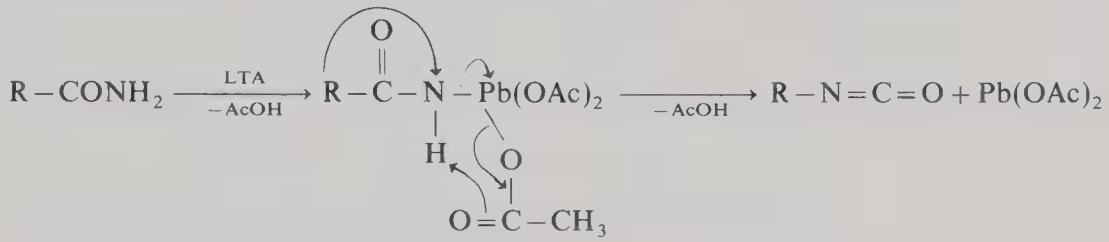


133

20%–90% 50%–93%

8.2. Amides

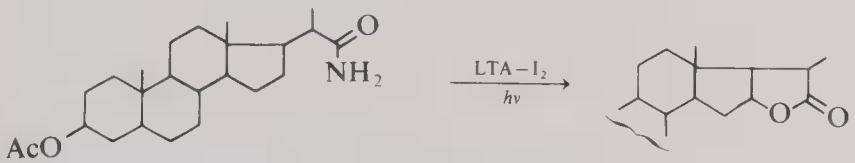
Unsubstituted amides react with LTA in aprotic solvents to give isocyanates,[452,453] in a process similar to the Hofmann-type rearrangement of amides. Since nitrene intermediates have not been detected, it appears that the reaction proceeds by a concerted mechanism.



The LTA oxidation of amides is usually performed in the presence of alcohols (or in alcohol itself), when the corresponding carbamates (RNHCOR′) are obtained in good yield.[454a] In the presence of carboxylic acids, the main products are acylamines.[454b]

88%

When the hypoiodite version of the LTA oxidation is applied to unsubstituted or monosubstituted amides possessing a γ-hydrogen, an intramolecular substitution at the non-activated carbon atom occurs, yielding γ-lactones as the final product.[455] This reaction is considered to proceed according to Scheme 11.[456]

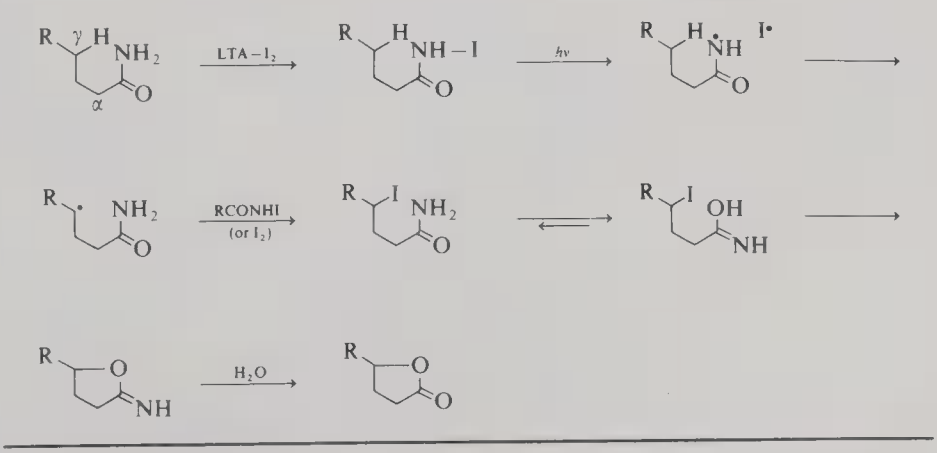


55%

8.3. Hydrazines

The course of the LTA oxidation of hydrazines is particularly sensitive to the structure of the substrate and reaction conditions. Thus, arylhydrazines are oxidized with LTA to give aryldiazonium ions,[457] while *N*,*N*′-disubstituted hydrazines afford azo compounds.

SCHEME 11



$$Ar-NHNH_2 \xrightarrow{LTA} Ar-N=NH \longrightarrow Ar-N_2^+$$

$$Ar-NHNH-Ar \xrightarrow{LTA} Ar-N=N-Ar$$

On the other hand, *N,N*-disubstituted hydrazine derivatives can give tetrazines **134** (formed by nitrene coupling) or products derived from further LTA oxidation.[458]

$$2(PhCH_2)_2N-NH_2 \xrightarrow{LTA} (PhCH_2)_2N-N=N-N(CH_2Ph)_2$$

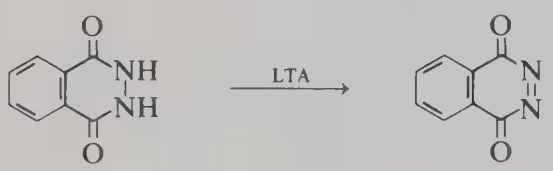
134

$$\xrightarrow{LTA} Ph-CH_2-N_3 + (PhCH_2)_2NH + Ph-CHO$$

76% 63% 75%

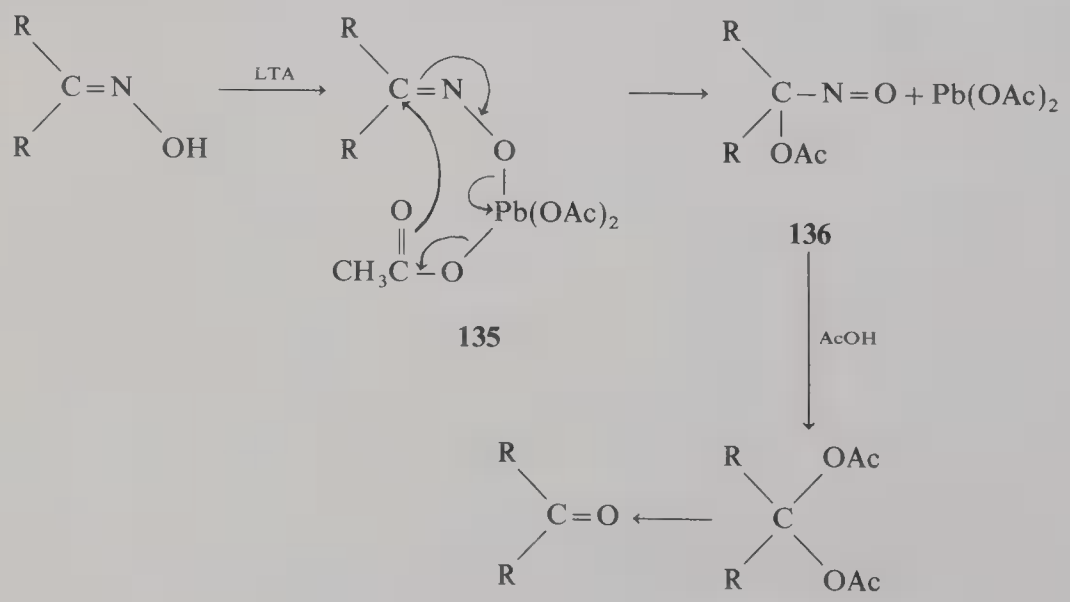
N-Alkyl-*N'*-acylhydrazines and *N,N'*-diacylhydrazines undergo dehydrogenation with LTA affording the corresponding azo compounds.[459,460]

$$Ar-NHNH-COAr' \xrightarrow{LTA} Ar-N=N-COR'$$

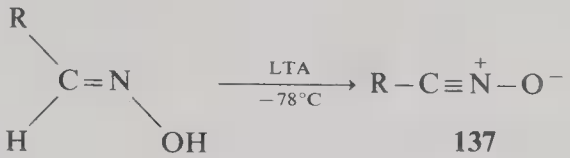


8.4. Oximes

The products obtained in the LTA oxidation of oximes vary with the structure of the substrate, the ratio of oxidant to substrate, solvent, temperature, and the presence of nitric oxide.[1,2,15,16] Aliphatic ketoximes, as nitrogen analogs of enols, when treated with LTA in an inert solvent, undergo acetoxylation at the α-carbon atom producing α-nitroso-α-acetoxyalkanes, **136** (in yields ranging up to 75%).[461–463] This reaction probably proceeds by intramolecular decomposition of the lead triacetate intermediate **135**. However, when



oxidation is performed in acetic acid, both aromatic and aliphatic ketoximes are transformed to the parent carbonyl compounds. It appears that carbonyl compounds arise from decomposition of the nitrosoacetates **136** in acetic acid.[461] With *syn*-aldoximes at low temperature (−78°C) nitrile oxides **137** (i.e., products of dehydrogenation) are obtained in high yield.[464]



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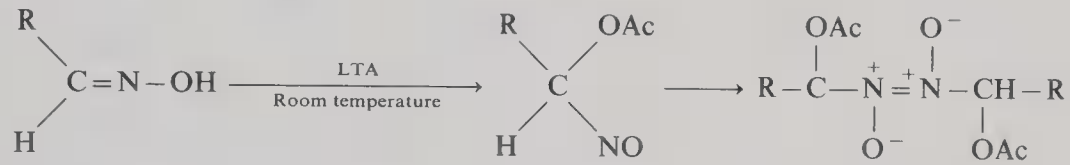
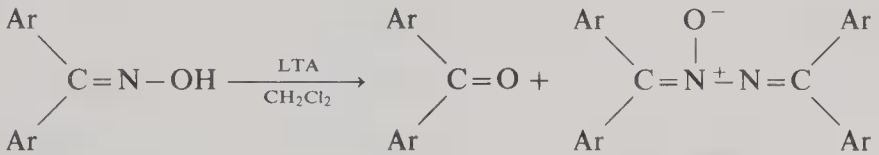
These compounds are of considerable synthetic value, since they readily undergo 1,3-dipolar cycloaddition reactions to give useful products.[465] When the LTA oxidation of aliphatic *syn*- or *anti*-aldoximes is performed at room temperature, nitroso-acetate dimers are formed in yields up to 70%[461,464] (see Table XA).



The LTA oxidation of aromatic ketoximes in neutral solvents affords the parent carbonyl compounds (see Table XB), in addition to some dimeric products, such as azine monoxides **138**, or other products derived from the iminoxy radical intermediates.[466]



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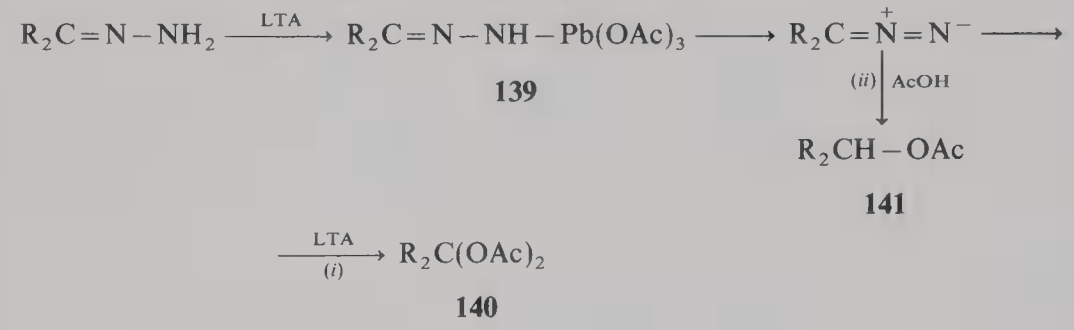
8.5. Hydrazones

The LTA oxidation of hydrazones can also give a variety of products, depending on the structure of substrate and reaction conditions.[1,2,15,16,19] The *N*-unsubstituted hydrazones of both aldehydes and ketones are oxidatively dehydrogenated (via the hydrazone-lead

TABLE X. Oxidation of Oximes

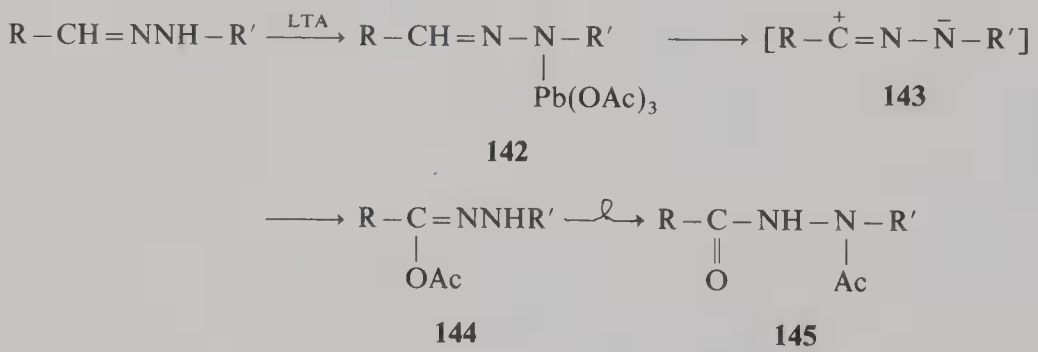
Oxime	Products	Yield (%)	Reference
	A. To α-Nitroso-α-acetoxyalkanes (in Et_2O)		
Acetone oxime	2-Nitroso-2-acetoxypropane	26–64	461
Diethylketone oxime	3-Nitroso-3-acetoxybutane	59	461
Cyclohexanone oxime	1-Nitroso-1-acetoxycyclohexane	35–75	461, 462
Cycloheptanone oxime	1-Nitroso-1-acetoxycycloheptane	50	461
	B. To Carbonyl Compounds (in Acetic Acid)		
Nonanal oxime	Nonanal	94	467
p-Methoxybenzaldoxime	*p*-Methoxybenzaldehyde	90	467
2-Heptanone oxime	2-Heptanone	90	467
5α-Cholestan-3-one oxime	5α-Cholestan-3-one	75	467

tracetate complex **139**), to give the corresponding diazo compounds. However, only the more stable diazo compounds, i.e., those containing electron-withdrawing substituents at the α-carbon atom, can be isolated.[470,471] Usually diazo compounds react further with LTA (when reaction is performed with two molar equivalents of oxidant) to give 1,1-diacetoxy derivatives **140**(*i*), or with acetic acid to give 1-monoacetoxy derivatives **141**(*ii*).[468,469] In addition, in some cases, azines and olefins can also be isolated, as the result of dimerization of, or nitrogen elimination from, the primarily formed diazo compounds.[468,469]



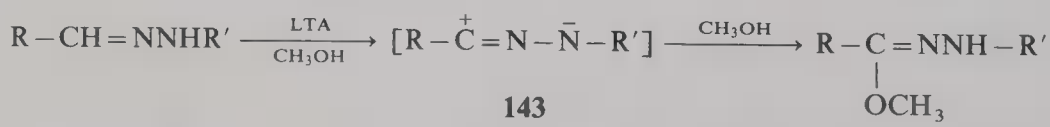
139 **141** **140**

Monosubstituted hydrazones of aldehydes undergo oxidative transformation when treated with LTA in acetic acid to give *N*-acetyl-*N'*-acylhydrazones.[145] Similarly to unsubstituted hydrazones, the reaction proceeds by cleavage of the nitrogen–lead bond in the initially formed *N*–lead triacetate intermediate **142**. The nitrilimine **143** so obtained reacts with acetic acid to give hydrazonyl acetate, **144**, which undergoes rearrangement to the final *N*-acetyl-*N'*-acylhydrazone **145**.[472–474]



142 **143** **144** **145**

When the LTA reaction is performed in alcoholic solution, in addition to the hydrazonyl acetate (**144**), the corresponding hydrazonyl ethers are also obtained.[472]



143

In general, the LTA oxidation of monosubstituted ketone hydrazones results in α-acetoxylation to give the corresponding azo-acetates **146**.[476] However, when the reaction is performed in alcoholic solvents, a mixture of azo-ethers and azo-acetates is obtained.[477,478]

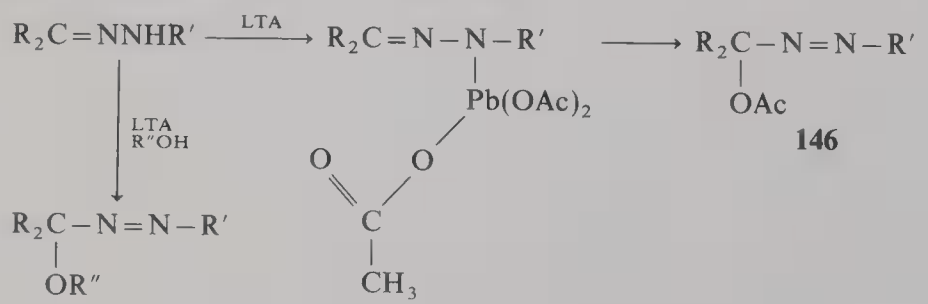


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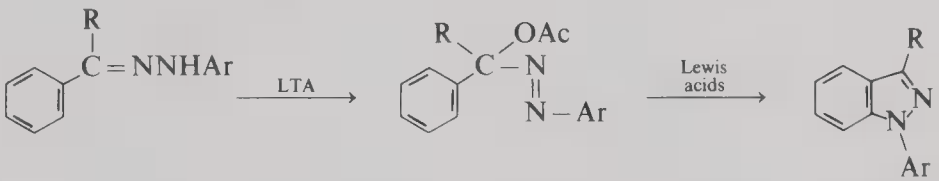
TABLE XI. Oxidation of Ketone Hydrazones to Azo-Acetates

Ketone hydrazone	Product	Yield (%)	References
Acetone phenylhydrazone	2-Phenylazo-2-acetoxypropane	83	476
Acetone *p*-bromophenyl-hydrazone	2-(*p*-Bromophenylazo)-2-acetoxypropane	90	476
2-Butanone phenylhydrazone	2-Phenylazo-2-acetoxybutane	81	476
Cyclopentanone 2,4-dinitro-phenylhydrazone	1-(2,4-Dinitrophenylazo)-1-acetoxycyclopentane	80	476
Benzophenone phenylhydrazone	Phenylazo-acetoxydiphenyl-methane	90	476

Since azo-acetates are useful synthetic intermediates, a wide range of ketone hydrazones has been oxidized with LTA[1,16,19] (see Table XI). Thus, the substituted 1-aryl-indazole **148** was conveniently prepared from the corresponding ketone hydrazone **147** by LTA oxidation and subsequent treatment of the initially formed azo-acetate with Lewis acids.[479] On the other hand, α,β-unsaturated ketone hydrazones upon treatment with LTA undergo cyclization to the corresponding pyrazole products.[480]



147 **148**

9. EXPERIMENTAL CONSIDERATIONS AND PROCEDURES

9.1. Hydrocarbons

LTA oxidations of unsaturated hydrocarbons are performed in acetic acid, benzene, or low molecular weight saturated alcohols, as solvents. An equimolar ratio of reactants or a considerable excess of oxidant has been used. Reactions are usually carried out under anhydrous conditions at boiling point of the solvent or at lower temperature. Depending on the structure of the substrate and the reaction products desired, different reaction conditions are applied.

Benzylic acetoxylations by LTA are preferably performed in refluxing acetic acid, although oxidations of more reactive benzylic C–H groups (in compounds possessing electron donating substituents attached to the aromatic ring) can be achieved at room temperature.

Oxidation of Cholesteryl Acetate by LTA to 7-Acetoxycholesteryl Acetate.[59] A suspension of 2.0 g of cholesteryl acetate, 4 g of lead tetraacetate (dried *in vacuo* over P_2O_5 and KOH), and 0.5 g of anhydrous $CaCO_3$ in 150 ml of thiophene-free benzene (dried over Na) was stirred at reflux for 36 h, after which time the oxidant was completely consumed (negative starch–iodine test). The cooled mixture was diluted with ether, filtered through a Celite mat, and the insoluble precipitate thoroughly washed with water, aqueous $NaHCO_3$, and water, and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crystalline residue (2.21 g) was chromatographed on 60 g of neutral Al_2O_3 (activity II). With light petroleum and light petroleum–benzene (9:1 and 8.2), 1.45 g (72.3%)

of the starting cholesteryl acetate was recovered. Elution with benzene gave a mixture (421 mg; 18.5%) of 7α- and 7β-acetoxycholesteryl acetate in a ratio of about 3:2.

Oxidation of 6-Methoxytetralin by LTA to 1-Acetoxy-6-methoxytetralin.[114] A mixture containing 100 g of LTA, 150 ml of glacial acetic acid, and 33 g of 6-methoxytetralin is stirred at room temperature for 16 h. In the beginning the reaction is slightly exothermic and is controlled by external cooling. If the oxidant is not completely consumed, it must be decomposed by addition of a small amount of glycerol (KI–starch test). After removing the solvent under reduced pressure, the oily residue is diluted with water and extracted with ether; the organic layer is successively washed with water, 10% aqueous Na_2CO_3, 2% aqueous NaOH, and finally with water and saturated aqueous NaCl solution, and then dried over anhydrous K_2CO_3. The oily residue obtained after evaporation of the solvent is distilled and 1-acetoxy-6-methoxytetralin collected at 132-139°C/1–2 mm Hg; yield 27.9 g (62%).

Oxidation of 1-Pyrrolidino-1-cyclohexene by LTA to Ethyl Cyclopentanecarboxylate[131]. To a mixture consisting of 4.53 g (0.03 mole) of 1-pyrrolidino-1-cyclohexene, 4.26 g (0.03 mole) of boron trifluoride etherate and 1.7 ml (0.03 mole) of ethanol in 50 ml of benzene, 14 g (0.032 mole) of LTA was added, and the reaction mixture was stirred for 30 h at room temperature. The precipitated lead salts were filtered off and the filtrate treated with dilute hydrochloric acid. The organic solution was washed with water and aqueous $NaHCO_3$, dried, and after the solvent was removed, distilled under reduced pressure, to give ethyl cyclopentanecarboxylate, b.p. 72–74°C/14 mm Hg, in 3.1 g (78%) yield.

9.2. Monohydroxylic Alcohols

Lead tetraacetate oxidations of monohydroxylic alcohols can be performed under thermal or photolytic conditions, or in the presence of iodine.

The thermal LTA reaction is usually carried out in benzene solution at reflux using a 1:1 molar ratio of substrate to oxidant; the other solvents, such as cyclohexane, methylcyclohexane, heptane, or chloroform have also been used,[140,178,189,196,198] but in these cases the yields of cyclic ethers may be lower. The polar and basic solvent pyridine should be used only when the formation of carbonyl compounds is desired. The use of acetic acid as solvent is unsuitable, since it prevents alkoxylation of lead tetraacetate and also converts the starting alcohol to the corresponding acetate.[139,140] However, the addition of some acetic acid and of anhydrous calcium carbonate (1–2 equivalents of each per equivalent of lead tetraacetate) to the reaction mixture in benzene,[139,140,148] appears to lead to optimal yields of cyclic ethers. In many cases the LTA oxidation does not proceed to completion, whereby the recovered alcohol and its acetate can be isolated in variable amounts.

The photolytic LTA oxidation of alcohols can be readily achieved at room temperature by uv irradiation (wavelengths above 300 nm) of the reaction mixture in benzene.[140,148,149] The yields of cyclic ethers (or β-fragmentation products when formed) are comparable to or even sometimes higher than those observed in the thermal reaction. The best results are obtained when a 1:2–3 molar ratio of alcohol to oxidant is used and when 3–4 molar equivalents of pyridine are present in the benzene solvent[149] (the role of the base being to shift the equilibrium towards alkoxylation of LTA by neutralizing acetic acid formed in the course of the reaction). Since the photolytic reaction is performed at room (or lower) temperature, it represents a particularly convenient synthetic method in those cases when the substrate or/and products are sensitive to heat.

The hypoiodite LTA oxidation of alcohols proceeds most efficiently in cyclohexane solution upon irradiation with light of a wavelength between 500 and 550 nm to induce decomposition of the O–I bond. Optimal yields are obtained when the molar ratios of substrate: I_2:LTA are about 1:1.2–1.8:5.

Oxidation of Alcohols by LTA to Tetrahydrofurans. Thermal Reaction.[5,135,137,227] In a 500-ml flask equipped with a sealed stirrer and reflux condenser are placed dry starting

alcohol (0.1 mol), at least 120–150 ml of dry benzene, lead tetraacetate (0.1 mol + 5%–10% excess; dried *in vacuo* over phosphorous pentoxide and potassium hydroxide), and calcium carbonate (0.1 mol + 10% excess, dried *in vacuo* over phosphorous pentoxide). It is not necessary for the oxidant to be completely dissolved; however, optimal yields of cyclic ethers are obtained when the reaction is carried out at higher dilution. The mixture is well stirred and heated to reflux; if at that point the reaction becomes vigorous, heating is interrupted until the mixture ceases to boil (usually requires a few minutes), and is resumed after the exothermic reaction has subsided. When the tetravalent lead has been completely consumed (negative starch–iodine test), refluxing is stopped and the mixture is allowed to cool to room temperature. If necessary, the reaction may be stopped before completion by addition of glycol or glycerol until the excess of lead tetraacetate has been destroyed.

The reaction mixture is treated with 100–200 ml of dry ether (in order to ensure complete precipitation of the lead and calcium salts) and allowed to stand for 1 h at 10–15°C. The solution is then decanted, 30–50 ml of benzene or ether added to the solid residue in the flask, and the mixture heated to reflux for 5 min. The mixture is cooled to room temperature and filtered, whereas the precipitate is returned to the flask and the extraction with warm ether or hot benzene repeated. (This extraction can also be carried out with a Soxhlet apparatus.) The combined organic filtrates are washed successively with saturated aqueous sodium hydrogen carbonate (until neutral) and saturated aqueous sodium chloride. After drying (anhydrous K_2CO_3 or $MgSO_4$) and removal of the solvents, the cyclic ethers are separated from other products by fractional distillation, gas chromatography, column chromatography, or occasionally by direct crystallization.

Photolytic Reaction.[149,227] In a cylindric irradiation vessel are placed the starting alcohol (0.02 mol), lead tetraacetate (0.04–0.06 mol), dry pyridine (0.06–0.08 mol), and dry benzene (200 ml). A high-pressure mercury lamp (Hanovia or Hanau Q 81, 70–80 W) in a water-cooled Pyrex jacket is inserted into the reaction vessel, and the magnetically stirred mixture is irradiated at room temperature until tetravalent lead disappears. The solid material (lead diacetate) is removed by filtration and thoroughly washed with warm ether or hot benzene. The combined filtrates are extracted with 1 N hydrochloric acid (in order to remove pyridine), and then washed successively with saturated aqueous solution of sodium hydrogen carbonate and sodium chloride. The extracts are dried (anhydrous K_2CO_3 or $MgSO_4$), the solvent removed by distillation (at atmospheric pressure or *in vacuo*), and the cyclic ethers and other products separated and isolated by appropriate methods. (For additional details see above procedure for the thermal LTA reaction.)

Hypoidite LTA Reaction. Oxidation of 5-Chloro-3β,6β-dihydroxy-5α-androstan-17-one 3-acetate.[281] A stirred suspension of LTA (90 g) and calcium carbonate (30 g) in 4 liters of cyclohexane is warmed to 80°C and then iodine (20 g) and 5-chloro-3β,6β-dihydroxy-5α-androstan-17-one-3-acetate (15 g) is added. This mixture is irradiated with a 500-W tungsten lamp at reflux. When the iodine color has almost disappeared (about 90 min) the mixture is cooled, filtered off, and the residue thoroughly washed with ether. The combined filtrates are washed with 10% aqueous sodium thiosulfate and water, dried, and evaporated under reduced pressure leaving a crystalline solid which gave 12.8 g (85%) of pure 5-chloro-3β-hydroxy-6β,19-oxido-5α-androstan-17-one 3-acetate (after recrystallization from ether–methanol).

Fragmentation of Alcohols by LTA to Acetoxy Compounds. Fragmentation of 19-Hydroxy Steroids.[268] A suspension of LTA (2 g) and calcium carbonate (2 g) in benzene (200 ml) is shortly heated under reflux. Upon cooling 19-hydroxyandrost-4-ene-3,17-dione (2 g) is added and the mixture heated under reflux with stirring for 14 h. The cooled reaction mixture is filtered through Celite, the residue washed with benzene, and the combined filtrates are washed successively with 5% aqueous potassium iodide, 10% sodium thiosulfate, and with water, dried, and evaporated under reduced pressure. The crude oily product (2.03 g) is then chromatographed on 60 g of neutral alumina. The combined benzene and benzene–ether (9:1) fractions gave 1.21 g (55.4%) of 10-acetoxy-19-nor-androst-4-ene-3,17-dione, m.p. 195–196°C (from acetone–petroleum ether).

Oxidation of Alcohols by LTA to Carbonyl Compounds (in Pyridine Solution).[140,152] The starting (primary or secondary) alcohol (0.02 mol) is dissolved in dry pyridine (20–40 ml) and stirred at room temperature. To this is added in portions 8.9 g (0.02 mol) of powdered lead tetraacetate. This mixture immediately turns deep red and becomes homogeneous within 30 min. After stirring for several hours, the color lightens and becomes pale yellow. At this point all of the lead tetraacetate is reduced to the diacetate, which precipitates upon addition of dry ether (20–40 ml) and cooling. The filtered organic solution is stripped of solvents by distillation and the carbonyl compound isolated by fractional distillation (if distillable) or by other usual procedures (upon treatment of the residue with ether, washing the ether extract with water, dilute mineral acid, and water, and evaporation of the solvent), depending on the physical properties of the products formed.

9.3. 1,2-Diols and Polyols

The LTA glycol cleavage is usually performed in acetic acid. The reaction is accelerated by addition of water or methanol.[284] It can also be efficiently performed in aprotic solvents, such as benzene, nitrobenzene, 1,2-dichloroethane, and 1,1,2,2-tetrachloroethane.[285] When 1,2-diols are unreactive in acetic acid, cleavage of the carbon–carbon bond can be catalyzed by the addition of acid[291] or base,[288] or the reaction can be carried out in a nucleophilic solvent, for example pyridine,[289] methanol,[290] or dimethyl sulfoxide.[337]

Oxidation of Indane-1,2-diol by LTA to 2-Formylphenylacetaldehyde.[338,339] To a solution of 4.5 g of indane-1,2-diol (30 mmol) in 200 ml of dry benzene, heated to 75°C, 13.4 g (31 mmol) of LTA is added over 5 min. The solution is then refluxed for 5 min, cooled, filtered, and the filtrate evaporated under reduced pressure. Ether (50 ml) is added, and the solution is extracted with water (20 ml). The organic layer is then washed with aqueous sodium hydrogen carbonate (2 × 20 ml), and water (3 × 15 ml), and dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure and the residue distilled to give 2.7 g (61%) of 2-formylphenylacetaldehyde, as colorless oil, b.p. 98°C/0.4 mm Hg.

Oxidation of D-*Glucose by LTA to Di-O-formyl-*D-*erithrose.*[309] D-Glucose (1.5 g, 8.3 mmol) dissolved in 3 ml of water is taken up in 150 ml of acetic acid. Lead tetraacetate (7.7 g, 17.4 mmol) is added to the rapidly stirred sugar solution over a period of 3–4 min. When the oxidant has dissolved, oxalic acid dihydrate (1.9 g) dissolved in acetic acid is added, and the suspension is stirred for an additional 30 min. The precipitate is filtered and washed with acetic acid and the filtrate is concentrated to a volume of a few milliliters. Ethyl acetate is added and the precipitate formed is triturated with several portions of ethyl acetate. The extracts are combined, filtered, and concentrated to a sirup, which is further purified twice by extraction into ethyl acetate, thus giving di-*O*-formyl-D-erythrose (1.3 g, 89%) as a clear, pale yellow oil, $[\alpha]_D^{25}$ +20°C. On hydrolysis with dilute acid the compound gives D-erythrose in 90% yield.

9.4. Phenols

The oxidations of phenols by LTA are carried out in acetic acid, benzene, chloroform, or ethyl acetate as solvents. An equimolar ratio of reactants or a slight excess of oxidant is usually used. Because of the reactivity of phenols towards LTA, the reactions are mostly performed at room temperature.

Oxidation of 2,4,6-Tri-t-butylphenol by LTA to 2-Acetoxy-2,4,6-tri-t-butylcyclohexa-3,5-dienone and 4-Acetoxy-2,4,6-tri-t-butylcyclohexa-2,5-dienone.[354] LTA (8.6 g) in 150 ml of benzene was added to 2,4,6-tri-*t*-butylphenol (5 g) in 50 ml of benzene, and the mixture was stirred overnight. It was then washed with water, dried, and the solvent evaporated under reduced pressure. The oily residue was chromatographed on alumina, and by elution with

light petroleum containing 10% of ether, it gave 2-acetoxy-2,4,6-tri-*t*-butylcyclohexa-3,5-dienone (60%) and 4-acetoxy-2,4,6-tri-*t*-butylcyclohexa-2,5-dienone (30%), in addition to a small amount of bis(2,4,6-tri-*t*-butylphenyloxy peroxide).

9.5. Carbonyl Compounds

α-Acetoxylation of carbonyl compounds with LTA, by using an equimolar ratio of reactants, is usually carried out in hot acetic acid or in boiling benzene. Acetoxylation is, in general, faster in acetic acid, but higher yields are obtained in benzene. Boron trifluoride strongly accelerates the LTA oxidation of carbonyl compounds.

Oxidation of Cyclohexanone by LTA to 2-Acetoxycyclohexanone.[371] A mixture of 19.6 g of cyclohexanone and 88.6 g of LTA in 150 ml of dry benzene is refluxed and stirred for 8 h, after which time the oxidant is completely consumed. The mixture is washed with water (4 × 50 ml) and the organic layer separated and dried over anhydrous $MgSO_4$. After removing the solvent, the residue is distilled under reduced pressure, to give unreacted cyclohexanone (3.6 g), boiling at 67–70°C/15 mm Hg, and 2-acetoxycyclohexanone (19 g, 59%), boiling at 123–126°C/16 mm Hg. Further distillation gave 1.1 g (2%) of 2,6-diacetoxycyclohexanone, b.p. 158–160°C/10 mm Hg.

9.6. Carboxylic Acids

There are many inert solvents, such as benzene, chlorobenzene, chloroform, dimethylformamide, tetrahydrofuran, acetonitrile, pyridine, dioxane, and dimethyl sulfoxide, which have been used in the decarboxylation of acids by LTA. In some cases, in order to retard hydrolysis and/or enhance solubility of LTA, a mixture of these solvents with acetic acid is recommended. Reactions are usually carried out in an inert atmosphere at elevated temperature (about 80°C) or at room temperature under uv irradiation conditions. LTA decarboxylations are accelerated by addition of pyridine, metal acetates (LiOAc or NaOAc), metal halides, and cupric salts, in the latter two cases products being specifically alkyl halides and alkenes, respectively. The presence of oxygen and phenols inhibits the decarboxylation reaction.

*Oxidation of 1-Carbomethoxy-2-*endo*-carbomethoxybicyclo[2.2.2]octane-5,6-*endo*-dicarboxylic Acid by LTA to Dimethyl Bicyclo[2.2.2]oct-5-ene-1,*exo*-2-dicarboxylate.*[430] To 83 ml of dry benzene, under nitrogen, 14.74 g (0.0471 mole) of 1-carbomethoxy-*2-endo*-carbomethoxybicyclo[2.2.2]octane-5,6-*endo*-dicarboxylic acid, 5.59 g (0.0707 mole) of dry pyridine, and 22 g (0.0471 mole) of LTA are added. The reaction mixture is heated to reflux with stirring, whereby the solid material dissolves with vigorous evolution of carbon dioxide. The mixture is refluxed for 2 h, during which time a white precipitate is formed. The solution is separated from the solid and washed with 30 ml of aqueous 2 *N* sodium carbonate, 40 ml of 2 *N* hydrochloric acid, and 10 ml of water. After drying over magnesium sulfate, benzene is removed by distillation and the residue is fractionated under reduced pressure to give 5.21 g (50%) of dimethyl bicyclo[2.2.2]oct-5-ene-1,*exo*-2-dicarboxylate, b.p. 86–87°C/0.26 mm Hg.

9.7. Nitrogen-Containing Compounds

Oxidation of n*-Heptylamine by LTA to* n*-Hexyl Cyanide.*[440] *n*-Heptylamine (11.5 g, 0.1 mole) was treated with 88.7 g (0.2 mole) of LTA in 200 ml of dry benzene, and the mixture stirred and refluxed until completion of the reaction (16 h). After cooling to room temperature, ether (100 ml) was added, the separated lead salts removed by filtration, and the solid washed with ether. The combined organic solutions were washed successively with

aqueous 3% HCl, aqueous 5% $NaHCO_3$, and water. After drying and evaporation of solvents, *n*-hexyl cyanide was distilled at 75–76°C/18 mm Hg, the yield being 6.9 g (62%).

Oxidation of Cyclohexanecarboxamide by LTA to N-Cyclohexylacetamide.[454b] Cyclohexanecarboxamide (1.5 g) and LTA (5.8 g) in 50 ml of acetic acid were stirred at 80–90°C until all of the lead(IV) salts had been consumed (18 h). The reaction mixture was then evaporated and the residue extracted with ethyl acetate. The organic extract was washed with water and with aqueous Na_2CO_3, dried, and stripped of solvent. The solid residue was recrystallized from hexane to give 1.3 g (78%) of pure *N*-cyclohexylacetamide.

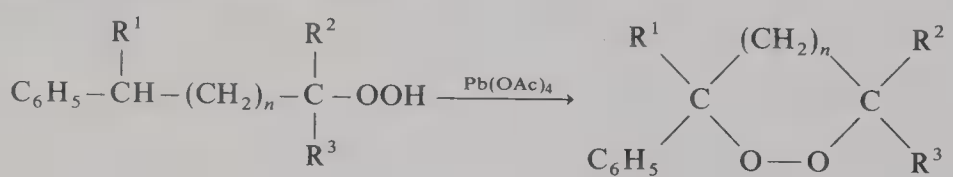
Oxidation of Cyclohexanone Oxime by LTA to gem*-Nitrosoacetoxyclohexane.*[461] To a stirred suspension of 11.1 g of LTA in 150 ml of ether, cooled to 0–5°C, 2.82 g (0.025 mole) of cyclohexanone oxime in 100 ml of ether is added. The mixture is stirred for another 2 h, and then water is added and the organic layer successively washed with water, aqueous $NaHCO_3$, and water, and dried over anhydrous $MgSO_4$. Ether is removed by distillation under reduced pressure and the blue oily residue is fractionated to give *gem*-nitroso-acetoxycyclohexane in 93% yield (3.9 g), b.p. 62–78°C/5 mm Hg.

Oxidation of Acetone Phenylhydrazone by LTA to 2-Acetoxy-2-phenylazopropane.[476] A solution of 14.8 g (0.1 mole) of acetone phenylhydrazone in 25 ml of methylene chloride is added, in the course of 15 min, to a stirred solution of 49 g (0.11 mole) of LTA in 200 ml of methylene chloride. During the addition of hydrazone, the slightly exothermic reaction is maintained at 0–10°C (ice bath), and the mixture is then warmed to room temperature and stirred for another 15 min. It is treated with 200 ml of water (with stirring), the formed lead dioxide is removed by filtration, and the methylene chloride layer is separated and washed successively with water and aqueous $NaHCO_3$. After drying over anhydrous Na_2SO_4, the solvent is removed under reduced pressure and the residue distilled to give 17 g (84%) of 2-acetoxy-2-phenylazopropane, b.p. 89°C/1 mm Hg.

10. ADDENDUM

10.1. Hydroperoxides

It has recently been reported that, similarly to alcohols, phenyl-containing hydroperoxides can also undergo cyclization when treated with lead tetraacetate (in pentane or light petroleum), to give, depending on the position of the –OOH group, cyclic peroxides of the 1,2-dioxolane ($n=1$, five-membered ring), 1,2-dioxane ($n=2$, six-membered ring) and 1,2-dioxepane type ($n=3$, seven-membered ring).[481] The yields of the cyclic products obtained are in general modest (10–27%) when $R^1=H$ or methyl, but increase considerably (amounting to 45–76%) when $R^1=$ phenyl.



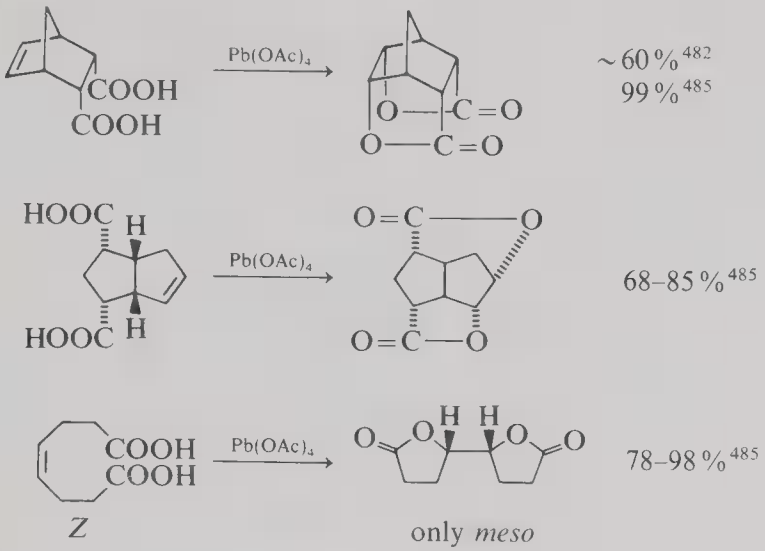
$R^1 = H, CH_3, C_6H_5$
$R^2 = CH_3, C_6H_5$
$R^3 = CH_3$, alkyl, C_6H_5

$n=1$, 15–76%
$n=2$, 15–45%
$n=3$, 10–14%

10.2. Olefinic Dicarboxylic Acids

When γ- or δ-unsaturated dicarboxylic acids (with suitable steric relationship between the carboxyl groups and the olefinic bond) are treated with LTA, they are not decarboxylated but undergo intramolecular (usually *cis*) addition of the two carboxylic oxygens to the double bond, with formation of the corresponding *bis*-lactones.[482–485] The yields obtained in

this valuable synthetic method are particularly good (up to 99%) when the reactions are performed in chloroform (with the free acid) or in acetonitrile (with the free diacid or, better, with the corresponding tetra-*n*-butylammonium salt).[484,485]



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15

BISMUTH-SALT OXIDATIONS

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1. INTRODUCTION

Compounds of bismuth were first proposed as useful oxidants for organic synthesis by Rigby[1–3] in 1949. Both the pentavalent and the trivalent states of bismuth were found to display oxidizing power. Bismuth(V) in the form of sodium bismuthate is an oxidant analogous to lead tetraacetate, being fairly specific for the fission of 1,2-diols. During the study of sodium bismuthate it was discovered that bismuth(III) salts can oxidize α-hydroxyketones to the corresponding diketone.[3] Following the discovery, bismuth trioxide was developed as a highly specific reagent for this purpose. The reduction of bismuth trioxide in this reaction leads to the formation of metallic bismuth. Neither sodium bismuthate nor bismuth trioxide has been used extensively in the years that followed their introduction. Both the reagents are heterogeneous oxidants and are normally employed in a medium of acetic acid. The rather harsh reaction conditions and uncertainty about the composition of commercial sodium bismuthate are probable reasons for the relative neglect of the reagents. The yields are generally good and separation of the products from the used reagent is easy in most cases. Sodium bismuthate was adopted for the direct oxidation and analysis of corticosteroids present in urine, tolerance of the reagent to water being essential in this application (in contrast to lead tetraacetate).[4]

A new class of bismuth oxidant was described by Barton in 1978, based on organobismuth(V).[5,6] These reagents are derivatives of triphenylbismuth dichloride. Unlike the earlier bismuth reagents, the organobismuth materials are used under very mild conditions of temperature and pH. These oxidants are useful for the conversion of alcohols, including allylic alcohols, to the corresponding carbonyl compound. Oxidation of the hydroxyl group takes place selectively in the presence of a variety of other functional groups, suggesting that these reagents will be of value in organic synthesis.

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2. SODIUM BISMUTHATE OXIDATIONS

2.1. Mechanism and Scope

Sodium bismuthate was investigated by Rigby[1,2] as an alternative to periodate and lead tetraacetate for 1,2-diol oxidative cleavage reactions. The reagent, an insoluble powder, is used as a suspension in aqueous or organic solvents, normally acidified with acetic or phosphoric acid. Sodium bismuthate ($NaBiO_3$) is reduced to a trivalent bismuth salt. Sodium bismuthate itself is a material of rather ill-defined composition. One analysis suggests that the commercial product is in fact a mixture of bismuth pentoxide, sodium carbonate, and sodium peroxide.[7] The color and reactivity of commercial samples are somewhat variable.[8] 1,2-diols are rapidly cleaved to the corresponding carbonyl compounds by sodium bismuthate at moderate temperatures. Like lead tetraacetate but unlike periodate, sodium bismuthate also cleaves α-hydroxycarboxylic acids and some α-hydroxyketones. The cleavage reactions of sodium bismuthate are shown, in general form, by Equations (1)–(3).

$$R_1R_2C(OH)-C(OH)R_3R_4 \xrightarrow{NaBiO_3} R_1R_2CO + R_3R_4CO \quad (1)$$

$$R_1R_2C(OH)-CO_2H \xrightarrow{NaBiO_3} R_1R_2CO + CO_2 \quad (2)$$

$$R_1CO-CH(OH)R_2 \xrightarrow{NaBiO_3} R_1CO_2H + R_2CHO \quad (3)$$

(R = H or alkyl)

The specificity of sodium bismuthate for 1,2-diol and related cleavage reactions is comparable to that of periodate and lead tetraacetate. Aldehydic products of bismuthate cleavage reactions are not oxidized further. Methanol and ethanol are oxidized only very slowly and may be used as solvents for the reaction. Sodium bismuthate is sometimes preferred to lead tetraacetate since anhydrous conditions are not required for its use. The diol fission reactions of sodium bismuthate are carried out with an excess of acetic or phosphoric acid. When acetic acid is used, a reddish brown suspension, assumed to be bismuth pentoxide,[2] is formed initially and gradually disappears as the oxidation proceeds, leaving a solution of bismuth triacetate. When the reagent is used in combination with phosphoric acid an orange-yellow suspension of unknown composition forms initially. As the oxidation takes place, this gives way to a white precipitate of bismuth triphosphate. It has been proposed that the mechanism of 1,2-diol fission by sodium bismuthate involves an intermediate bismuthate di-ester,[2] although no difference was observed between the rates of reaction of *cis* and *trans* cyclohexane-1,2-diols.

Various other oxidation reactions of sodium bismuthate have been studied in addition to 1,2-diol and related fissions. The reagent has been investigated, although not used widely, for the oxidation of phenols. These reactions are interesting since the nature of the products is dependent upon the solvent used and particularly on the presence or absence of acid. When sodium bismuthate is employed as a suspension in a nonpolar solvent, radical coupling products, typical of one-electron oxidation, predominate.[9] However, sodium bismuthate oxidation of phenols carried out in a medium containing acetic acid normally yields two-electron oxidation products. The action of sodium bismuthate in acetic acid towards phenols resembles that of lead tetraacetate.

The reaction in acetic acid is a two-stage process whereby the initially formed radicals are further oxidized to the carbonium ion before extensive coupling can occur.[10] Thus the products of phenolic oxidation by sodium bismuthate in acetic acid are typically of quinonoid or cyclohexadienone structure. Oxidative dealkylation of *ortho* and *para* alkoxyphenols by sodium bismuthate may occur in acetic acid.[11,12] Similarly sodium bismuthate oxidation may result in the debromination of bromophenols.[12] Products of this

nature from the oxidation of substituted phenols are typical of the action of strong oxidants. The mechanism involves nucleophilic attack by acetate ion on the carbonium ion intermediate.[11]

One further class of reactions performed by sodium bismuthate is the oxidation of olefins.[13,14] Olefin oxidation by bismuthate is slow compared with the rate of diol cleavage. The products of olefin oxidation are the corresponding diacetoxy derivatives.[13] The products of this reaction have also been isolated in partially hydrolyzed form as the hydroxy acetates.[14] The reaction with olefins proceeds via the formation of a bismuth–carbon bond. Heterolysis of this bond, in the sense of carbonium ion formation, results in the observed products.[14] Although the yields generally obtained are low to moderate, the mild reaction conditions and the heterolysis of the organometallic bond may offer some advantage over the more traditional oxymetallation reagents, lead tetraacetate and thallium triacetate.[14]

2.2. Experimental Considerations and Procedures

2.2.1. Availability of the Reagent

Sodium bismuthate is available in technical, reagent, and analytical grades. The analytical grade has been found to offer definite practical advantages owing to its finely powdered physical state.[2] Even analytical grade samples of sodium bismuthate have an oxidizing capacity which normally is only equivalent to about 85% of pure $NaBiO_3$. The oxidizing power of a particular sample may be determined using the following procedure.[2] A sample of the reagent (0.45 g) is stirred with ferrous sulfate solution (25 ml, 0.125 *N* in 4 *N* sulfuric acid) until it is dissolved. Phosphoric acid (5–10 ml, 85%) is added and the solution is back-titrated with potassium dichromate (0.1 *N*) using a diphenylamine indicator.

2.2.2. 1,2-Diol and Related Oxidations

Two general procedures have been developed for the cleavage of 1,2-diols and related oxidations by sodium bismuthate. The reaction may be carried out in aqueous or 100% acetic acid at or slightly above room temperature. In this case a clear, colorless solution remains when reaction is complete. Bismuth may conveniently be removed from the solution by precipitation as the phosphate. Alternatively the diol, dissolved in water or aqueous dioxan, is stirred with sodium bismuthate and a slight molar excess of phosphoric acid is slowly added. When this procedure is followed a bright yellow suspension, formed at first, is finally replaced by a white precipitate of bismuth triphosphate which may be removed by filtration. In either case, one equivalent or slightly more of bismuth reagent (based on determination of the sample) may be used. Complete reaction may take from a few minutes to several hours. The phosphoric acid procedure is preferable for the cleavage of α-hydroxyketones since this prevents a competing oxidation by trivalent bismuth at elevated temperatures, which leads to formation of the diketone. Some heat may be generated during the more rapid oxidations of sodium bismuthate and cooling may be necessary. The following example represents a typical oxidation procedure using sodium bismuthate and phosphoric acid.[2] Ethyl tartrate (51.5 g, 0.25 mole) was stirred with water (120 ml) and sodium bismuthate (0.25 mole). Phosphoric acid (100 ml of 68%) was added over a period of 30 min while the temperature was maintained at 35–40°C. The reaction mixture was maintained at this temperature for a further 30 min. The precipitate of bismuth phosphate was filtered off. The filtrate was shaken with calcium carbonate (30 g) and refiltered. Ethyl glyoxylate was separated from the aqueous solution as an azeotropic mixture with ethanol in 51% yield by reduced pressure distillation after the addition of benzene and ethanol. The yield in this preparative scale example is relatively low. Somewhat higher yields were reported from a series of smaller-scale reactions (0.01 moles) in which the aldehydic product was isolated from the reaction mixture as a crystalline derivative. Examples of these reactions are listed in Table I.

TABLE I. 1,2-Diol Cleavage and Related Reactions of Sodium Bismuthate[a]

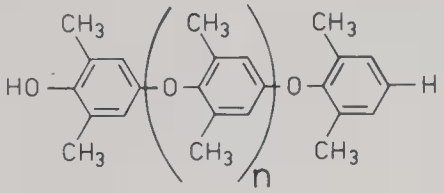
Substrate	Time (min)	Temperature (°C)	Product	Yield (%)
Diols				
Ethane-1,2-diol	45	20	Formaldehyde	90[b]
cis- or *trans*-Cyclohexane-1,2-diol	150	30–40	Hexane-1,6-dial	70[c]
trans-1,2-Dihydroxy-1,2,3,4-tetrahydronaphthalene	360	40	*o*-(2-Formylethyl)-benzaldehyde	77[d]
2,3-Dimethylbutane-2,3-diol	180	30–40	Acetone	99[d]
Hydrobenzoin	330	40–50	Benzaldehyde	75[e]
α-Hydroxy acids				
Mandelic acid	210	20	Benzaldehyde	64[e]
2-Methyl-2-hydroxypropionic acid	30	20	Acetone	82[d]
Diphenylglycolic acid	90	50–60	Benzophenone	99
Lactic acid	—	—	Acetaldehyde	72[d]
Hydroxy ketone				
Benzoin	120	40–50	Benzaldehyde	79[e]

[a] Reference 2.
[b] Isolated as the 4-nitrophenylhydrazone.
[c] Isolated as the oxime.
[d] Isolated as the 2,4-dinitrophenylhydrazone.
[e] Isolated as the phenylhydrazone.

One application of the sodium bismuthate cleavage reactions which received considerable attention was the analytical determination of urinary corticosteroids.[4,15–18] The technique relied on the selective oxidative fission of the corticosteroid side chain. Analysis of the reaction products for 17-ketosteroids and formaldehyde was used to identify the corticosteroids originally present. A large excess of the reagent was used in these experiments. Sodium bismuthate was chosen for this purpose since, unlike periodate, it cleaves α-hydroxyacids and unlike lead tetraacetate it can be applied directly to urine samples. The types of steroid side chain which are susceptible to cleavage by sodium bismuthate are shown in Table II.

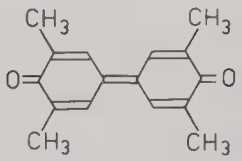
2.2.3. Oxidation of Phenols

Sodium bismuthate behaves as a heterogeneous one-electron oxidant for phenols when a nonpolar solvent such as benzene or cyclohexane is used. Either reflux or ambient temperature conditions may be employed. Several hours to one or two days may be required for completion of the reaction. Typical of this procedure is the oxidative polymerization of 2,6-xylenol[9] to the corresponding polyphenylene oxide (**1**). Sodium bismuthate (33.0 g, 0.118 mole) was added to a solution of 2,6-xylenol (4.1 g, 0.033 mole) in benzene (100 ml). The mixture was stirred for 2 h while boiling under reflux. After cooling, the residual sodium bismuthate was removed by filtration and washed with benzene. The combined benzene solutions were washed with dilute aqueous sodium hydroxide, dried, and evaporated to yield crude polymer. This material was purified by dissolving in chloroform (25 ml) and



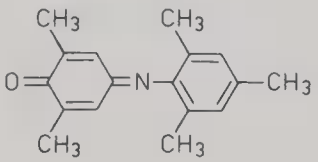
1

coagulating by pouring into methanol (200 ml). The coagulate was filtered off and dried to yield the polyphenylene oxide (**1**) (3.05 g, 74%). The "tail to tail" coupled product, 3,3′,5,5′-tetramethyldiphenoquinone (**2**) (0.047 g, 12%) was isolated from the supernatant liquor.

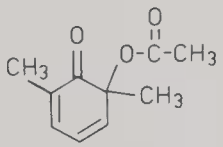


2

Polyphenylene oxides of molecular weights in the region of 20,000 were obtained using sodium bismuthate. This compares well with other heterogeneous oxidants such as activated manganese dioxide, although higher molecular weight polymers may be obtained using the homogeneous system, cuprous halide–pyridine–oxygen.[19] Sodium bismuthate has also been used for the oxidative depolymerization of a polyphenylene oxide oligomer (**1**) with 2,4,6-trimethylaniline,[20] resulting in the formation of the anil (**3**) in 87% yield.



3



4

TABLE II. Fission of Corticosteroid Side Chains by Sodium Bismuthate

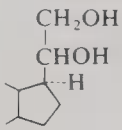
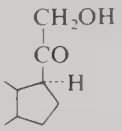
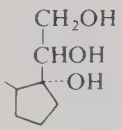
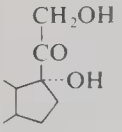
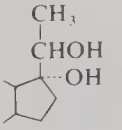
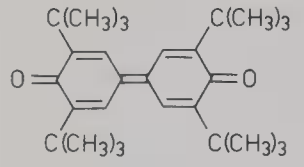
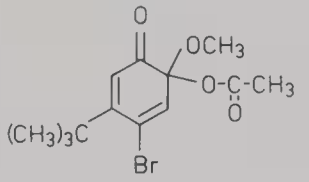
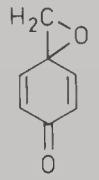
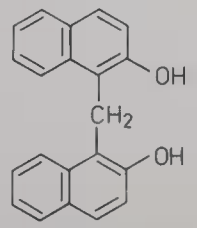
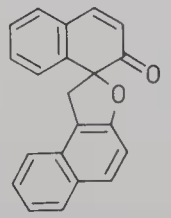
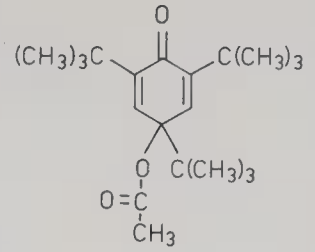
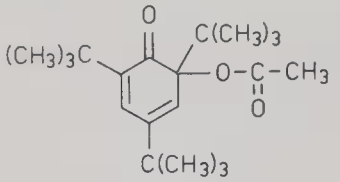
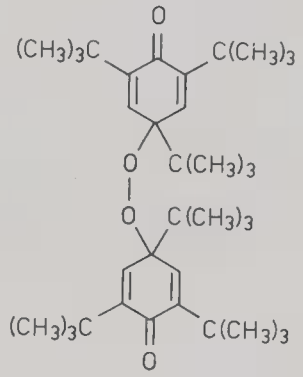
	⟶		+ HCHO
	⟶		+ HCHO
	⟶		+ HCHO
	⟶		+ HCHO + CO_2
	⟶		+ CH_3CHO

TABLE III. Oxidation of Phenols by Sodium Bismuthate

Phenol	Solvent	Time (min)	Temperature (°C)	Product	Yield (%)	Reference
2,6-Di-*t*-butylphenol	*a*	120	80	Compound **5** 	91	9
2-Methoxy-4-bromo-5-*t*-butylphenol	*b*	10	20	Compound **6** and 2-methoxy-5-*t*-butyl-1,4-benzoquinone 	65	12
4-Hydroxybenzyl alcohol	*c*	30	20	Compound **7** and 1,4-benzoquinone 	20 5	21
4-Hydroxy-3,5-dimethylbenzyl alcohol	*c*	30	20	2,6-Dimethyl-1,4-benzoquinone and 4-hydroxy-3,5-dimethyl benzaldehyde	43	22
Compound **8** 	*a*	180	20	Compound **9** 	95	23

2,4,6-Tri-*t*-butylphenol	*b*	4320	20	Compound **10**		62	10
				and compound **11**		22	
				and compound **12**		5	

[a] Benzene.
[b] Acetic acid.
[c] Acetic acid–water (4:1).

TABLE IV. Oxidation of Olefins by Sodium Bismuthate[a]

Olefin	Time (days)	Product	Yield (%)
2-Phenylpropene	3	1-acetoxy-2-phenylpropan-2-ol	39 (62)[c]
		and acetophenone	9
		and α-acetoxyacetophenone	1
1-Phenylcyclohexene	3	*cis*-2-acetoxy-1-phenylcyclohexanol	37
2,6-Dimethyloct-2-ene	7	2,6-dimethyl-3-acetoxyoctan-2-ol	21 (42)[c]

[a] Reference 14.
[b] All reactions were carried out in acetic acid at room temperature.
[c] The yield in parentheses is corrected for recovered starting material.

Oxidation of phenols by sodium bismuthate in the presence of acetic acid leads to products which are typical of two-electron oxidation. The change in the reactivity of the oxidant is illustrated by the following example, in which 2,6-xylenol is oxidized in acetic acid as solvent.[10] Sodium bismuthate (33 g, 0.118 mole) was added to a solution of 2,6-xylenol (4.1 g, 0.033 mole) in acetic acid (100 ml) and stirred at room temperature for three days. The residual solid was filtered off and washed with a small amount of acetic acid. The combined acetic acid solutions were diluted to 500 ml with water and extracted with ether. The extract was neutralized by washing with dilute sodium bicarbonate solution, dried, and evaporated. The residue was purified by chromatography (silica gel–chloroform) to yield 2-acetoxy-2,6-dimethylcyclohexa-3,5-dienone (**4**) (1.7 g, 38%). The residual solid from the reaction was washed with ether and treated with concentrated hydrochloric acid. A red solid remained, which was identified as **2** (0.63 g, 15%). Further examples of one- and two-electron oxidation of phenols are listed in Table III.

2.2.4. Oxidation of Olefins

Oxidation of olefins to the corresponding 1-hydroxy-2-acetoxy compounds using sodium bismuthate has been carried out at room temperature in acetic acid.[14] Thus, α-methylstyrene (5.92 g, 0.05 mole), acetic acid (100 ml), and sodium bismuthate (16.62 g, 0.05 mole) were stirred at room temperature for three days. The mixture was poured into ether and washed first with water and then with sodium bicarbonate solution. The ether solution was dried and evaporated. The crude product was purified by chromatography on silica gel to yield 1-acetoxy-2-phenyl-2-propanol (39%). The yield is not improved by the use of excess reagent. It is probable that the hydroxy acetate isolated is formed by hydrolysis during work-up of an initially formed diacetoxy compound.

The observation of diacetoxy derivatives as the products of olefin oxidation by sodium bismuthate appears in an earlier report.[13] It is also suggested that competing reactions leading to carbonyl compounds may be minimized by using chloroacetic acid as solvent instead of acetic acid.[13] The products and yield of sodium bismuthate oxidation of various olefins are listed in Table IV.

3. BISMUTH TRIOXIDE OXIDATIONS

3.1. Mechanism and Scope

Trivalent bismuth in the form of bismuth trioxide is a reagent specific for the oxidation of α-hydroxyketones to the corresponding diketone.[3,24–28] The oxidation is performed in

acetic acid at about 100°C and the reagent is reduced to metallic bismuth. Bismuth trioxide is soluble in acetic acid under these conditions, forming bismuth triacetate, which appears to be the active oxidizing agent. Bismuth triacetate may be used directly but offers no particular advantage. Oxidation of simple α-hydroxyketones is rapid, but more highly substituted compounds may require several days for complete reaction. Reaction of bismuth trioxide with α-hydroxy ketones is confined to examples possessing an α-hydrogen atom. It has been suggested that reaction occurs via formation of an enediol. An intermediate species possessing C–O–Bi linkages has been proposed.[3] The observation that bismuth trioxide oxidations are retarded when carried out under nitrogen remains unexplained.[24] Bismuth triacetate may act as an acetylating agent towards alcohols and amines [Eq. (4)].[29] This reaction occurs only at high temperature, however, (about 200°C—no solvent) and would not normally interfere with the oxidation of α-hydroxyketones.

$$Bi(O_2CCH_3)_3 + ROH \longrightarrow CH_3CO_2R + BiO(O_2CCH_3)_3 + CH_3CO_2H \qquad (4)$$

3.2. Experimental Considerations and Procedures

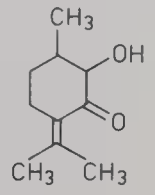
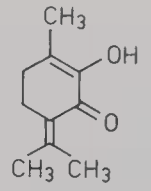
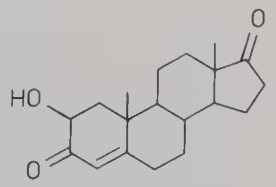
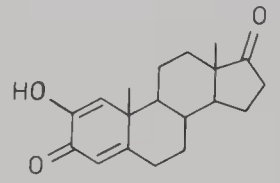
Reagent grade bismuth trioxide, an amorphous yellow powder, is suitable for the oxidation of α-hydroxyketones. In a typical procedure the α-hydroxyketone, dissolved in acetic acid, is heated on a steam bath with 1.2 equivalents of bismuth trioxide. During the course of the reaction, black metallic bismuth is deposited. Unhindered substrates are normally oxidized in less than an hour under these conditions. The reaction mixture is filtered to remove metallic bismuth and excess reagent. Water is added to the reaction mixture and the product is extracted into ether. Yields of greater than 90% may be obtained. The use of a mixture of acetic acid and 2-ethoxyethanol (1:3) as solvent instead of pure acetic acid is reported[3] to give slightly higher yields and purer products, although the reaction takes longer in the mixed solvent. Examples of α-hydroxyketone oxidations by bismuth trioxide are given in Table V. Sugars are not oxidized by the reagent, and neither is ascorbic acid.[3] The presence in the reaction mixture of certain polyhydroxy compounds such as glucose and catechol inhibits the oxidation of α-hydroxyketones owing to the formation of bismuth containing compounds with these materials.[3]

4. ORGANOBISMUTH REAGENTS

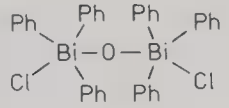
4.1. Mechanism and Scope

A new class of bismuth oxidants has recently been developed, based on triphenyl derivatives of pentavalent bismuth.[5,6,30] The reagent μ-oxo-bis(chlorotriphenylbismuth) (**17**) is a stable white solid, soluble in organic solvents. This oxidant converts alcohols to the corresponding carbonyl compound in high yield. In contrast to the earlier bismuth reagents, this reaction proceeds under very mild conditions of temperature and pH. The alcohol to be oxidized is added to a solution of the reagent **17** in dichloromethane and stirred with solid potassium carbonate or bicarbonate at or slightly above room temperature. The presence of carbonate in the reaction mixture is essential for rapid and complete oxidation. The function of the carbonate is more complicated than simply neutralizing acid formed in the reaction since soluble organic bases do not have the same effect. μ-Oxo-bis(chlorotriphenylbismuth) and carbonate is suitable for the oxidation of saturated primary and secondary alcohols as well as allylic and benzylic alcohols. 1,2-diols are smoothly cleaved by the reagent to give the two carbonyl fragments. Aldehydes formed by oxidations with the reagent **17** undergo no further reaction.

TABLE V. Oxidation of α-Hydroxyketones to Diketones by Bismuth Trioxide

Hydroxyketone	Time (min)	Temperature (°C)	Product	Yield (%)	Reference
Benzoin	60[a]	104	Benzil	95	3
Anisoin	60[b]	105	Anisil	95	3
Piperoin	75[c]	104	Piperil	97	3
Furoin	45[c]	100	Furil	92	3
Butyroin	15[d]	100	Octane-4,5-dione	64	3
2-Hydroxy-pulegone (**13**) 	10[d]	110	Diosphenolene (**14**) 	94[e]	26
2α-Hydroxyandrosta-4-ene-3,17-dione (**15**) 	60[d]	100	2-Hydroxyandrosta-1,4-diene-3,17-dione (**16**) 	68	27

[a] Solvent = acetic acid: 2-ethoxyethanol (2:3).
[b] Solvent = acetic acid: 2-ethoxyethanol (1:2).
[c] Solvent = acetic acid: 2-ethoxyethanol (1:3).
[d] Solvent = acetic acid.
[e] Crude yield.



17

In the absence of any oxidizable substrate either triphenylbismuth dichloride or the reagent **17** when stirred with potassium carbonate in dichloromethane forms an insoluble white compound, triphenylbismuth carbonate. Triphenylbismuth carbonate is itself useful as a heterogeneous oxidant for the oxidation of allylic and benzylic alcohols and for the oxidative fission of 1,2-diols.[6,30] Saturated alcohols are slowly oxidized by triphenylbismuth carbonate, although the reagent is less active in this respect than the mixture of reagent **17** and solid potassium carbonate. The selectivity of triphenyl bismuth carbonate is such that on treatment of an equimolar mixture of cholestan-3β-ol and cholest-4-en-3β-ol with the reagent only the allylic alcohol was oxidized and the saturated alcohol was recovered.[6,30] Similarly only cholest-4-en-3β-ol was oxidized, despite the presence of an equimolar quantity of thiophenol. In the absence of any competing alcohol, thiols are oxidized by triphenylbismuth carbonate to the corresponding disulfide.[6,30] The thiocarbonyl group in xanthates, dialkylamino thionocarbamates, and di-*t*-butyl thioketone is unaffected by the reagent. Aniline, dimethylaniline, pyrollidine, indole, and 3-pyrollidino-cholesta-3,5-diene are likewise inert under the standard reaction conditions.

The mechanism of oxidation by reagent **17** and triphenylbismuth carbonate is believed to involve the formation of an intermediate of structure **18** (Fig. 1). The preferential oxidation of the more hindered 6β-hydroxyl group of cholestan-3β-6β-diol suggests that it is the breakdown rather than the formation of this intermediate which is the rate-determining step.[5,30] Studies with deuterium-labeled substrates have shown that two competing pathways, shown in Fig. 1, exist for the breakdown of intermediate **18**. The cleavage of a phenyl to bismuth bond (Fig. 1, pathway B) is of significance since it can lead to a competing side reaction in the oxidation of certain alcohols. For example, during the oxidation of quinine (**19**) (Fig. 2) by triphenylbismuth carbonate the expected product, quininone **20**, reacts further with the bismuth reagent to form a derivative **22** which has been arylated in the position α to the carbonyl group.[30,31] It has been proposed that the arylation reaction occurs via the formation of a bismuth enolate (Fig. 2, structure 21) intermediate. This side reaction might therefore be expected to occur during the oxidation of any alcohol, the expected

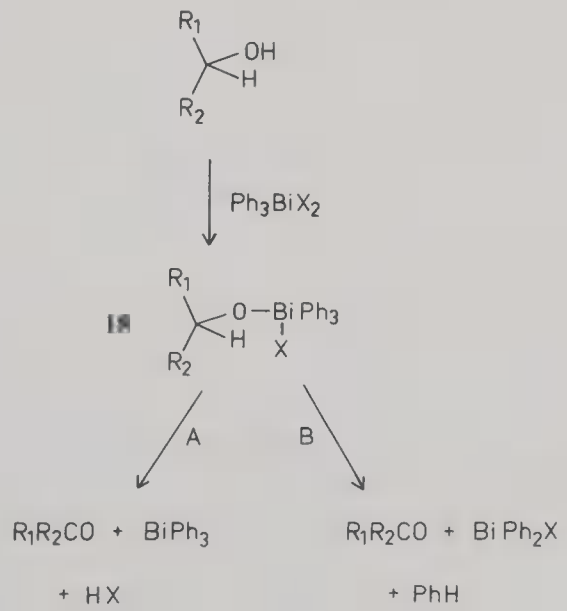


FIGURE 1. Mechanism of oxidation of alcohol by organobismuth reagent.

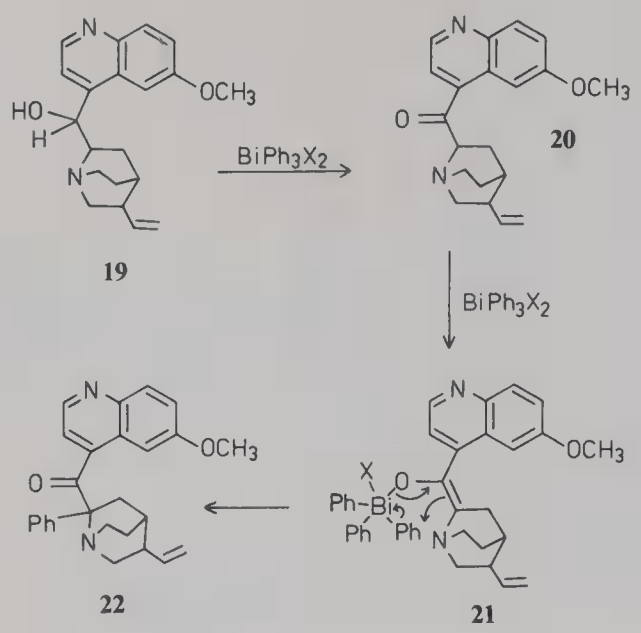


FIGURE 2. Oxidation and phenylation of quinine by organobismuth reagent.

product of which is a readily enolizable ketone. This competing arylation reaction, which is an inconvenience during the oxidation of alcohols has led to the development of triphenylbismuth carbonate as a reagent for the phenylation of ketones.[31,32] For example, the reaction of ethyl acetoacetate with triphenylbismuth carbonate gives ethyl α-phenylacetoacetate in 59% yield.[31] Ketones in the form of the corresponding potassium enolate are likewise phenylated by triphenylbismuth carbonate. Thus, the sequential treatment of cholestan-3-one with potassium hydride and the reagent gave 2,2-diphenylcholestan-3-one in 64% yield.[31] Phenols are also phenylated in the 2 position using triphenylbismuth carbonate.[31]

In their use as oxidants for alcohols, the organobismuth reagents do not generally suffer from the problems due to electrophilicity and one-electron transfer which are sometimes associated with chromium-based reagents. For instance, the oxidation of *t*-butylphenylmethanol by chromium trioxide gives rise to an intermediate chromate ester which undergoes electron transfer, elimination of the *t*-butyl radical, and formation of benzaldehyde.[33] In contrast, the oxidation with triphenylbismuth carbonate proceeds cleanly to give the corresponding ketone.[30]

4.2. Experimental Considerations and Procedures

4.2.1. Preparation of the Reagents

Both μ-oxo-bis(chlorotriphenylbismuth) (**17**) and triphenylbismuth carbonate are prepared from triphenylbismuth dichloride. Triphenylbismuth dichloride, in turn, is prepared by the action of chlorine on triphenylbismuth. Triphenylbismuth is prepared by the action of phenylmagnesium bromide on commercially available bismuth trichloride.

A convenient preparation of triphenylbismuth is as follows (adapted from the preparation of triphenylantimony[34]). A suspension of bismuth trichloride (20 g, 0.063 mole) in dry ether (40 ml) is added dropwise to a stirred solution of phenyl magnesium bromide, prepared from magnesium (5.25 g, 0.216 mole) and bromobenzene (34 g, 0.216 mole) in dry ether (110 ml) using the usual Grignard reaction procedure. After complete addition the mixture is heated on a steam bath for 1 h. The resulting suspension is poured into ice water (200 ml) and filtered. The ether layer is separated, the aqueous layer is extracted with ether

(2 × 30 ml), and the ether solutions are combined. The combined ether solutions are washed with saturated brine (2 × 60 ml) and evaporated to dryness. The oily residue is crystallized from hexane to yield triphenylbismuth (20.5 g, 74%, melting point 77°C).

Triphenylbismuth dichloride is prepared according to the following procedure from triphenylbismuth.[35] Chlorine gas is bubbled into a solution of triphenylbismuth (15 g, 0.034 mole) in chloroform (90 ml) maintained at 0°C. When an excess of chlorine is apparent (solution turns slightly yellow) the solution is diluted with methanol (50 ml) and evaporated down to about 40 ml. The white crystals which separate are filtered off and dried *in vacuo* to yield triphenylbismuth dichloride (14.5 g, 83%, melting point 140–150°C).

μ-Oxo-bis(chlorotriphenylbismuth) is prepared as follows, from triphenylbismuth dichloride.[36] Triphenylbismuth dichloride (14.3 g, 0.028 mole) is dissolved in acetone (50 ml) and treated with a solution of sodium hydroxide (1.12 g, 0.028 mole) in methanol (50 ml). The mixture is stirred for 2 h and then filtered. The filtrate is evaporated to one third of its former volume and diluted with water (50 ml). The resulting suspension is allowed to stand at 4°C for 30 min and then filtered; the white powder, thus obtained, is dried *in vacuo* to yield μ-oxo-bis(chlorotriphenylbismuth) (12.5 g, 92%, melting point 148–154°C, with decomposition).

Triphenylbismuth carbonate is prepared by the action of potassium carbonate on triphenylbismuth dichloride using the following procedure.[30] Potassium carbonate (3.6 g) in water (20 ml) is added to a well-stirred solution of triphenylbismuth dichloride (13.0 g, 0.025 mole) in acetone (100 ml). After five minutes, the precipitated triphenylbismuth carbonate is filtered, washed with acetone, and dried (yield 12.7 g, 100%, decomposes 155°C)

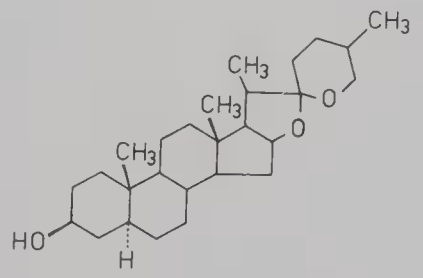
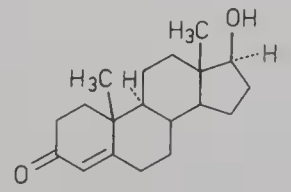
4.2.2. Oxidation with Organobismuth Reagents

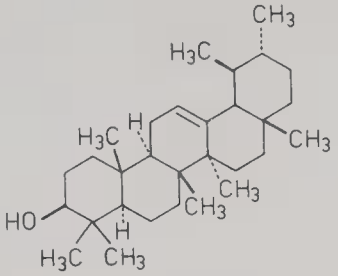
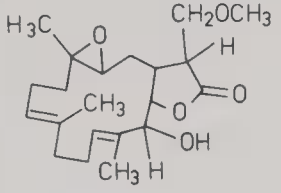
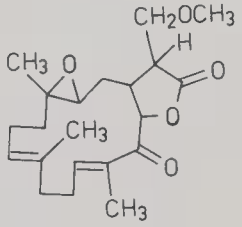
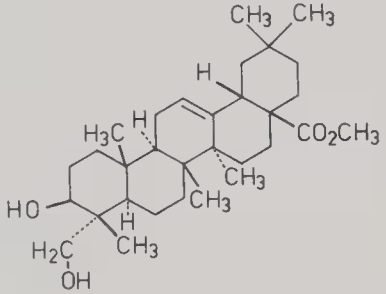
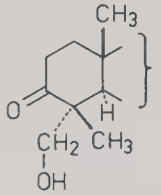
Both μ-oxo-bis(chlorotriphenylbismuth) (**17**) and triphenylbismuth carbonate suffer, as practical oxidants for preparative scale work, from the disadvantage that the principal by-product, triphenyl bismuth, is very soluble in organic solvents. In consequence, the reaction products must normally be isolated by chromatography in order to separate the triphenyl bismuth. In practice, this separation is usually straightforward since triphenylbismuth is very nonpolar and runs well in advance of the desired oxidation products on silica gel or alumina chromatography. Alternatively the triphenylbismuth by-product may be destroyed by adding acetic acid to the reaction mixture and heating on a steam bath for 30 min. The reaction mixture is then diluted with water, filtered, and extracted with ether. The ether layer is then washed with sodium bicarbonate solution, dried, and evaporated to yield crude product, largely free from bismuth compounds. Clearly this method of work-up negates the mild conditions of the oxidation reaction itself and would not normally be used.

μ-Oxo-bis(chlorophenylbismuth) is soluble in dichloromethane, chloroform, tetrahydrofuran, and hot benzene. In a typical procedure the reagent **17** (0.2 mole) in chloroform or dichloromethane and the alcohol (0.25 mole) to be oxidized are stirred together with an excess of potassium carbonate or sodium bicarbonate (200 mg) until the reaction is complete by aliquot monitoring. It is preferable to use reflux temperatures for the oxidation of saturated alcohols as the reaction may otherwise be inconveniently slow. In exceptional cases of very slow oxidation it may be necessary to add a greater excess of the reagent to allow for the slow decomposition of the reagent which occurs under the reaction conditions. When the reaction is complete, the reaction mixture is filtered and evaporated to dryness. The residual solid material is chromatographed on a silica gel column and eluted with 20% ether in hexane until the eluent is free from triphenylbismuth. The percentage of ether in the eluting solvent is increased, if necessary, to collect the product. Reaction conditions and yields for the oxidation of a variety of alcohols with μ-oxo-bis(chlorotriphenylbismuth) are given in Table VI.

A similar general procedure is used for oxidations with triphenylbismuth carbonate. The reagent (1.1–2 equivalents) is stirred with a solution of the substrate (1 equivalent) in dichloromethane. As the reaction proceeds the solution becomes homogeneous. When all

TABLE VI. Oxidation of Alcohols by μ-Oxo-bis(chlorotriphenylbismuth)

Alcohol	Time (h)	Conditions	Product	Yield (%)	Reference
Primary					
Pentan-1-ol	6	*a*	Pentanal	79[b]	5, 30
Secondary					
Cholestanol	30	*c*	Cholestanone	75	5, 30
Tigogenin (**23**) 	4	*a*	Tigogenone	80	5, 30
Testosterone (**24**) 	4	*a*	Androst-4-ene-3,17-dione	88	5, 30

α-Amyrin (**25**)		15	*c*	α-Amyrone		86	5, 30
Compound (**26**)		24	*c*	Compound (**27**)		59	37
Methyl hederagenin (**28**)		24	*c*	Methyl hederagonate (**29**)		36	5, 30

[a] Reaction in refluxing dichloromethane, stirred with solid sodium bicarbonate.
[b] Isolated as the 2,4-dinitrophenylhydrazone derivative.
[c] Reaction in dichloromethane at room temperature, stirred with solid potassium carbonate.

Table continued

TABLE VI. *Continued*

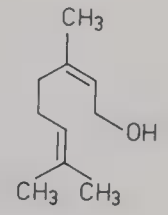
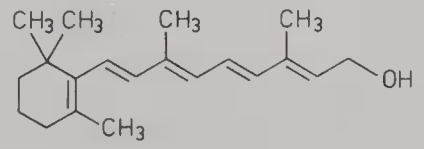
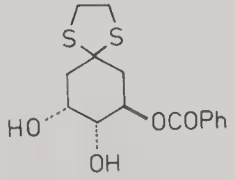
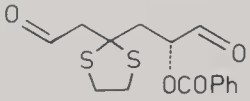
Alcohol	Time (h)	Conditions	Product	Yield (%)	Reference
Benzyl					
Benzyl alcohol	15	*c*	Benzaldehyde	82[b]	5, 30
p-Nitrobenzyl alcohol	1	*a*	*p*-Nitrobenzaldehyde	87[b]	5, 30
Anisyl alcohol	1	*a*	Anisaldehyde	75[b]	5, 30
Allylic					
Cinnamyl alcohol	15	*c*	Cinnamaldehyde	83[b]	5, 30
Geraniol (**30**) 	15	*c*	Geranial	95[b]	5, 30
Vitamin A alcohol (**31**) 	15	*c*	Vitamin A aldehyde	68[b]	5, 30
Crotyl alcohol	5	*a*	Crotonaldehyde	76[b]	5, 30
Cholest-1-en-3β-ol	6	*c*	Cholest-1-en-3-one	85	5, 30
Cholest-4-en-3β-ol	6	*c*	Cholest-4-en-3-one	89	5, 30
(-)-Carveol	6	*c*	Carvone	84[b]	5, 30
3-Methylbut-2-en-1-ol	2	*a*	3-Methylbut-2-enal	90[b]	5, 30
1,2-Diols					
meso-Hydrobenzoin	3	*c*	Benzaldehyde	80[b]	5, 30
1,2,5,6-Di-*O*-isopropylidene-D-mannitol	0.25	*a*	2,3-Isopropylidene-D-glyceraldehyde	76	5, 30

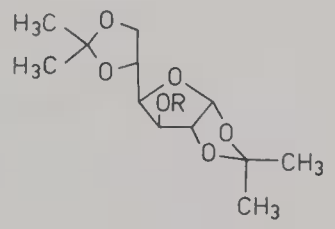
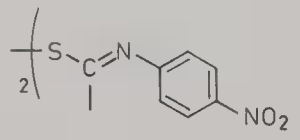
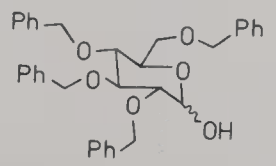
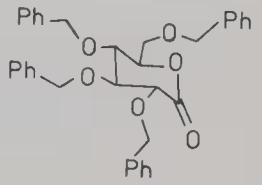
TABLE VII. Oxidation of Hydroxyl and Other Functional Groups by Triphenylbismuth Carbonate

Substrate	Time (h)	Temperature (°C)	Product	Yield (%)	Reference
Secondary alcohol					
t-Butylphenylmethanol	18	40	*t*-Butylphenylketone	90	6, 30
Allylic alcohols					
(-)-Carveol	1.5	40	Carvone	84	6, 30
Cholest-4-en-3β-ol	18	20	Cholest-4-en-3-one	97	6, 30
Geraniol	2.5	40	Geranial	95[a]	6, 30
Thiols					
Thiophenol	18	20	Diphenyldisulfide	70	6, 30
o-Thiocresol	3	20	Di-*o*-tolyldisulfide	90	6, 30
p-Thiocresol	3	20	Di-*p*-tolyldisulfide	89	6, 30
1,2-Diols					
cis-Cyclohexane-1,2-diol	2	40	Hexane-1,6-dial	100[a]	6, 30
meso-Hydrobenzoin	1.5	40	Benzaldehyde	97[a]	6, 30
1,2,5,6-Di-*O*-propylidene-D-mannitol	2	40	2,3-*O*-Isoropylidene-D-glyceraldehyde	89[a]	6, 30
Compound **32** 	—	—	Compound **33** 	*b*	38

[a] Isolated as the 2,4-dinitrophenylhydrazone derivative.
[b] Not isolated but reduced immediately to the corresponding diol with sodium borohydride (25% yield).

Table continued

TABLE VII. *Continued*

Substrate	Time (h)	Temperature (°C)	Product	Yield (%)	Reference
Miscellaneous					
Benzophenone hydrazone	5	20	Diphenyldiazomethane	97	6, 30
5-α-Cholestan-3-one oxime	15	20	5-α-Cholestan-3-one	60	6, 30
Hydrazobenzene	1.5	20	Azobenzene	90	6, 30
Phenylhydrazotriphenylmethane	4	20	Phenylazotriphenylmethane	89	6, 30
Compound **34** 	17	40	Compound **35** R = 	81	6, 30
Compound **36** 	4	40	Compound **37** 	89	6, 30
2,6-Dimethylphenol	—	—	Compound **2**	92	32
Reactions leading to arylation					
β-Naphthol	—	20[c]	1-Phenyl-2-naphthol	76	31
Quinine (**19**)	—	—	Compound **22**	75	31

[c] The reaction was carried out in the presence of tetramethylguanidine.

TABLE VIII. Compounds Not Oxidized by Triphenylbismuth Carbonate[a]

Compound	Time (h)	Temperature (°C)
Benzophenone phenylhydrazone	24	40
Benzophenone 2,4-dinitrophenylhydrazone	24	40
Benzophenone semicarbazone	72	20
5α-Cholestan-3-one tosylhydrazone	24	20
Tri-*O*-acetal glucal	24	20
Aniline	18	20
N,*N*-Dimethylaniline	24	20
3-Pyrollidino-cholesta-3,5-diene	24	20
Di-*t*-butylthionoketone	16	40
3β-Cholestanyl-*S*-methyl xanthate	24	40
3β-Cholestanyl-*N*,*N*-diethyl thionocarbamate	24	40

[a] References 6, 30.

Summary of the Reactivity of Bismuth Oxidants

Reagent	Substrate	Product
Sodium bismuthate	1,2-Diol	Fission to carbonyl compounds
Sodium bismuthate	α-Hydroxycarboxylic acid	Fission to CO_2 and carbonyl compound
Sodium bismuthate	α-Hydroxyketone	Fission to carbonyl compound and carboxylic acid
Sodium bismuthate	Phenol	Radical coupling product or quinonoid derivative
Sodium bismuthate	Olefin	Di-acetoxy derivative
Bismuth trioxide	α-Hydroxyketone	Diketone
μ-Oxo-bis(chloro-triphenylbismuth)	Alcohol (saturated, allylic or benzyl)	Carbonyl compound
μ-Oxo-bis(chloro-triphenylbismuth)	1,2-Diol	Fission to carbonyl compounds
Triphenylbismuth carbonate	Allylic alcohol	Carbonyl compound
Triphenylbismuth carbonate	Thiol	Disulfide
Triphenylbismuth carbonate	1,2-Diol	Fission to carbonyl compounds
Triphenylbismuth carbonate	Hydrazo compound	Azo compound

starting material has been consumed, the reaction mixture is filtered. Isolation of the product requires the same procedure as that described above for μ-oxo-bis(chlorotriphenylbismuth) oxidations. The yields and reaction conditions for the oxidation of a variety of functional groups with triphenylbismuth carbonate are listed in Table VII.

In contrast to activated manganese dioxide oxidations, reaction of alcohols with the

organobismuth reagents does not require rigorously anhydrous conditions. The selectivity of triphenyl bismuth carbonate is illustrated by the list of functional groups (Table VIII) which are unaffected by the reagent.

5. THE TOXICITY OF BISMUTH

The relatively low toxicity of certain inorganic bismuth compounds such as the subcarbonate, taken in the past for stomach ailments, appears to be associated with the low solubility of bismuth in this form. Other compounds such as the subnitrate and the subgallate are quite harmful. A great many organobismuth compounds were investigated as therapeutic agents prior to the introduction of antibiotics. A disadvantage of "bismuth therapy" was the toxicity of the agents concerned. In view of the known toxicity of some bismuth compounds it is advisable to treat all bismuth reagents with due care, consistent with good laboratory practice.

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16

Oxidations with Metal Compounds and Peroxides

Yoshiro Ogata and Yasuhiko Sawaki

1. INTRODUCTION

The origin of oxidations with peroxides induced by metal compounds can be traced back to 1894, when H. J. H. Fenton reported the oxidation of tartaric acid with hydrogen peroxide catalyzed by ferrous salt.[1] Thence a mixture of H_2O_2–Fe^{2+} has been called the Fenton reagent. Afterwards, Morrell and Crafts[2] studied the oxidation of a series of hydroxyl compounds including sugars, but the complexity of oxidation products limited the general use of this reagent.

Meanwhile, the easy generation of free radicals by Fenton reagent extended its use as a polymerization initiator,[4] i.e., the well-known redox polymerization (e.g., of acrylonitrile).

Since 1934 some other metal compounds, which act via quite different schemes, were found to be effective in the H_2O_2 oxidation of organic substrates. Ghosh and Kar[5] used molybdate for the oxidation of cystine to cysteic acid. Milas[6] and Criegee[7] used OsO_4 for the *cis*-dihydroxylation of olefins; Treibs[8] used vanadium pentoxide or vanadate with H_2O_2 for *trans*-dihydroxylation of olefins; but Mugdan and Young[9] found that tungstic acid was much more effective for *trans*-dihydroxylation of olefins. Similarly, selenium dioxide can give glycols from olefins, but it was less effective than OsO_4 or H_2WO_4[9,10] until the recent report using SeO_2 with *t*-BuOOH in nonhydroxylic solvents. (See Section 3.2.2.)

Peroxydisulfuric acid was prepared early in 1891 and has been called Marshall acid.[11] Soon the catalytic effect of silver salts on the oxidation by Marshall's salt ($S_2O_8^{2-}$) was observed in the oxidation of oxalic acid[12]; for example, *p*-benzoquinone[12] and thymol gave dithymol.[13] Since peroxydisulfate salt is soluble and stable in water it is widely used as a redox vinyl polymerization catalyst in the presence of Cu^+ or Fe^{2+} ions, which act as an electron donor to produce $SO_4^{\cdot-}$ from $S_2O_8^{2-}$.

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A typical example of a large-scale industrial application of peroxide–metal oxidation is the Halcon process, i.e., the molybdenum-catalyzed epoxidation of propylene with hydroperoxides derived from isobutane or ethylbenzene.[14] For example, ethylbenzene gives propylene oxide and styrene, both of which are industrial organic materials.

A general treatment of the various mechanisms occurring with peroxide–metal compound oxidations, distinguishing between different reaction types is given in the mechanism section of this chapter to provide a basic insight into the reaction possibilities for synthetic applications.

The peroxide–metal oxidation method is a versatile tool in synthetic organic chemistry. Oxidations of a wide range of substrates, alcohols, carbonyl compounds, active CH compounds, nitrogen and sulfur compounds and epoxidation of double bonds will be dealt with in the scope and limitations and experimental sections of this chapter.

2. MECHANISM

Various mechanisms are conceivable for peroxide–metal compound oxidations depending on the metal, peroxide, and substrate used. Some are still inconclusive, but generally, the mechanism can be classified into three main categories:

a. A radical mechanism via a redox reaction between peroxides and metallic ions such as Fe^{2+}, Ti^{3+}, Cu^{+}, Ag^{+}, or Pd^{2+}. The oxidation proceeds by way of H atom abstraction from the substrate, substitution or addition reactions, or ligand transfer of intermediary radicals.

b. An ionic mechanism via formation of metallic peroxide or metal-peroxide complexes. Mo, W, V, Se, and Os compounds are commonly used in this category.

c. An ionic mechanism via formation of a peroxide–Lewis acid complex which can generate an electrophilic oxonium ion which can be used for aromatic oxidations.

2.1. Radical Mechanism via Redox Reactions (Category a)

The mechanism for the generation of free radicals by Fenton's reagent was studied by Haber and Weiss,[3] who postulated that the initial step is the formation of a hydroxyl radical generated by an electron transfer from the ferrous ion to H_2O_2.

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + HO^{\cdot} \qquad (1)$$

This category (a) also involves metals such as Ag^{+}, Ti^{3+}, Pd^{2+}, and Cu^{+} which are easily oxidized to higher valence ions by peroxides.

$$Ag^{+} + S_2O_8^{2-} \longrightarrow Ag^{2+} + SO_4^{-\cdot} + SO_4^{2-} \qquad (2)$$

Also this category involves the oxidation of peroxides by metallic ions of higher valences; for example,

$$ROOH + Co^{3+} \longrightarrow ROO^{\cdot} + Co^{2+} + H^{+} \qquad (3)$$

The Haber–Weiss mechanism [Eq. (1)][3] for the generation of $HO^{\cdot}$ radicals is accepted as the most general scheme for the initiation of Fenton and related reactions.[5] Another system Fe^{3+}/H_2O_2 can also generate radicals, but the initially formed radical $HO_2^{\cdot}$ may be a chain inhibitor ($Fe^{3+} + HO_2^{\cdot} \rightarrow Fe^{2+} + O_2 + H^{+}$), so that the concentration of $HO^{\cdot}$ is much lower than in the Fe^{2+}/H_2O_2 system. The effect of Cu^{2+} is much smaller than Fe^{3+}, but the

addition of Cu^{2+} to the system Fe^{3+}/H_2O_2 accelerates the Fenton oxidation reaction, which is ascribed to the following reasons:

i. Rapid oxidation of $HO_2^{\cdot}$ radical to O_2 and the regeneration of Cu^{2+} by oxidation of resulting Cu^{+} with Fe^{3+}[16]:

$$HO_2^{\cdot} + Cu^{2+} \longrightarrow O_2 + Cu^{+} + H^{+} \quad (4a)$$

$$Cu^{+} + Fe^{3+} \longrightarrow Fe^{2+} + Cu^{2+} \quad (4b)$$

$$Fe^{2+} + H_2O_2 \longrightarrow FeOH^{2+} + HO^{\cdot} \quad (4c)$$

ii. The specific ability of Cu^{2+} to oxidize an organic radical to a carbonium ion, which can easily react with nucleophiles present, as shown later.

The main reaction types in which a radical mechanism via a redox system is involved are as follows:

i. H abstraction[17–24];
ii. Aromatic and other substitution reactions[25–28];
iii. Addition to double and triple bonds.[17,29–30]

2.1.1. H Abstraction

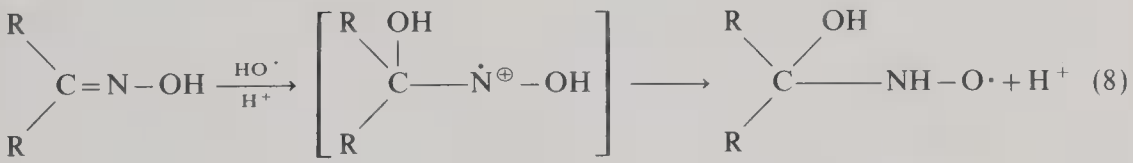
Alcohols react with the Fenton reagent to give carbonyl compounds via H abstraction. Kolthoff postulated the following mechanism for this reaction[21–24]:

$$RCH_2OH + HO^{\cdot} \longrightarrow R\dot{C}HOH + H_2O \quad (5)$$

$$R\dot{C}HOH + Fe^{3+} \longrightarrow R\overset{+}{C}HOH + Fe^{2+} \quad (6)$$

$$R\overset{+}{C}HOH \longrightarrow RCH{=}O + H^{+} \quad (7)$$

An analogous abstraction is observed in the attack of $HO^{\cdot}$ derived from H_2O_2/Ti^{3+} to an oxime[30]:



(8)

β-hydroxynitroxide
(a stable radical)

Peroxydisulfate oxidations are catalyzed by metallic ions such as Ag^{+}, Fe^{2+}, and Cu^{2+} in an analogous way, where the redox system generates sulfate radicals[31–32].

$$S_2O_8^{2-} + Ag^{+} \longrightarrow Ag^{2+} + SO^{4-\cdot} + SO_4^{2-} \longrightarrow Ag^{3+} + 2SO_4^{2-} \quad (9a)$$

$$S_2O_8^{2-} + Fe^{2+} \longrightarrow Fe^{3+} + SO_4^{-\cdot} + SO_4^{2-} \quad (9b)$$

The formed species, $SO_4^{-\cdot}$, $Ag^{2+} \cdot Ag^{3+}$, etc. abstract an electron or a hydrogen atom from organic compounds or they add to unsaturated compounds as in the case of HO.[33] For example, toluene gives a benzyl radical $PhCH_2^{\cdot}$ which reacts further to form benzaldehyde PhCHO and benzylsulfate $PhCH_2OSO_3H$.

The α-hydrogens of alcohols are abstracted by $SO_4^{\cdot-}$. The resulting radicals are (i) oxidized further to carbonyl compounds, (ii) dimerized to glycols, or (iii) converted to degradation products by cleavage at the β-position, for example,

$$SO_4^{\cdot-} + CH_3OH \longrightarrow \dot{C}H_2OH + SO_4^{2-} + H^+ \quad (10)$$

$$\dot{C}H_2OH + S_2O_8^{2-} \longrightarrow CH_2O + H^+ + SO_4^{2-} + SO_4^{\cdot-} \quad (11)$$

$$2 \cdot CH_2OH \longrightarrow HOCH_2CH_2OH \quad \text{(Ref. 34a)} \quad (12)$$

$$SO_4^{\cdot-} + PhC(CH_3)_2(OH) \xrightarrow{-SO_4^{2-}} \left[PhC(CH_3)_2(OH) \right]^{\cdot+}$$

$$\longrightarrow PhCCH_3(OH) + .CH_3 \quad \text{(Ref. 34b)} \quad (13)$$

Secondary and tertiary alcohols $Ph(CH_2)_n C(OH)MeR$ give fragmentation products on reaction with $SO_4^{\cdot-}$, when $n = 0$–2 and R = H or CH_3, but when $n = 3$ and R = CH_3, the alcohol is relatively unreactive.

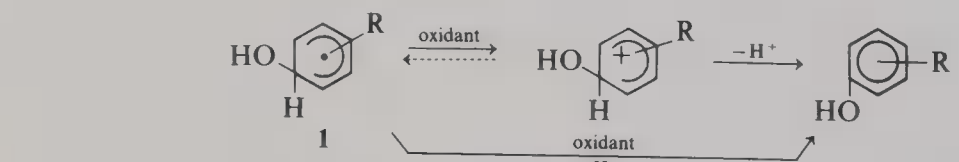
Diacyl peroxide with $NiBr_2$ can oxidize alcohols to carboxyl compounds. The reaction, which is a nice method to prepare aldehydes from primary alcohols, is reported to go by way of benzoyl hypobromite. The aldehydes formed by this method may be protected by $NiBr_2$, through complex formation (see Experiment 1).

$$NiBr_2 + (PhCOO)_2 \longrightarrow PhCOOBr + (PhOO)NiBr \quad (14a)$$

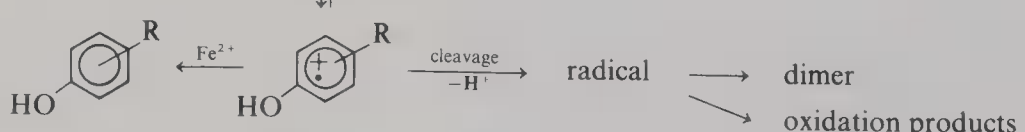
$$RCH_2OH + PhCOOBr \longrightarrow RCHO + PhCOOH + HBr \quad (14b)$$

2.1.2. Aromatic and Other Substitution Reactions

A hydroxyl radical can add to ordinary aromatic compounds, giving cyclohexadienyl radicals (**1**), which then yield phenols by oxidation with HO·, etc. Alternatively, cyclohexadienyl radicals may be oxidized to radical cations, which are then converted by Fe^{2+} to the starting aromatic compounds or dimerize via side chain cleavage.



(15)

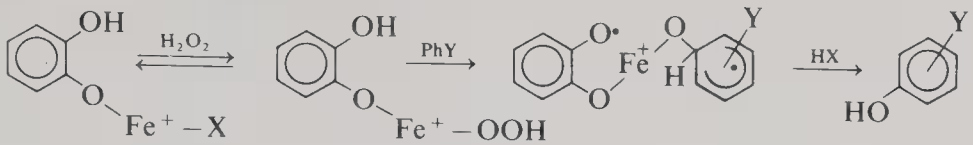


(16)

Substituted benzenes give *o*-, *m*-, and *p*-hydroxylation products, e.g., nitrobenzene gives nitrophenols in a ratio of *o*:*m*:*p* = 0.56:0.44:1.00, which is in accord with the Wheland theory.[26] The isomer distribution depends not only on the substituent, but also on the oxidants (Fe^{3+}, Cu^{2+}, O_2, etc.).[25]

A catalyst consisting of Fe^{3+} and an enediol (e.g., catechol) is effective in the H_2O_2 hydroxylation of aromatic compounds (benzene, nitrobenzene, and anisole). The orientation

is different from that resulting from the Fenton reaction and a mechanism involving an intermediary complex (**2**) was postulated[22,27]:

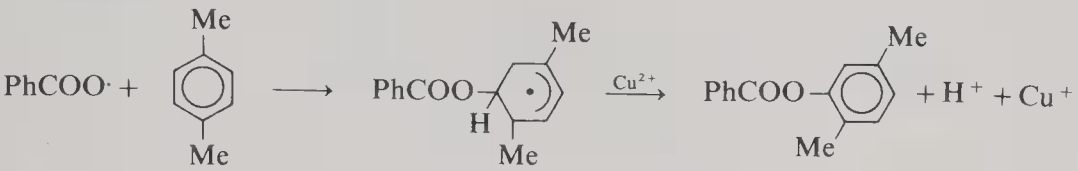


(17)

2

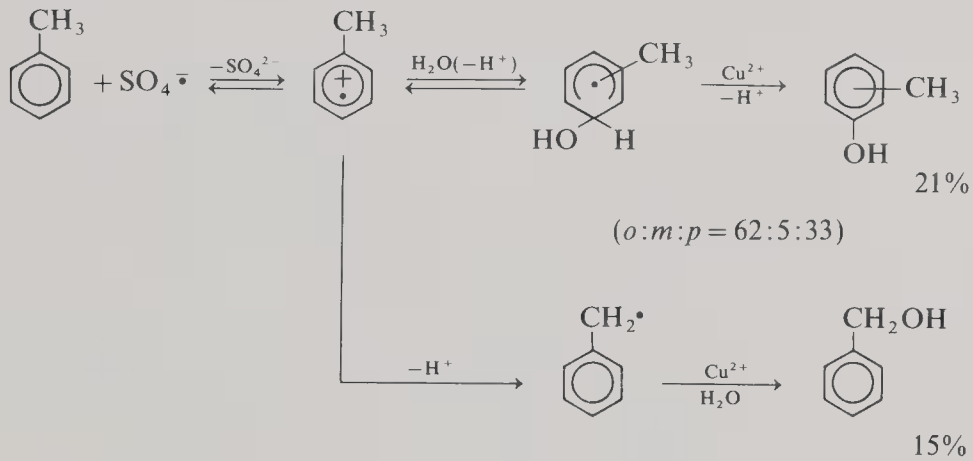
An analogous $-O-Fe-OOH$-type complex was postulated for the stereospecific *cis*-hydroxylation of cyclohexanol.[28]

Dibenzoyl peroxide with Cu^{2+} can generate benzoyloxy radicals, which can add to an aromatic ring, leading to aryl benzoates. For example, *p*-xylene gives *p*-xylene benzoate (Section 3.5.5).[35b]



(18)

Peroxydisulfate can be used in the absence of metals for hydroxylation of phenols and aromatic amines (Elbs reaction),[36] but when a mixture $S_2O_8^{2-}/Fe^{2+}/Cu^{2+}$ is used, aromatic compounds are more effectively hydroxylated, where Cu^{2+} acts as an electron abstractor (oxidant) towards carbon radicals.[37]



(19a)

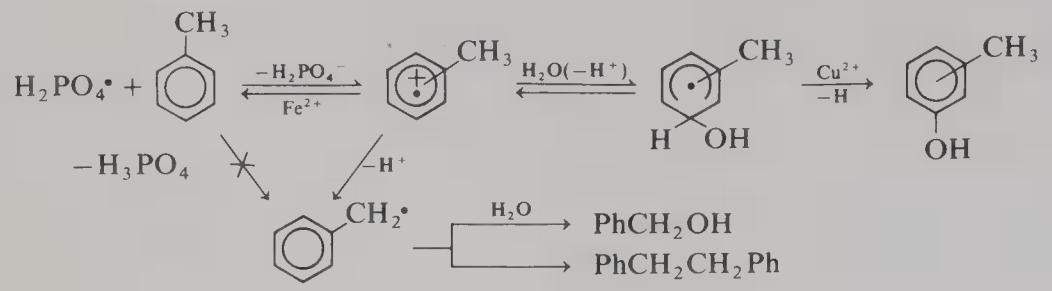
(19b)

Thus the yield of phenol from benzene can be increased to 64% with Fe^{2+}/Cu^{2+} compared with the yield of 26% (and biphenyl 24%) in the absence of Cu^{2+}.

Peroxydiphosphate, e.g., $K_4P_2O_8$, which is prepared by the electrolytic oxidation of phosphate salt in the presence of F^-,[38] can effect metallic ion-catalyzed oxidations similar to those with $S_2O_8^{2-}$. Ferrous ion can give phosphate radicals which are in equilibrium with the protonated species [Eq. (20b)]; hence the products depend on the acidity of the solution. Cupric ions accelerate the aromatic hydroxylation. Toluene is attacked mainly at the side chain in the absence of Cu^{2+} at $[H^+] = 0.87$ to give benzyl alcohol (14%) and bibenzyl (34%), while in the presence of 0.2 *M* Cu^{2+} it gives cresols (25%) and bibenzyl (10%). The oxidation mechanism of toluene with $P_2O_8^{4-}/Fe^{2+}/Cu^{2+}$ may be as follows[39]:

$$H_2P_2O_8^{2-} + Fe^{2+} \longrightarrow HPO_4\cdot^- + HPO_4^{2-} + Fe^{3+} \qquad (20a)$$

$$PO_4^{2-}\cdot \underset{}{\overset{+H^+}{\rightleftharpoons}} HPO_4\cdot^- \overset{+H^+}{\rightleftharpoons} H_2PO_4\cdot \qquad (20b)$$

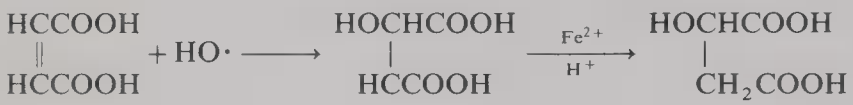


(20c)

The cresols produced have an isomer distribution $o:m:p = 66:9:25$, similar to the $SO_4^{\cdot-}$ or HO· reactions.[39]

2.1.3. Addition to Double and Triple Bonds

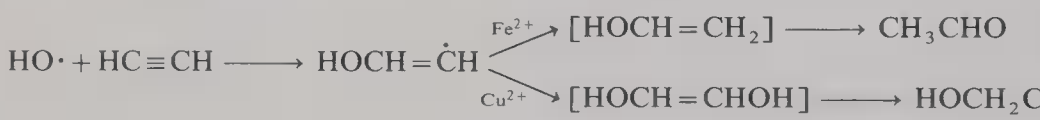
Double bonds of α,β-unsaturated acids are readily attacked by HO· giving hydration products; e.g., malic acid is formed from maleic acid.[17]



(21)

Fumaric and acrylic acids give similar results, but crotonic acid is attacked by HO· to give an H atom abstracted product as well as a hydration product.[17]

Acetylene is attacked by HO· to give an enol radical, which is reduced by Fe^{2+} to acetaldehyde or oxidized by Cu^{2+} to glycolaldehyde.[40]



(22a)

(22b)

2.2. Ionic Mechanism via Formation of Metallic Peroxide or Metal–Peroxide Complexes (Category b)

Oxidation with H_2O_2 and alkyl hydroperoxide is promoted by Mo, W, V, Os, Ti, Se, and Cr compounds, which can form metallic peroxides or metal peroxide complexes acting as oxygen transfer agents. Thus alkyl hydroperoxides can be used for the epoxidation of olefins[40,41] and for the preparation of *N*-oxides from tertiary amines.[42]

Since iron or cobalt compounds cannot be the catalysts and the oxidation shows a similarity with the peracid oxidation, this type of oxidation is considered to be of an ionic rather than a radical nature.

The following oxygenation reactions are observed in those oxidations where an ionic mechanism via formation of metallic peroxide or metal–peroxide complexes is involved:

i. epoxidations;

ii. oxygenation of sulfides and sulfoxides;

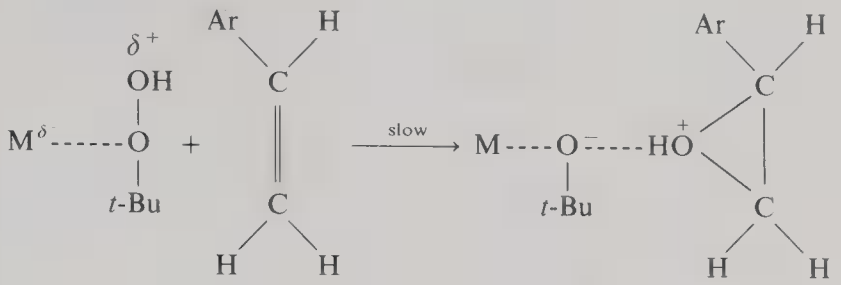
iii. oxygenation of amines;

iv. formation of glycols.

2.2.1. Epoxidations

The epoxidation mechanism of double bonds with *t*-BuOOH/Mo catalysts is illustrated with the case of styrenes. The substituent effect is connected with a negative Hammett value,

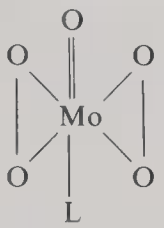
suggesting a rate-determining electrophilic attack of hydroperoxide oxygen on the double bond.[43]



(23)

(M is an activated metallic catalyst)

As to the molybdenum (VI) peroxo compounds, Mimoun found out that complex **3** epoxidizes olefins stoichiometrically in organic solvents.[44] The coordination equilibrium of olefin to complex **3** is generally favored by the presence of alkyl substituents on the double bond carbon atoms of olefins, although a steric effect of the alkyl group is also operative to a certain extent.[45] An alternative complex structure has been proposed.[46]

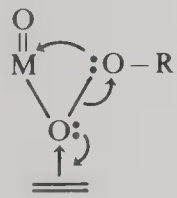


3

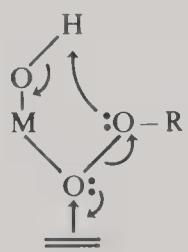
(L: hexamethylphosphoramide)

When complex **3** is labeled with ^{18}O uniquely at the oxo oxygen, **3** will not give a labeled epoxide. Further, the epoxidation with alkylhydroperoxide in heavy water $^{18}OH_2$ does not yield the labeled epoxide.

These facts together with the exceptional high reactivity of the intermediate allyl alcohol compared with saturated alcohols suggest the following transition states, **4** or **5**[47] for the epoxidation.



4



5

2.2.2. Oxygenation of Sulfides and Sulfoxides

The Na_2MoO_4-catalyzed H_2O_2 oxidations of sulfide (thiodiglycol) leads to sulfoxide ($(HOOCH_2CH_2)_2S + H_2O_2 \rightarrow (HOCH_2CH_2)_2SO$). The pH profile suggests that the reaction is acid-catalyzed and the most active species may be H_2MoO_6.[48]

$$MoO_4^{2-} + 2H^+ + 2H_2O_2 \overset{\text{fast}}{\rightleftharpoons} H_2MoO_6 + 2H_2O \qquad (24a)$$

$$H_2MoO_6 + 2(HOCH_2CH_2)_2S \xrightarrow{\text{slow}} H_2MoO_4 + 2(HOCH_2CH_2)_2SO \qquad (24b)$$

Kinetic and polarographic studies of the Na_2WO_4-catalyzed H_2O_2 oxidation of dimethyl sulfoxide to dimethyl sulfone reveal that the actual attacking species at pH 4 may be both HWO_5^- and HWO_8^-, even if peroxypolytungstate is initially present.[49a] The rate with a catalytic amount of Na_2WO_4 is independent of $[H_2O_2]$ and expressed as $v \cdot k_2[Me_2SO][Na_2WO_4]_{stoich}$, suggesting the following mechanism:

$$(a+b)HWO_4^- + (a+4b)H_2O_2 \underset{}{\overset{\text{fast}}{\rightleftharpoons}} aHWO_5^- + bHWO_8^- + (a+4b)H_2O \quad (25a)$$

$$HWO_5^- + Me_2SO \xrightarrow{\text{slow}} Me_2SO_2 + HWO_4^- \quad (25b)$$

$$HWO_8^- + Me_2SO \xrightarrow{\text{slow}} Me_2SO_2 + HWO_7^- \quad (25c)$$

$$HWO_7^- + H_2O_2 \xrightarrow{\text{fast}} HWO_8^- + H_2O \quad (25d)$$

(Peroxypolytungstates are converted to peroxytungstates)

The effect of acidity on the rate (Fig. 1) suggests the depolymerization of polytungstic acid at pH $5.5 \rightarrow 3.0$ (acceleration), protonation of peroxytungstate (e.g., $HWO_5^- \rightarrow H_2WO_5$) at pH $2.5 \rightarrow$ O (acceleration), and protonation of Me_2SO to Me_2SOH^+ at $-Ho$, $1 \rightarrow 5$ (retardation).

Alkali vandate is generally less effective as a catalyst for H_2O_2 oxidations. For example, sulfides give sulfoxides and then sulfones,[49b,49c] but the rate is slower; the mechanism may involve polymeric as well as monomeric peroxyvandate as effective oxidants.

2.2.3. Oxygenation of Amines

A kinetic study on the oxidation of benzylamine with H_2O_2–tungstate showed a base catalysis and a pH profile which is in agreement with the calculated one based on the following mechanism with $k_H = 1.2 \times 10^{-9}\ M^{-1}$ and $k_2 = 7.24 \times 10^{-2}\ M^{-1}\ s^{-1}$ at 25°C[50]:

$$PhCH_2NH_2 + H^+ \underset{\text{fast}}{\overset{k_H}{\rightleftharpoons}} PhCH_2NH_3^+ \quad (26a)$$

$$PhCH_2NH_2 + TOOH \xrightarrow[\text{slow}]{k_2} PhCH_2\overset{+}{N}H_2OH + T{-}O^- \quad (26b)$$

$$PhCH_2NHOH + H_2O_2 \xrightarrow{\text{fast}} PhCH{=}NOH + 2H_2O \quad (26c)$$

(TOOH may be HWO_5^-, HWO_6^-, HWO_8^-, or their polymeric forms)

Kinetic studies and the effect of pH on the rate of oxidation of *N*,*N*-dimethylaniline by H_2O_2–SeO_2 suggest the following mechanism involving peroxyselenous acid[51]:

$$H_2O_2 + SeO_2 \longrightarrow HO{-}\overset{\overset{O}{\uparrow}}{Se}{-}OOH \xrightarrow{PhNMe_2} \overset{\overset{O}{\uparrow}}{PhNMe_2} + SeO_2 + H_2O \quad (27)$$

In a kinetic study on the oxidation of anilines with a mixture of *t*-BuOOH and a V or Mo catalyst, a mechanism was postulated involving a rapid equilibrium for the formation of a peroxide–catalyst complex followed by rate-determining O–O heterolysis.[52]

$$\begin{array}{l} \overset{\delta^-}{V}\text{-----}O\delta^- \\ \quad\quad | \\ \quad\quad t\text{-Bu} \end{array} \begin{array}{l} \delta^+ OH \\ | \\ \quad\quad \end{array} \begin{array}{l} \quad\quad H \\ \quad\quad \diagup \\ + N{-}Ph \\ \quad\quad \diagdown \\ \quad\quad H \end{array} \xrightarrow{\text{slow}} \begin{array}{l} \quad\quad H \\ \quad\quad \diagup \\ HO{-}\overset{+}{N}{-}Ph \\ \quad\quad \diagdown \\ \quad\quad H \end{array} + V\text{-----}\bar{O}{-}t\text{-Bu} \quad (28)$$

The substituent effect in anilines ($\rho = 1.63$ with σ and -1.42 with σ^+) suggests an electrophilic attack of HO^+ on nitrogen.[52]

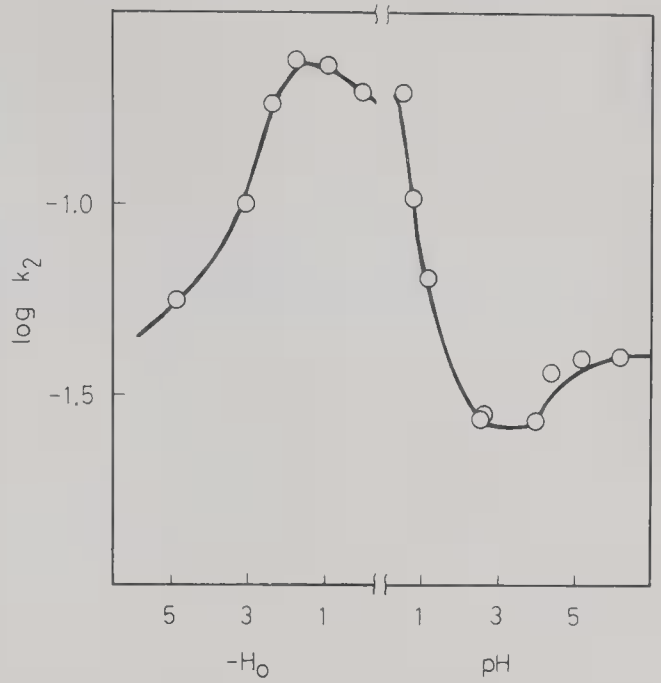
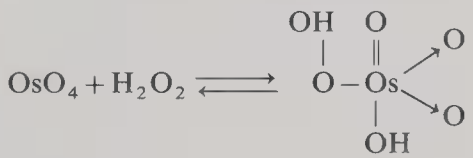


FIGURE 1. Effect of acidity of solution on the second-order rate constant k_2 for the H_2O_2 oxidation of DMSO at 25°C. $[Na_2WO_4]_0 = 1 \times 10^{-3}$ *M*, $[H_2O_2]_0 = 3.0 \times 10^{-2}$ *M*, $[DMSO]_0 = 2.5 \times 10^{-2}$ *M*.

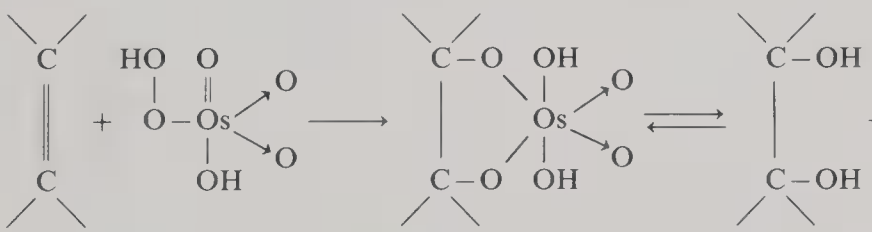
2.2.4. Formation of Glycols

A comprehensive treatment of OsO_4 oxidations is given in Chapter 12 by Singh.

A mixture OsO_4/H_2O_w or OsO_4/t-BOOH can oxidize olefins to *cis*-glycols as in the case of OsO_4 alone. The active species may be perosmic acid which adds to the double bond forming a cyclic intermediate,[53] which is isolable by chromatography (Experiment 7).



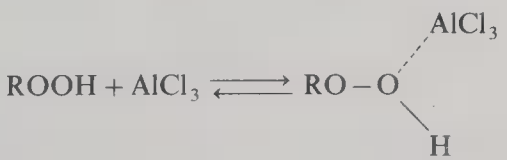
(29a)



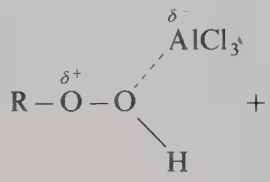
(29b)

2.3. Ionic Mechanism via Lewis Acid Activation

Lewis acids such as $AlCl_3$, BF_3, etc. can activate H_2O_2, peracids, alkyl hydroperoxides, and diacyl peroxides as electrophilic oxidants, i.e. (R: H, R′CO, Alkyl),[53]

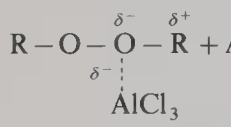


(30a)

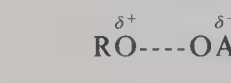


$$+ \mathrm{ArH} \longrightarrow \mathrm{R-O-Ar} + \mathrm{AlCl_2(OH)} + \mathrm{HCl} \qquad (30b)$$

The mechanism is similar to that with protic acids such as HF and FSO_3H-SO_2ClF.[56] The $AlCl_3$-induced reaction of di-*t*-butyl peroxide with toluene gives *t*-butyl cresols (66%) (*o*:*m*:*p* = 59:10:31) and *t*-butyltoluene (60%), presumably according to the following scheme[57]:



$$+ \mathrm{ArH} \longrightarrow \mathrm{R-Ar} + \mathrm{ROOAlCl_2} + \mathrm{HCl} \qquad (31a)$$



$$+ \mathrm{ArH} \longrightarrow \mathrm{ROAr} + \mathrm{AlCl_2(OH)} \qquad (31b)$$

$$\mathrm{ROAr} + \mathrm{ArH} + \mathrm{AlCl_3} \longrightarrow \mathrm{ArOAlCl_2} + \mathrm{Ar-R} + \mathrm{HCl} \qquad (31c)$$

3. SCOPE AND LIMITATIONS

3.1. General Considerations

The organic chemistry of peroxides[58,59] and peroxide oxidations has been reviewed comprehensively.[58–61] Many useful oxidations involving metal compounds were developed with peroxides,[62,63] including dialkyl (ROOR) and diacyl peroxides $(ROO\text{-})_2$,[64] peresters (RCO_2OR'),[65] hydroperoxides (ROOH),[66] hydrogen peroxide,[15,67] peroxydisulfate,[15b,67] and peroxydiphosphate.[38] They are classified in three types (cf. Section 2).

The following shows various types of useful oxidations which are classified primarily by the substrates: alcohols to aldehydes and ketones, carbonyl compounds to carboxylic acids, olefins to epoxides (sometimes regio- and stereoselective), to glycols and to ketones, activated C–H and aromatic compounds to their hydroxyl and acyloxyl derivatives, amines to amine oxides, oximes and aldehydes, sulfides to sulfoxides and sulfones.

3.2. Oxidation of Alcohols

3.2.1. Alcohols

The Fenton oxidation of primary and secondary alcohols often affords complex mixtures of products, but there are a number of useful applications in polyol oxidations.[68] For example, galactitol is oxidized to isogalactose in 30% yield.[69] Relatively high yields of aldehydes are obtained from primary alcohols with Ag^+-catalyzed peroxydisulfate oxidation.[70]

$$\mathrm{PhCH_2OH} \xrightarrow[75\%\ (\text{isolated})]{S_2O_8^{2-}/Ag^+} \mathrm{PhCHO} \qquad (32)$$

Similarly, 5-hydroxymethyluracil is oxidized to the aldehyde (>70%).[71,72]

The Fenton oxidation of α-phenyl alcohols to ketones accompanies C–C scission to benzaldehyde.

$$\underset{\underset{\text{OH}}{|}}{\text{PhCHR}} \xrightarrow{H_2O_2/FeSO_4} \underset{\underset{\text{O}}{\|}}{\text{PhCR}} + \text{PhCHO} \qquad (33)$$

Benzaldehyde is a minor product, when R = Me or Et, but it is predominant, when R = *i*-Pr or *t*-Bu.[34] An efficient conversion of secondary alcohols to ketones is attained by the H_2O_2/W^{6+} system using 2-pyridinecarboxylate as a ligand; e.g., 2-octanol to 2-octanone (70%).[73]

3.2.2. Cleavage of Glycols and Related Compounds

C–C scission of 1,2-glycols is usually carried out by HIO_4 or $Pb(OAc)_4$, but it is also attainable by $S_2O_8^{2-}/Ag^+$; e.g., the scission of styrene diol (61%), cyclohexanediol (41%), and pinacol (100%).[74]

$$\underset{\underset{\text{OH}}{|}\quad\underset{\text{OH}}{|}}{\text{R}^1\text{R}^2\text{C}-\text{CR}^3\text{R}^4} \xrightarrow{S_2O_8^{2-}/Ag^+} \text{R}^1\text{R}^2\text{C}=\text{O} + \text{R}^3\text{R}^4\text{C}=\text{O} \qquad (34)$$

α-Oxy ketones and acids are likewise subject to C–C cleavage,[75] but acetoin bearing an α-H is oxidized to biacetyl instead of the C–C scission.[76] The oxidation of L-gulono-γ-lactone to L-ascorbic acid with H_2O_2–Fe^{2+} is the same type of oxidation.[77]

3.3. Oxidation of Carbonyl Compounds

3.3.1. Aldehydes

The H_2O_2/SeO_2 reagent oxidizes aldehydes selectively to acids even in the presence of an isolated C=C bond (Experiment 3),[78,79] e.g.,

$$\text{CH}_2=\text{CHCHO} \xrightarrow[t\text{-AmOH:90\%}]{H_2O_2/SeO_2} \text{CH}_2=\text{CHCO}_2\text{H} \qquad (35)$$

An exception is the formation of vinyl formate via Baeyer–Villiger oxidation of allylic aldehyde.[80]

3.3.2. Ketones

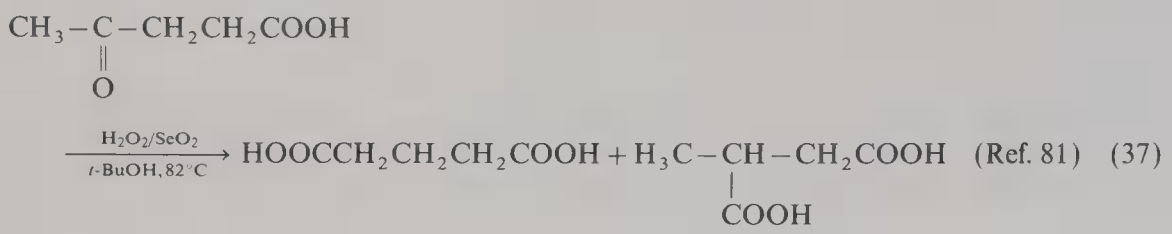
Cyclic ketones are oxidized to ring-contracted acids with H_2O_2/SeO_2.[81–85]

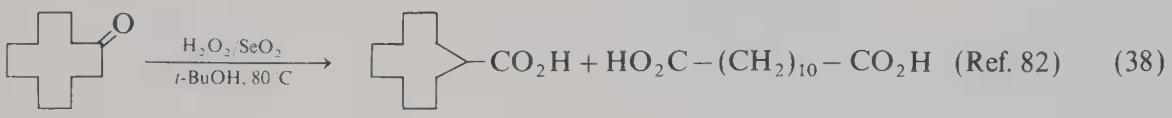
$$\overset{\text{(CH}_2)_n \quad \text{C=O}}{\frown\!\!\!\!\!\!\smile} \xrightarrow[t\text{-BuOH}]{H_2O_2/SeO_2} \overset{\text{(CH}_2)_{n-2}\text{CH}-\text{CO}_2\text{H}}{\frown\!\!\!\!\!\!\smile} \qquad (36)$$

Here, *n* and percent yields are *n* = 4 (23%), 5 (32%), 11 (32%), etc. The reaction has been applied to steroidal ketones.[84] The same reaction is attainable with Tl(III).[86] Similar migrations of alkyl groups occur with acyclic ketones, where the migratory aptitutde[87] increases with decreasing number of alkyl carbon number.

$ROOCH-B_2O_3$ achieves Baeyer–Villiger oxidation; i.e., cyclohexanone is converted at 170°C to ε-caprolactone (70%).[88] The oxidative C–C scissions of α-diketones,[89]

α-ketoacids,[90] and α-ketols[91] are effectively achieved by H_2O_2/NaOH/MeOH. It is of interest to note that alkyl group rearrangement or ring contraction occurs during the H_2O_2–SeO_2 oxidation of ketones.



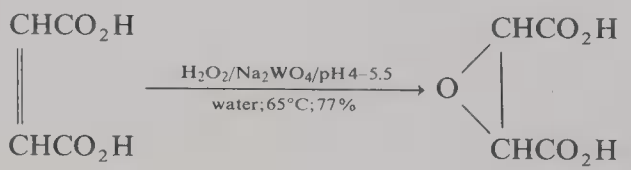


3.4. Oxidation of Double Bonds

3.4.1. Epoxidation of Olefins

Since epoxides are sensitive to acid-catalyzed cleavage, the general way of epoxidation with peracids is not always appropriate for some epoxides.[61,92] In these cases metal-catalyzed epoxidation with H_2O_2 or ROOH is preferable.

Hydrogen Peroxide. In the H_2O_2–metal oxidation of olefins in aqueous solution, epoxides may be isolated at neutral pH.[9,93,94] One of the useful applications is the epoxidation of maleic and fumaric acids with H_2O_2/Na_2WO_4,[95,96] which is not attainable with peracids. For example,



(39)

Although α,β-unsaturated ketones can be epoxidized with alkaline H_2O_2 or *t*-BuOOH,[97] this method is not effective for α,β-unsaturated acids.

The epoxides are formed with high selectivity (>90%)[98] with metal compounds such as $W(CO)_6$, AS_2O_3, B_2O_3, etc.[15a] in anhydrous solvents (dioxane, acetonitril).

Since no ROH is produced as is the case with hydroperoxides, the reaction is advantageous for large scale. Epoxidation with H_2O_2 is possible with basic alumina[99] and with selenic acids as phase transfer catalysts.[100]

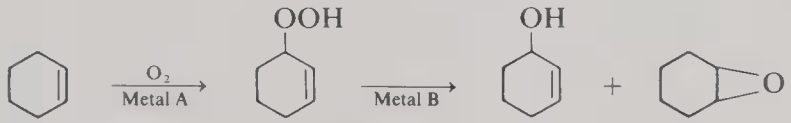
Hydroperoxides. In organic solvents, alkyl hydroperoxides may epoxidize olefins at elevated temperatures with low (<50%) selectivities,[101,102] which are improved by addition of catalysts such as Mo or W compounds[41] (Halcon process).[14,103]

Catalytic activities for epoxidation of cyclohexene with *t*-BuOOH are in the order of $Mo^{6+} > W^{6+} > Ti^{4+}$; the extent of autoretardation by the resulting *t*-BuOH is $W^{6+} < Mo^{6+} < Ti^{4+} < V^{4+}$.[104] Good solvents for the epoxidation are nonpolar ones such as benzene and polychlorohydrocarbons, while coordinating solvents, e.g., alcohols, DMF, THF, and dioxane are inappropriate.[105] Mo^{6+} catalysts are the best with regards to rate and selectivity.[104,106] Besides soluble catalysts such as $Mo(Co)_6$ (Experiment 5), solid metal catalysts supported on carriers are also effective as is claimed in patents. Borate catalysts not containing any metals are also effective.[107]

Vanadium by its high coordination ability is the best catalyst for stereoselective epoxidation (Section 3.4.2) of allylic alcohols.[108]

These epoxidations are electrophilic in nature, i.e., the rate is increased by substitution of alkyl groups on the double bond.[43,108,109]

An interesting example is the oxidation of cyclohexene with two different metal compounds to afford cyclohexanol and cyclohexeneoxide.[110]



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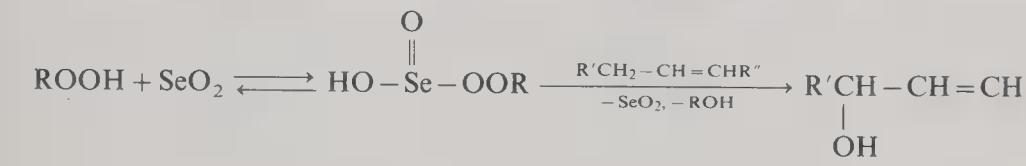
Metal system A is $Co(acac)_2$ or $RhCl(PPh_3)_3$, which initiates the autoxidation, and Metal system B is the epoxidation catalyst.

When a mixture of *t*-BuOOH/SeO_2 in dichloromethane is employed instead of aqueous H_2O_2/SeO_2, allyl alcohols can be obtained from olefins in high yields.[111]



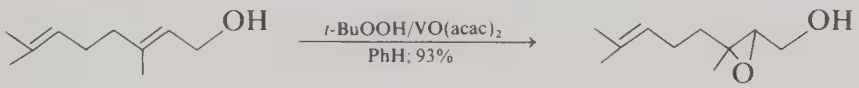
(41)

3.4.2. Regio- and Stereoselective Epoxidations[116]

Regio- and stereoselective epoxidations are important for preparing industrial fine chemicals.[112] Some directing effects are observed with peracid epoxidation (e.g., *cis/trans* = 9:1 with 2-cyclohexenol),[113] *syn*-direction with $OH > CO_2H > CO_2R > OCOR$[114] and a high stereoselectivity with OH and other groups,[115] but the tendency to *cis*-epoxidation with the OH-containing substrate is higher with ROOH/metal catalysts[116]; e.g., cyclohexene-3-ol is epoxidized mainly to the *cis*-product with *t*-BuOOH/$Mo(CO)_6$.[117]

Epoxidation catalyzed by $Mo(CO)_6$ or $VO(acac)_2$ is accelerated by OH groups to products with *cis*-configurations (Table I).[117,118]

The V-catalyzed reaction is fast at room temperature,[119a] e.g., 2-epoxygeraniol from geraniol (Experiment 6).



(42)

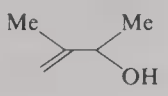
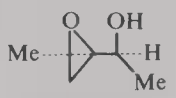
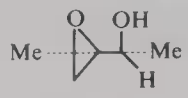
Diolefinic alcohols are thus epoxidized at the double bond nearer to the OH group.[120]

TABLE I. Relative Rates of Epoxidation with Various Oxidants and the *cis/trans* Ratios of Resulting Epoxides[a]

	Oxidant					
	Perbenzoic acid		*t*-BuOOH/$Mo(CO)_6$		*t*-BuOOH/$VO(acac)_2$	
Cyclohexene	Relative rate	*(cis/trans)*	Relative rate	*(cis/trans)*	Relative rate	*(cis/trans)*
Unsubstituted	1.0	—	1.0	—	1.0	—
3-OH	0.55	(92/8)	4.5	(98/2)	>200	(98/2)
3-OAc	0.046	(37/63)	0.07	(40/60)	—	—
4-OH	0.42	(60/40)	11	(98/2)	10	(98/2)

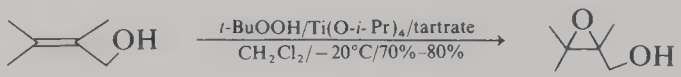
[a] Reference 117, with permission of the American Chemical Society.

TABLE II. Regio- and Stereoselective Epoxidation with Peroxides/Metal Compounds

Olefins	Oxidant	Products (ratio or %)		Reference
		 erythro	 threo	119b
	MCPBA[a]	55	45	
	t-BuOOH/Mo^{6+}	84	16	
	t-BuOOH/V^{5+}	95	5	
3-Cyclooctenol		*cis*-Epoxide	*trans*-Epoxide	118b
	MCPBA[a]	0.2	99.8	
	t-BuOOH/V^{5+}	97	3	
α-Hydroxymethyl-*cis*-stilbene	*t*-BuOOH/Ti^{4+}/Tartrate	*cis*-Epoxide (95% ee)		124

[a] MCPBA, *m*-chloroperbenzoic acid.

Asymmetric epoxidations of allylic alcohols. With chiral peracids the low yield of <10% ee[121] is improved by *t*-BuOOH/Mo or V bearing chiral ligands. For example, 33% at maximum ee is obtained with *N*-alkylephedrine-Mo,[122] and up to 50% ee with a chiral hydroxamate-V catalyst.[123] Over 90% ee is obtained with a tartrate–Ti system [Eq. (49)][124] (see Table II).



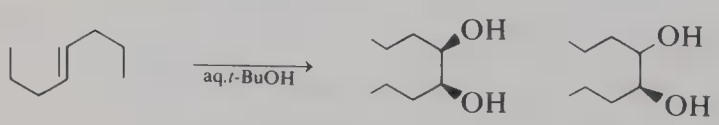
(43)

The yields in epoxidation of hydrocarbon olefins (see Table III) are low (1%–14% ee) with *t*-BuOOH/Mo-(+)-tartrate,[125a] but 60%–100% yields ee are attained with (+)-3-trifluoroacetylcamphor as a ligand.[125b]

3.4.3. *Dihydroxylation of Olefins*

The H_2O_2 oxidation of olefins catalyzed by V_2O_5,[126] H_2WO_4,[94] and SeO_2[127,128] affords *trans*-glycols. Maleic acid is dihydroxylated to DL-tartaric acid in high yield only by H_2O_2/H_2WO_4 at 80–100°C,[129] but the yields are not always that high.

The OsO_4-catalyzed *cis*-dihydroxylation[6,53] with H_2O_2 [Eq. (33)] is improved by using aqueous *t*-BuOOH/OsO_4/Et_4NOH in *t*-BuOH,[130] e.g.,



(44)

H_2O_2/OsO_4	<20%	30%
$BuOOH/OsO_4/Et_4NOH$	73%	7%

The use of base is essential, e.g., Et_4NOAc in *t*-butanol (Experiment 7).[131]

TABLE III. Typical Oxidations of Olefins with Peroxides/Metal Compounds

Olefins	Oxidants	Conditions	Products (yield, %)	Reference
A. Epoxidation				
1-Octene	*t*-BuOOH/$Mo(CO)_6$	PhH, 90°C	Epoxide (92)	106
1-Octene	*t*-BuOOH/MoO_3	105°C	Epoxide (92)	109
Cis-4-Me-2-pentene	$PhCMe_2OOH/MoO_3$	80°C	*cis*-Epoxide (97)	109
Cyclohexene	*t*-BuOOH/$MoO_2(acac)_2$	PhH, 90°C	Epoxide (94)	104
Allyl ethyl ether	*t*-BuOOH/$Mo(CO)_6$	PhH, 95°C	Epoxide (77)	108
Allyl alcohol	*t*-BuOOH/$Mo(CO)_6$	PhH, 100°C	Epoxide (10)	108
Allyl alcohol	*t*-BuOOH/VO $(acac)_2$	PhH, 100°C	Epoxide (83)	108
B. Dihydroxylation				
Maleic acid	H_2O_2/H_2WO_4	H_2O, 80–100°C	*DL*-Diol (95)	129
Cyclohexene	H_2O_2/SeO_2	aq. *t*-BuOH, 55–60°C	*trans*-Diol (65)	128
Cyclohexene	*t*-BuOOH/OsO_4/Et_4NOH	*t*-BuOH	*cis*-Diol (62)	130
cis-4-Octene	*t*-BuOOH/OsO_4/Et_4NOAc	Acetone	threo-Diol (81)	131
C. Oxidative C=C Cleavage				
ArCH=CHMe	H_2O_2/OsO_4	Et_2O	ArCHO (60–75)	7

3.4.4. Oxidative Cleavage

Prolonged reactions often lead to oxidative C=C cleavages as reported with H_2O_2/OsO_4,[7] H_2O_2/SeO_2,[132,133] *t*-BuOOH/OsO_4,[134] and *t*-BuOOH/$Mo(CO)_6$ in the case of enol ethers,[135] e.g.,[7]

$$p\text{-}MeOC_6H_4CH{=}CHMe \xrightarrow[\text{ether; 75\%}]{H_2O_2/OsO_4} p\text{-}MeOC_6H_4CHO \qquad (45)$$

These C=C cleavages occur also with ozone or permanganate.

3.4.5. Ketones from Terminal Olefins

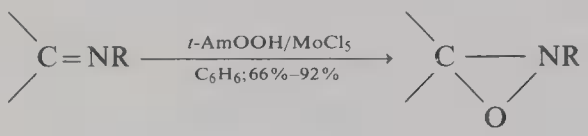
Terminal olefins are oxidized to methyl ketones by *t*-BuOOH/Pd salts.[136]

$$RCH{=}CH_2 \xrightarrow{t\text{-BuOOH/Pd(OCOCF}_3)_2} RCOCH_3 \qquad (46)$$

For example, 1 hexene and styrene are converted to 2-hexanone and acetophenone, respectively (>98%), but internal olefins do not react[136] (Experiment 8). Subsequent reduction affords secondary alcohols $RCH(OH)CH_3$, in contrast to another process which leads to primary alcohols ($RCH{=}CH_2 \xrightarrow{t\text{-BuOOH}-MoO_3}$ epoxide $\xrightarrow{H_2Ni} RCH_2CH_2OH$).[137]

3.4.6. Oxidation of C=N Bonds

Oxidation of imines to oxaziranes is usually done with peracids,[138] but is also possible with $ROOH/MoCl_5$,[139]



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3.5. Oxidation of C–H Bonds

This section treats hydroxylation (see Table IV) and acyloxylation (see Table V) of aliphatic, aromatic, and activated C–H bonds such as allylic C–H bonds by the metal-catalyzed acyloxylation with peresters or diacyl peroxides followed by alkaline hydrolysis.

3.5.1. Direct Hydroxylation of Aliphatic C–H Bonds

Although alkanes are oxidized by 30% H_2O_2/CF_3CO_2H,[140] H_2O_2/super acid,[141] etc., hydroxylations are not selective, e.g., cyclohexane with *t*-BuOOH/$Cr(acac)_2$ affords cyclohexanol and cyclohexanone,[142] and pentane with $ROOH/B_2O_3$ gives pentanals (only 4%–20%).[143]

An efficient way of α-hydroxylation of olefins (allylic hydroxylation) is to employ 90% *t*-BuOOH with SeO_2[111]

$$PhC(CH_3)=CH_2 \xrightarrow[CH_2Cl_2;54\%]{t\text{-BuOOH}/SeO_2} Ph(CH_2OH)=CH_2 \qquad (48)$$

A formyl group is unattacked; acetylenes are also hydroxylated.[111] This reagent is superior[111,144] to SeO_2 alone or aqueous H_2O_2/SeO_2.

TABLE IV. Hydroxylation of C–H Bonds

Substrate	Conditions	Products (percent yield: *o*:*m*:*p*)	Reference
A. Hydroxylation of Aliphatic C–H Bonds			
1-Decene	*t*-BuOOH/SeO_2/CH_2Cl_2	3-Hydroxy-1-decene (61)	77
1-Decyne	*t*-BuOOH/SeO_2/CH_2Cl_2	3-Hydroxy-1-decyne (48)	77
Cyclohexane	*t*-BuOOH/Cr^{2+}/108°C	Cyclohexanone (42) $C_6H_{11}OH$ (22)	142
B. Hydroxylation of Aromatic Rings[a]			
Toluene	90% $H_2O_2/AlCl_3$/0–5°C	Cresols (40; 60:8:32), ClC_6H_4Me (16)	54
Toluene	$S_2O_8^{2-}/Fe^{2+}/Cu^{2+}$	Cresols (81; 63:3:33), $PhCH_2OH$ (63)	165
PhCl	$S_2O_8^{2-}/Fe^{2+}/Cu^{2+}$	HOC_6H_4Cl (50; 19:3:78)	164
PhCl	H_2O_2/Fe^{2+}/Catechol	HOC_6H_4Cl (24; 45:15:40)	27
Mesitylene	*t*-BuOOH/B_2O_3/100°C	Mesitol (81)	143

[a] Percent yield are based on peroxides charged.

3.5.2. Oxidation of Ethers

The Fenton and persulfate–metal oxidations of ethers start by α-H abstraction,[68,145] but then afford a complex mixture. α-Acyloxylation of ethers with peresters/Cu^+ is applicable to organic synthesis.

3.5.3. Oxidation of Benzylic C–H Bonds

Although the oxidation of an alkylbenzene with H_2O_2/Fe^{2+} results in complex mixture,[146,147] oxidations with $S_2O_8^{2-}/Ag^+$ give preferentially benzaldehyde (51%) from toluene[70] and acetophenone from ethylbenzene[148]:

$$PhCH_2CH_3 \xrightarrow[65\text{–}70\,^\circ C;\,73\%]{(NH_4)_2S_2O_8/AgNO_3} PhCOCH_3 \qquad (49)$$

Tetraline is similarly oxidized to tetralone (65%) with H_2O_2/V_2O_5,[126] and anthracene to anthraquinone (80%) with $H_2O_2/Fe(OAc)_3$ at 110°C,[149] β-diketones,[150] and lactones.[151] α-Acyloxylation of ketones is done via enamines followed by acyloxylation with benzoyl peroxide/HCl.[152,153] The α-acyloxylation with perester is inefficient for amines,[154] but well applicable to *N*,*N*-dialkylamides.[155,156]

3.5.4. Direct Hydroxylation of Aromatic Rings

In analogy to the hydroxylation with peracid alone,[157] aromatic hydroxylation is attained with H_2O_2 or ROOH using acid catalysts such as $AlCl_3$,[54,158] HF,[55] pyridine-HF,[159] H_2SO_4,[160] phosphoric acids,[161] metaborate,[107a] and super acids[56,141,162]; e.g., toluene with $H_2O_2/AlCl_3$ yields cresols ($o:m:p = 56:8:36$).[158]

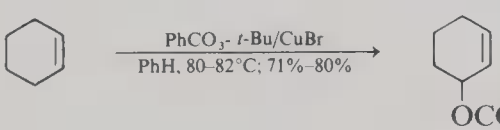
The Fenton (H_2O_2/Fe^{2+}) hydroxylation gives a mixture of products including the side chain oxidations,[146,163] whereas rather higher yields of phenols are obtained by H_2O_2/Fe^{2+}/catechol [Eq. (17)].[27] The hydroxylation of benzene with $S_2O_8^{2-}/Fe^{2+}$ (26% yield) is improved on addition of Cu^{2+} (64% yield)[164]; toluene with $S_2O_8^{2-}/Fe^{2+}/Cu^{2+}$ affords 81% yield of cresols ($o:m:p = 63:3:33$) [Section 2.1.3, Eq. (19)].[165] These redox reactions, however, are conducted in aqueous solutions, which are too dilute for synthetic applications.

3.5.5. Acyloxylation of Allylic C–H Bonds[166]

Useful acetoxylation agents of activated C–H bonds are peresters[167] or diacyl peroxides[166] with metal ions or with irradiation via R′COO• radicals.

$$RH + R'CO_3\text{-}t\text{-}Bu \xrightarrow[R' = Me \text{ or } Ph]{\text{Metal ion or } h\nu} ROCOR' + t\text{-}BuOH \qquad (50)$$

Allylic C–H bonds are acycloxylated on heating with peresters/Cu^+ (Experiment 14); e.g.,[168]



(51)

The acyloxylation is accompanied by migration of the double bond, affording a mixture of isomers, e.g., either 1- or 2-butene yields a 9:1 mixture of $CH_3CH(OCOR)=CH_2$ and $CH_3CH=CHCH_2OCOR$.[169]

Predominant formation of terminal olefins is often observed by the double bond migration (Table V).[170,171] The addition of excess acid $R'CO_2H$ enables the introduction of a $R'CO_2$ group.[170] The formation of 7-*t*-butoxy-[172] and 7-benzoyloxy-norbornadiene[173] from

TABLE V. Acyloxylation of C–H Bonds

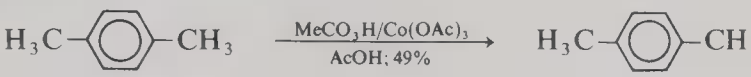
Substrate	Conditions	Products (percent yield; $o:m:p$)	Reference
A. Acyloxylation of Allylic C–H Bonds			
Cyclohexene	$PhCO_3Bu/CuBr/PhH$	3-Benzoyloxycyclohexene (80)	168
Cyclohexene	$PhCO_3Bu/CuBr/AcOH$	3-Acetoxycyclohexene (57)	170
$R'CH_2CH=CH_2$	$PhCO_3Bu/CuX$	$RCHCH=CH_2$ (OCOPh) + $RCH=CHCH_2$ (OCOPh) (80; 85:15)	170, 16a, 171a
$Me_2C=CMe_2$	$PhCO_3Bu/Cu(OCOR)_2$	$Me_2C(OCOPh)C(Me)=CH_2$ (78)	171b
B. Acyloxylation of Other Activated C–H Bonds			
$PhCHMe_2$	$MeCO_3Bu/Cu(Ac)_2$	$PhC(Me)_2OAc$ (28)	171a
$PhOCH_2CH_3$	$PhCO_3Bu/CuBr$	$PhOCH(OBz)CH_3$ (37	180
EtOEt	$PhCO_3Bu/Cu(OCOR)_2/hv$	$EtOCH(OBz)CH_3$ (77)	155[a]
$PhCH_2SR$	$PhCO_3Bu/CuBr$	PhCH(OBz)SR (30–91)	183
THF	$MeCO_3Bu/CuBr/hv$	2-Acetoxy-THF (75)	155
C. Acyloxylation of Aromatic C–H Bonds			
Toluene	$(PhCO_2\text{-})_2/CuCl_2$	Benzoates (38; 56:18:26)	191
Toluene	$(i\text{-}PrOCO_2\text{-})_2/CuCl_2$	Carbonates (85; 56:18:26)	191
PhCOMe	$(i\text{-}PrOCO_2\text{-})_2/CuCl/MeCN$	Carbonates (27; 50:33:17)	195
Naphthalene	$(i\text{-}PrCO_2\text{-})/CuCl/MeCN$	Carbonates (89; $\alpha:\beta = 92:8$)	195

[a] $Cu(OCOR)_2$: Cu(II) 2-ethylhexoate.

norbornadiene (Experiment 15) and 3-benzoyloxy-1-butene from 2-butene[174] belongs to this type of radical reaction. But the acetoxylation of olefins with diacyl peroxide/Cu^+ often results in a mixture of products via addition and H abstraction reactions.[167,174]

3.5.6. Acyloxylation of Other Activated Aliphatic C–H Bonds[166]

Activated C–H bonds are likewise acetoxylated with peroxides/Cu^+. Benzylic C–H bonds give lower yields[171a]; e.g., the isde chain acyloxylation of cumene gives 40% yield with RCO_3-*t*-Bu/CuBr[171a,175] and 20% with *t*-BuOOH/CuCl/$PhCO_2H$.[176] Peracid/Co^{3+} can oxidize aromatic methyl groups[177], e.g.,



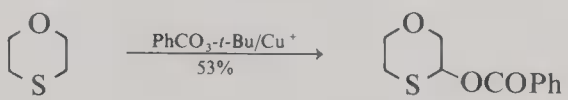
(52)

Heating xylene with diacyl peroxide/$CuCl_2$ results in selective ring acyloxylation[35a] (Section 3.5.7).

The perester/Cu^+ oxidant is useful for α-acetoxylation of ethers, thioethers, etc., although it is possible with diacyl peroxides alone.[178,179]

$$R^1OCH_2R^2 + RCO_3\text{-}t\text{-}Bu \xrightarrow{Cu^+/Cu^{2+}} R^1OCHR^2 + t\text{-}BuOH \qquad (53)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OCOR$$

Thus anisole[180] and diethyl ether are acyloxylated[155] in 23% and 82% yields, respectively. The acyloxylation of benzyl alkyl ethers occurs preferentially at the benzyl CH_2.[181] Tetrahydrofuran affords mainly α-*t*-butoxy-THF 41% with $MeCO_3$-*t*-Bu, probably via α-acetoxylation, elimination to α,β-unsaturated ether, and then addition of *t*-BuOH.[182] Thioethers are acyloxylated similarly.[180,183,184] The following reaction exemplifies the activation by S rather than by O[185]:



(54)

Formyl groups are acyloxylated to yield anhydrides[154]; thus,

$$PhCHO \xrightarrow[70\%]{PhCO_3\text{-}t\text{-}Bu/CuBr} PhCOCPh \qquad (55)$$
$$\qquad\qquad\qquad\qquad\qquad\quad \| \;\; \|$$
$$\qquad\qquad\qquad\qquad\qquad\quad O \;\; O$$

This reaction enables syntheses of mixed anhydrides. The acyloxylations with perester/CuX are inefficient for α-C–H bonds of ketones, acids, and esters; e.g., diethyl malonate with $PhCO_3$-*t*-Bu/CuCl affords low yields of $PhCO_2CH(CO_2ET)_2$ (16%) and *t*-$BuOCH(CO_2Et)_2$ (26%),[185] but the acyloxylation of malonate is effective with benzoyl peroxide/EtONa (78%).[186,187] The same oxidation with peroxide alone is efficient for β-ketoesters.[188]

3.5.7. Acyloxylation of Aromatic Rings

Aromatic acyloxylations are attained with diacyl peroxides $(RCOO\text{-})_2/Cu^{2+}$ via acyloxy radicals (RCOO·) [Eq. (18)]. Benzoyl peroxide (R = Ph) (Experiment 9) and diisopropoxy peroxy dicarbonate (R = *i*-PrO) are often used. Aliphatic diacyl peroxides (R = alkyl) do not work, since decarboxylation ($RCO_2\cdot \longrightarrow R^\cdot + CO_2$) is very fast. The additional oxidants in Eq. (18) may be oxygen,[189] iodine,[190,191] and $CuCl_2$[35a,192,193]; the isomer distributions do

not differ with changing the oxidants.[190,193] Polycyclic aromatics such as naphthalene[194] and anthracene[195] are acyloxylated (20%–80%) even without additional oxidants.

The aromatic oxygenation with dialkoxyperoxydicarbonates is efficiently conducted with $CuCl_2$ (better than with CuCl) in acetonitrile.[196,197] The yields are over 80% for benzenes with electron-releasing groups. The reaction is less efficient for chlorobenzene.[198,199]

Aromatic acyloxylation with diacyl peroxides catalyzed by $AlCl_3$ [Eq. (30)],[200] CF_3CO_2H,[201] HNO_3,[202] or $(NH_4)_2Ce(NO_3)_6$[203] is unsatisfactory; other acyloxylations were attempted with $S_2O_8^{2-}/Pd(OAc)_2/AcOH$[204] and $S_2O_8^{2-}/Cu(OAc)_2/AcOH$,[205] the former reaction favoring *m*-substitution.

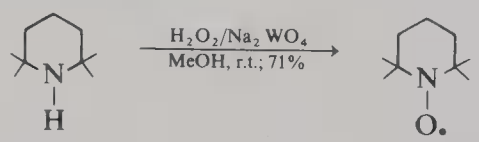
3.6. Oxidation of Nitrogen Compounds

Tertiary Amines. Although oxidation of tertiary amines to *N*-oxides is facile with H_2O_2[206,207] or peracid alone,[208] it can still be improved by using hydroperoxide/V salt[42,139,209] or Mo[209] salt (Experiment 17)[42]:

$$n\text{-}C_{12}H_{25}NMe_2 \xrightarrow[t\text{-BuOH, 65–90°C; 76%–83%}]{t\text{-BuOOH/VO(acac)}_2} n\text{-}C_{12}H_{25}\underset{\displaystyle O}{\overset{\displaystyle \downarrow}{N}}Me_2 \qquad (56)$$

Similarly, pyridines are oxidized with $ROOH/MoCl_5$.[52,210] The products in Eq. (56) can be easily isolated.

Secondary Amines. Secondary amines are oxidized with H_2O_2 alone to hydroxylamines,[211] then with *t*-BuOOH to nitrones.[212] Amines without α-hydrogen are oxidized to nitroxyl radicals with $t\text{-BuOOH/Na}_2WO_4$[213] the method is useful for the preparation of nitroxyl radicals,[214] e.g.,



(62)

Primary Amines. The reaction course for primary amines varies with the peroxide and the catalyst. The oxidation with H_2O_2/WO_4^{2-} affords oximes; i.e., 40%–90% yield with R = Et, Ph, cyclohexyl, etc.[215,216] [Eq. (63a) and Experiment 10]. In the case of $S_2O_8^{2-}/Ag^+$, intermediate imines are hydrolyzed to aldehydes (60%–90%).[217]

$$RCH_2NH_2 \xrightarrow[\text{aq. EtOH}]{H_2O_2/Na_2WO_4} RCH{=}NOH \quad \text{(Refs. 215, 216)} \qquad (57a)$$

$$RCH_2NH_2 \xrightarrow[\text{water}]{S_2O_8^{2-}/AgNo_3/NaOH} RCHO \quad \text{(Ref. 217)} \qquad (57b)$$

In analogy to peracid oxidation,[218] catalytic hydroperoxide oxidations of anilines give azoxybenzenes and nitrobenzenes (Experiment 11).

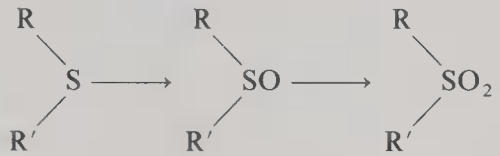
$$ArNH_2 \xrightarrow[70°C; 92\%–100\%]{t\text{-BuOOH/Ti}^{4+}} ArN{=}\underset{\displaystyle O}{\overset{\displaystyle \downarrow}{N}}Ar \quad \text{(Ref. 219)} \qquad (58a)$$

$$ArNH_2 \xrightarrow[160–170°C]{t\text{-BuOOH/VO(acac)}_2} ArNO_2 \quad \text{(Ref. 220)} \qquad (58b)$$

Oxidation to nitrobenzenes is also possible with CF_3CO_3H[221] or $H_2O_2/(CF_3)_2C{=}O$.[138]

3.7. Oxidation of Sulfur Compounds

Sulfides are easily oxidized to sulfoxides and then to sulfones:



(59)

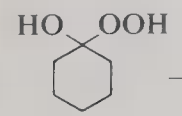
Sulfoxides are obtained by heating sulfides with H_2O_2 alone,[222] $H_2O_2/VO(acac)_2$,[223a,223b] $H_2O_2/NaVO_3$,[49b] $H_2O_2|SeO_2$,[224] or ROOH/Mo or V catalysts.[48,225] Asymmetric sulfoxides are formed with low (<10% ee) optical yields with *t*-BuOOH/$VO(acac)_2$ in optically active alcohols.[226]

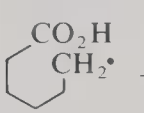
While the oxidation to sulfones is generally done with peracids, the systems with H_2O_2/Na_2WO_4[49,222] and ROOH/$MeO_2(acac)_2$ are also effective.[227] The relative reactivity is in the order $R_2S > R_2SO > C{=}C$.[225a]

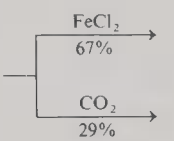
3.8. Miscellaneous Types of Oxidation

3.8.1. Functionalization via Ligand Transfer

The carbon radicals, formed by the redox decomposition of tertiary hydroperoxides with Fe^{2+}, are subject to ligand transfer reaction as well as coupling as shown in Experient 4,[19,228] e.g., cyclohexanone peroxide gives products of Eq. (67).



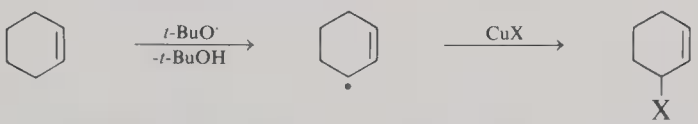




$Cl(CH_2)_5CO_2H$ (Ref. 22b) (60a)

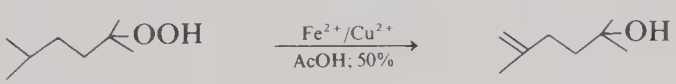
$HO_2C(CH_2)_5CO_2H$ (Ref. 229) (60b)

The substitutions at allylic carbon are attained by *t*-BuOOH/Fe^{2+}/CuX using the ligands X or Cl, Br, I, N_3, SCN, CN, S_2O_3Na, etc.,[230–233] e.g.,



(61)

Interestingly, an intramolecular remote functionalization is possible which includes the Cu^{2+} oxidation of the intermediate radical to olefins,[234] e.g.,



(62)

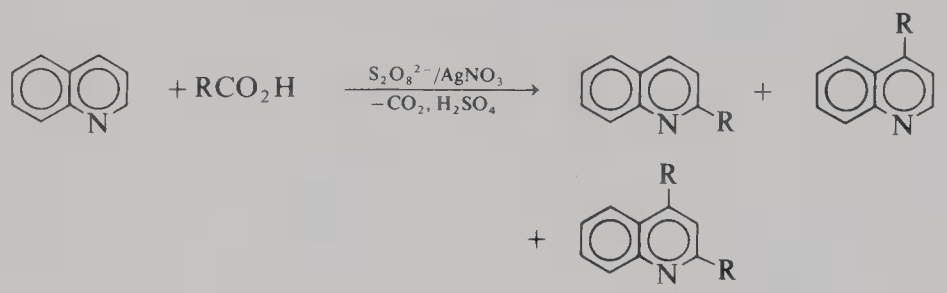
Another application is a redox reaction including β-scission of intermediate alkoxy radicals from hydroperoxide to the lactone recifeiolide (**6**).[235]

(63)

6

3.8.2. *Alkylation and Acylation of Heteroaromatic Bases*[236]

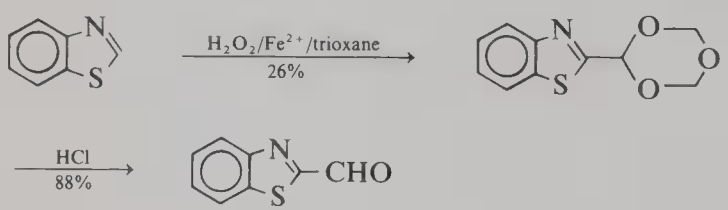
Alkylation and acylation of protonated heteroaromatic bases, which do not undergo Friedel–Crafts reactions, are possible by substitutions with alkyl and acyl radicals.[236] Alkyl radicals are produced by oxidative decarboxylation of carboxylic acids with $S_2O_8^{2-}/Ag^+$. For example, quionolines are alkylated at the 2- and 4-positions with R = Me, Et, *i*-Pr, $PhOCH_2$, etc. or at the 2-position with R = *t*-Bu.[237,238] See also Experiment 12.



(64)

Acyl radicals R′CO$^\bullet$ are formed by H atom abstraction of aldehydes R′CHO with $ROOH/Fe^{2+}$ in acidic media[234]; e.g., quinoxaline (Experiment 13)[239a] and benzothiazol[239b] are 2-acylated with R′ = Me, Et, *t*-Bu, allyl, and Ph 50%–80%, while quinoline is 2,4-diacylated.[239c]

Carboxylations are also possible via the $\cdot CO_2Et$ radical produced from ethyl pyruvate $(CH_3COCO_2Et)/H_2O_2/Fe^{2+}$.[240] Carboxyamidations with the $Me_2N\dot{C}{=}O$ radical are attained by H_2O_2 or *t*-BuOOH/Fe^{2+} in the presence of DMF ($Me_2NCH{=}O$) accompanying α-amidoalkylation with $\cdot CH_2NMeCHO$.[241] When trioxane $(CH_2O)_3$ is used, benzothiazole is substituted with the CHO group via substitution with trioxane.[242]

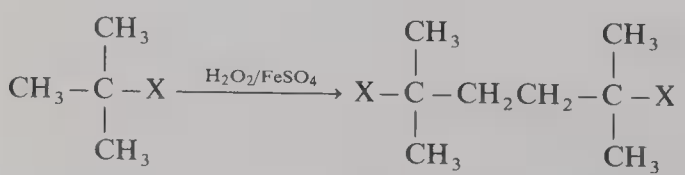


(65)

A similar alkylation is possible with dioxane/H_2O_2/Fe^{2+} and MeOH/H_2O_2/Fe^{2+}.[243]

3.8.3. *Dimerization*

Dimerizations induced by the Fenton reagent are reported for alcohols, amines, nitriles, acids, esters, ethers, and ketones.[15,67] Most of these reactions yield complex mixtures, hence inappropriate for syntheses. However, rather high yields are obtained with the dimerizations of pivalic acid (37%), pivalonitrile (52%),[244] and *t*-butanol (46%),[245] where hydrogen abstraction by HO$^\bullet$ affords only one radical (Experiment 18).

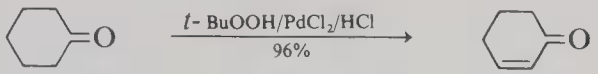


(66)

The dimerization of phenols is possible with H_2O_2/Fe^{2+},[246] but better results are obtained with $S_2O_8^{2-}/Ag^+$; e.g., 60% yield with $S_2O_8^{2-/Ag}{}_+$ for dimerization of 2,6-dimethylphenol at the 4-position,[247] whereas the use of $S_2O_8^{2-}/OH^-$ results in Elbs hydroxylation, affording 2,6-dimethylhydroquinone.[248]

3.8.4. Dehydrogenation

A useful dehydrogenation is reported with ketones using ROOH/Pd[249]



(67)

3.8.5. Decarboxylation

Aliphatic acids are oxidized via a decarboxylation reaction ($RCOO\cdot \rightarrow R\cdot + CO_2$) to olefins with $S_2O_8^{2-}/Ag^+/Cu^{2+}$; e.g., butyric acid to propene (85%).[250] Likewise, the reaction of diacyl peroxide $(RCO_2\text{-})_2$ with Cu^{2+} gives radical R·, which is oxidized either to an olefin or a carbonium ion.[251,252]

4. EXPERIMENTAL CONSIDERATIONS AND PROCEDURES

4.1. General Comments

When planning experiments using peroxides, one should keep in mind that peroxides are explosive in nature and some of them are eye irritants, so that handling, storage, and disposal of mixtures containing peroxides should be done carefully. Since the extent of danger varies with each peroxide and condition, one should beforehand read reviews on their hazards.[253,254] *t*-Butyl hydroperoxide, cumyl hydroperoxide, benzoyl peroxide and $<60\%$ aqueous H_2O_2 are practically safe with ordinary careful treatment, but low molecular weight peroxides in neat form are very dangerous. The extent of their hazard increases with the content of active oxygen. Thus high concentrated H_2O_2, acetyl peroxide, acetone peroxides, and performic acid are highly explosive, so that their use should be avoided.

The hazard of peroxides is evaluated by the burning test, rapid heating test, flash point, shock sensitivity,[254] and pressure vessel test.[255] Acetyl, benzoyl, ketone peroxides, and peroxydicarbonate are ranked as shock sensitive, leading to detonation hazard.

Instructions for handling dangerous peroxides are as follows:

a. Safety glasses and gloves should be worn and the reaction conducted behind a safety shield.
b. The reaction should be started by dropping peroxide carefully into a substrate or solvent with efficient stirring. Never add in reverse order. Never start sudden stirring.
c. The reaction should be conducted in a dilute solution; if possible avoid the isolation distillation of peroxides.
d. Use a minimum amount of peroxide. Conduct experiments on a minimum scale.
e. The remaining peroxide should be reduced completely with a reducing agent after oxidation or before distillation of the products.
f. Avoid the use of a metallic spatula or contamination of metallic compounds and dust. Never use a ground-glass stopper in contact with peroxides.
g. Since peroxides may evolve oxygen gas, a storage bottle with a vent and a sparkless refrigerator are recommended. But overcooling may lead to the deposit of hazardous crystals of peroxide.

There has been no hazardous accident in our laboratory, although we have been treating peroxides for 25 years.

4.2. Availability and Handling of Peroxides

Syntheses, availability, and properties of organic peroxides have been summarized[15,256]; also details for each peroxide[59] and hydrogen peroxide[15] are published. In the following paragraphs are given brief special comments on some peroxides.

Hydrogen Peroxide (m.p. −89°C).[15] Aqueous 30% H_2O_2 is relatively stable. Before handling 60%–100% H_2O_2, detailed precautions,[255,257] a brief review,[258] and also handling instructions from suppliers should be read. Pertinent precautions are summarized as follows.

Mixing 35% H_2O_2 with an organic substance may lead to an explosive mixture.[15] When the mixture is separated in two phases, each phase may be over the explosive limit. Hence the reactions should be conducted with lower contents of H_2O_2, e.g., $<10\%$ ($<3\ M$) H_2O_2.

Anhydrous ethereal solutions of H_2O_2 are prepared by dehydration with $Na_2SO_4 + MgCO_3$,[259] and an anhydrous *t*-BuOH solution is likewise obtained for 30% H_2O_2 and *t*-BuOH (1:4) using Na_2SO_4 and $CuSO_4$.[6]

Peroxydisulfate Salts. Anhydrous ammonium, potassium, and sodium salts are stable at room temperature for a long time. The peroxide is hydrolized slowly in aqueous solutions; in the presence of sulfuric acid it is easily hydrolyzed to yield peroxymonosulfuric acid (Caro acid).

t-Butyl Hydroperoxide (liquid, flash point 36°C). Commercial 70 and 90% *t*-BuOOH contain *t*-BuOH, water and sometimes *t*-Bu_2O_2. The contamination of *t*-Bu_2O_2 is dangerous, when products are to be distilled (aqueous *t*-BuOOH is free of *t*-Bu_2O_2). Aqueous 70% *t*-BuOOH is dehydrated by azeotropic distillation from benzene or dichloroethane solutions (70% *t*-BuOOH: $Cl-CH_2CH_2Cl = 10:17$ vol). *t*-BuOOH is purified by vacuum fractionation behind a safety shield.[260] Special precautions for handling *t*-BuOOH are as follows:

a. Never add a strong acid (even a drop) to concentrated *t*-BuOOH.
b. Never work with over 95% peroxide.

Cumene Hydroperoxide (liquid, flash point 54°C). Commercial 70% hydroperoxide includes cumene, acetophenone, and water. The peroxide is widely used as a curing agent and an initiator for radical reactions, but it is not appropriate for general preparative oxidations because product isolations are less easy than with *t*-BuOOH.

Peracid. *m*-Chloroperbenzoic acid (>85% pure) is available commercially, and stable at room temperature. Perbenzoic acids are prepared by the reaction of benzoyl chlorides or peroxides with alkaline H_2O_2,[261] or benzoic acid with 70% H_2O_2 in methanesulfonic acid.[262]

Commercial peracetic acid ($\leqslant 40\%$ solution) decomposes gradually during storage even in a refrigerator. The peracid obtained via autoxidation of acetaldehyde is free of sulfuric acid or water.[263] Trifluoroperacetic acid is prepared from the anhydride with 90% H_2O_2.[258] Preparations of peracids are reviewed.[61,264] Peracetic acid may often contain or produce acetyl peroxide, which is a violent explosive.[265]

Peresters. *t*-Butyl perbenzoate (neat or 50% solution) and peracetate (50%–75% solution) are available commercially. Peresters are easily prepared by adding *t*-BuOOH to a stirred mixture of acyl chloride and pyridine in inert solvents.[266]

Diacyl Peroxides. Benzoyl peroxide (m.p. 107°C) of over 98% purity is available commercially. Substituted benzoyl peroxides are easily synthesized from aroyl chlorides and Na_2O_2.[267]

Acetyl peroxide (m.p. 30°C) is available as 25% solution in dimethyl phthalate, which may precipitate explosive crystals on overcooling. Various diacyl peroxides are prepared by addition of acyl chloride to a mixture of 30% H_2O_2 and pyridine.[268]

Peroxydicarbonates.[269] Dialkoxyperoxydicarbonates are unstable at room temperature and should be stored in a refrigerator. Diisopropoxyperoxydicarbonate is the most general one available as solid (m.p. 8–10°C) or as 50% solution. This is one of the most dangerous peroxides.[42,255,268]

Dialkyl Peroxides. Dicumyl and di-*t*-butyl peroxides are available neat, but applications for synthesis are rare because of their poor reactivity.

Shock sensitivities of peroxides are especially high for solid, so that one should be careful of solvent evaporation or overcooling. *t*-BuOOH, $PhCMe_2OOH$, $PhCO_3$-*t*-Bu, and *t*-Bu_2O are not shock sensitive, while $(MeCOO\text{-})_2$ and $(PhCOO)_2$ are.[254,255,269]

4.3. General Procedures

4.3.1. General Precautions

Safety handlings of peroxides are reviewed and summarized in detail for organic peroxides overall,[253] H_2O_2,[255] *t*-BuOOH,[116] and peracids.[270] Additional precautions for general workup are summarized as follows:

a. Peroxides are explosive and should be handled carefully. A safety shield or a vent for gas are essential.
b. Peroxidic solutions of less than 5% active oxygen are generally safe.[271]
c. An attempted reaction should be conducted possibly on a very small scale. Any scale up from the reported one is dangerous in some cases due to uncontrolable reaction temperature rise.
d. The remaining peroxides after the reaction should be reduced until negative for peroxide test (iodometry). Also avoid accumulation of peroxide during the reaction.

4.3.2. Catalysts and Solvents

In organic solvents, some metal catalysts are made soluble by using ligands such as CO, acetylacetonate (acac), acetate (AcO), etc., which are available commercially. OsO_4 and SeO_2 are highly toxic. The other heavy metallic ions may be more or less toxic.

Reactions using H_2O_2 are generally carried out in water soluble solvents such as alcohols and acetonitrile. Acetone is inappropriate because of the formation of explosive peroxides. Ethers (including tetrahydrofuran) and dimethyl sulfoxide are not suitable, since they may be oxidized.

Suitable solvents are those of unreactive nature; e.g., acetonitrile, benzene, dichloromethane, or dichloroethane. Alcohols or ethers cannot be used for the redox reactions involving radicals. DMF is not appropriate since it interacts with metals. Thus the choice of solvents depends on the reactions.

4.3.3. Work-up Procedures

Remaining peroxides should be decomposed before product isolation after estimating it iodometrically. Water soluble peroxides, e.g., H_2O_2, $S_2O_8^{2-}$, and peracetic acid are easily washed out with water. H_2O_2 may be decomposed catalytically by platinum oxide[272] or catalase.[273]

Generally, reductions of peroxides in organic solvents are carried out by shaking with aqueous $NaHSO_3$, Na_2SO_3, or $FeSO_4$. These reducing agents should be added separately in small portions, since the reduction may proceed exothermally.

Peracids are conveniently reduced by adding dimethyl sulfoxide (DMSO). Some problems remain for peroxides which are not easily reduced, e.g., *t*-Bu_2O_2. Perester is reduced with KI in AcOH[274] or decomposed by repeated hydrolysis with 2N NaOH.[275] Decomposition of easily reducible peroxides is also possible only by passing over alumina,[276] basic ion-exchange resins,[277] or zeolite columns.[278]

4.3.4. Analysis of Peroxides

Analyses of peroxides are performed by chemical (i.e., the reduction with iodide or arsenite, etc.) and physical methods (e.g., GLC, ir, polarography, etc.).[279] Iodometric titrations are the most general ones, their conditions depending on the reactivity of peroxides. For example, rapidly reducible peroxides such as peracids, H_2O_2, hydroperoxides, diacyl peroxides, and peroxydicarbonates are refluxed with NaI in AcOH-*i*-PrOH (1:10).[280] Peroxydisulfates are determined after 5 min standing in 10% KI–H_2O–AcOH.[281] Dialkyl peroxides may be analyzed by GLC.[282]

4.4. Typical Procedures

Some of the typical experimental procedures using peroxides are shown in the following paragraphs. Also the reactions described in *Organic Syntheses* are included at the end only by their subjects. Reference pages are indicated at the end of subjects.

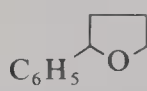
Experiment 1: $NiBr_2$-Catalyzed Oxidations of Alcohols to Carbonyl Compounds by Benzoyl Peroxide.[35] *

$$PhCH_2CHPhOH + (PhCOO\text{-})_2 \xrightarrow[CH_3CN]{NiBr_2} PhCH_2COPh + 2PhCOOH$$

A homogeneous solution of 1,2-diphenylethanol (1.98 g, 12.7 mmol), and either anhydrous $NiBr_2$ or the more soluble $NiBr_2$-1,2-dimethoxyethane complex (2.6 mmol) in 20 ml of anhydrous acetonitrile is heated at 60°C for 24 h. The reaction solution is then cooled and aqueous KI is added to decompose excess peroxide. Following extraction with ether, subsequent acid and base washings of the ether solution, and solvent removal, 2-phenylacetophenone is obtained as the sole product (1.84 g, 9.40 mmol, 94%). Analogously, other secondary alcohols are converted to the ketones (85%–95% yield) and primary alcohols to the aldehydes (58%–96% yield) and esters. $NiBr_2$ is quantitatively recovered.

Experiment 2: Ag^+-Catalyzed Peroxydisulfate Oxidation of 4-Phenylbutan-1-ol to 4-Phenyltetrahydrofuran.[72]

$$C_6H_5-(CH_2)_4OH + Na_2S_2O_8 \xrightarrow{AgNO_3/Cu(OAc)_2}$$



$$+ 2\ NaHSO_4$$

A solution of 4-phenylbutan-1-ol (0.03 mol), $AgNO_3$ (0.005 mol), and $Cu(OAc)_2$ (0.002 mol) in water (10 ml) and CH_3CN (10 ml), vigorously stirred and refluxed, was slowly added with aqueous $Na_2S_2O_8$ (0.02 mol) in water (10 ml).

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Stirring and refluxing were continued for a further 4 h. The mixture was diluted with water after cooling and extracted three times with ether. After removal of the solvents under vacuum, a crude oil (3.96 g, 88%) was analyzed by GLC using a column packed with 10% Carbowax 20M on Chromosorb W DMCS, 80–100 mesh. After recovering 4-phenylbutan-1-ol (62.5%), there is obtained 2-phenyltetrahydrofuran (37.5%) based on converted alcohol, 2-Phenyltetrahydrofuran was isolated on a silica gel column using hexane-CH_3CO_2Et (8:2) as an eluant.

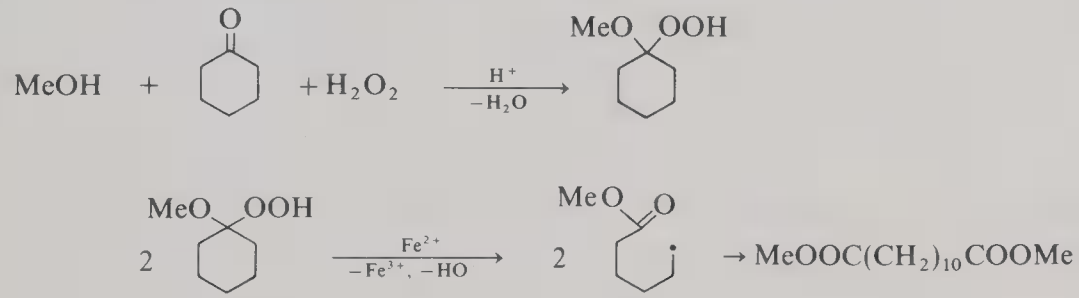
Experiment 3: Oxidation of Methacrolein to Methacrylic Acid with H_2O_2/SeO_2 [Eq. (35)].[78]*

$$CH_2{=}C(CH_3)CHO + H_2O_2 \xrightarrow{SeO_2} CH_2{=}C(CH_3)CO_2H + H_2O$$

Caution: Selenium dioxide is toxic and 90% H_2O_2 is explosive on contract with iron etc.

A solution of 5 g of selenium dioxide in 350 g of *t*-BuOH was combined with 105 g (1.5 mol) of methacrolein and stirred while 38 g (1.0 mol) of 90% H_2O_2 was added dropwise in 17 min. Cooling was applied to keep the temperature at 60°C. After 1.5 h a titration indicated that 0.95 equivalents of metacrylic acid had been generated. The product was stripped of all volatile material by warming in a water bath at 55–60°C (80 mm) and finally at 75°C (1 mm). This left 11 g of red residue and took overhead 484 g of distillate containing 0.937 equivalents of acid. A 434-g portion of the distillate was redistilled through a small helically column having four copper wires running through the packing for the length of the column to act as a polymerization inhibitor. A piece of copper wire was also suspended in the stillhead. After the alcohol and a small intermediate cut of 4.5 g, methacrylic acid (43.5 g) was collected at 69–71°C.

Experiment 4: Preparation of Dimethyl Dodecane-1,12-dioate from Cyclohexanone with $H_2O_2/FeSO_4/MeOH$.[19c]†



Methanol (3,200 g, 100 mol), cyclohexanone (490 g, 5 mol), and concentrated H_2SO_4 (20 g, ca. 0.2 mol) are mixed in a vessel at 5°C and stirred. Aqueous 35% H_2O_2 (580 g H_2O_2, 6 mol) was gradually introduced while keeping the temperature at 5°C, and stirred for a further 10 min to form methoxycyclohexyl hydroperoxide.

In another vessel were placed methanol (1,760 g, 55 mol) and $FeSO_4 \cdot 7H_2O$ (2,000 g, 7.2 mol) at 10°C after replacing the internal air with nitrogen. The methanolic peroxide solution was introduced while stirring slowly into the methanolic $FeSO_4$ solution. The temperature rose to 42°C during further stirring until the completion of the reaction.

After recovery of methanol (4,710 g) by distillation, the dark brown residue (3,380 g) was separated into two layers; the upper layer contains ester and the lower layer contains iron salts.

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The upper layer was washed with water, dried, and afforded dimethyldodecane-1,12-dioate (70% yield by GLC analysis). The crude product consisted of 9.3% dimethyldodecane-1,12-dioate (b.p. 180–200°C/2 mm Hg) and 8.7% methyl oxycaproate (b.p. 120–130°C/2 mm Hg).

$Mo(CO)_6$.[116]*

$$CH_3(CH_2)_7CH{=}CH_2 + t\text{-BuOOH} \xrightarrow{Mo(CO)_6} CH_3(CH_2)_7CH\!\!\diagup\!\!\diagdown\!\!O\!\!\diagup\!\!\diagdown\!\!CH_2 + t\text{-BuOH}$$

A 2-liter, three-necked round-bottomed flask is equipped with a Teflon coated magnetic stirring bar, a reflux condenser, a 500-ml dropping funnel, and a nitrogen inlet. All glassware was dried in an oven, and the system flushed with nitrogen. The flask is charged with 1 liter of reagent-grade 1,2-dichloroethane, 146.14 g (1.00 mol) of 1-decene (95%), 0.668 g (0.0025 mol, 0.25 mol%) of $Mo(CO)_6$, and 1.0 g (0.007 mol) of anhydrous Na_2HPO_4 freshly ground into powder. The dropping funnel is charged with 490 ml (ca. 2 mol) of a solution of anhydrous *t*-BuOOH in dichloroethane. The stirrer is started, and the reaction mixture is brought to a gentle reflux. Dropwise addition of the *t*-BuOOH solution is started and then the source of heat is removed from the reaction vessel. The *t*-BuOOH solution is added to the stirred mixture at a rate which is sufficient to maintain reflux. The addition requires ca. 0.5 h. When the addition is complete, heat is reapplied and refluxing is continued until the olefin is consumed (monitor by GLC, TLC, or other appropriate methods). In the present experiment with 1-decene, this required ca. 10 h at reflux (GLC revealed <1% olefin).

The reaction vessel is then cooled in an ice bath and 300 ml (ca. 0.24 mol) of fresh 10% Na_2SO_3 is added dropwise while stirring. When addition is complete, the ice bath is removed and stirring is continued for 3 h. At this point the organic phase should give a negative peroxide test using acidified starch–iodide test paper. If the test is positive, additional aqueous sulfite solution should be added and stirring continued. The aqueous and organic phases are separated, and the organic layer is washed twice with 250-ml portions of water, once with 250 ml of brine, dried ($MgSO_4$), and concentrated to afford oil. Distillation of this oil afforded 137.4 g (center cut, b.p. 52–54°C/1 mm) of 1-decene oxide which was 98% pure by GLC analysis (therefore, 86% yield).

Other isolated olefins can also be epoxidized in 85%–95% yields.

Experiment 6: Regioselective Epoxidation of Geraniol with t-BuOOH/VO-(acac)$_2$ [Eq. (42)].[117]†

$$(CH_3)_2C{=}CHCH_2CH_2\underset{\displaystyle CH_2OH}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}{=}CH + t\text{-BuOOH} \xrightarrow{VO(acac)_2} (CH_3)_2C{=}CHCH_2CH_2\underset{\displaystyle O\ CH_2OH}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}\!\!\diagup\!\!\diagdown\!\!C{-}H + t\text{-BuOH}$$

To a solution of pure (*E*)-geraniol (20 g, 0.129 mol) and of vanadyl acetyl-acetonate (0.5 g, 0.0018 mol) in 150 ml of refluxing benzene was added, dropwise over a period of

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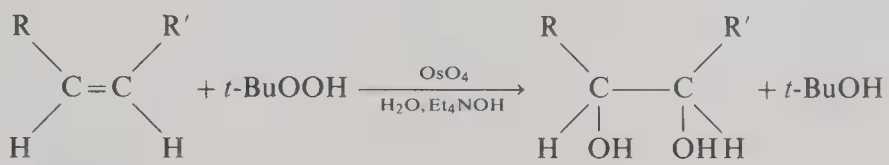
20 min, 17.6 g (0.142 mol) of 72.5% *t*-BuOOH. The initially colorless solution of geraniol in benzene turned bright green upon addition of the $Vo(acac)_2$. The color faded as the reflux temperature was approached and then turned deep red as the *t*-BuOOH was added. The reaction was monitored by TLC and judged complete after 4 h reflux. During this time the deep red color turns to yellow and then to light green. If the organic phase is washed at this point with aqueous $NaHSO_3$ and concentrated, the desired epoxy alcohol is obtained in 98% yield. Since this epoxy alcohol decomposed upon attempted distillation, it was acetylated to obtain a pure product.

The reaction mixture was cooled to 25°C and a solution of 50 ml of acetic anhydride in 70 ml of pyridine was added. After stirring for 6 h the resulting solution was poured onto ice and then washed sequentially with water, 1 *N* HCl, $NaHSO_3$, dried over $MgSO_4$, and concentrated to give 33.7 g of crude epoxy acetate. Distillation afforded 25.2 g (93%) of 2,3-epoxygeranyl acetate, b.p. 104–106°C (0.025 mm), which contains only 2% of its isomer, 6,7-epoxygeranyl acetate.

Experiment 7: cis-Dihydroxylation of Olefins with t-BuOOH/OsO_4 [Eq. (44)].[130]*



Caution: Osmium tetroxide is highly toxic.

A 500-ml one-necked round-bottomed flask was charged with 200 ml of *t*-BuOH, 15 ml of 10% aqueous Et_4NOH (ca. 10 mol), and 100 mmol of olefin. This solution was cooled to ca. 0°C by stirring in an ice–salt bath, and 18 ml (ca. 160 mmol) of 90% *t*-BuOOH was added, followed by 10 ml of 0.5% OsO_4 in *t*-BuOH (ca. 0.2 mmol). The resulting brownish purple solution was stirred for 2 h at 0°C then stored in a refrigerator (0–5°C) overnight. At this point the solution was either pale yellow or colorless, and 100 ml of 5% aqueous $NaHSO_3$ was added and the mixture was allowed to warm to room temperature while stirring. This mixture was concentrated on a rotary evaporator to remove most of the *t*-BuOH and water, and the residue was extracted with ether.

The organic extract was washed with saturated brine, dried ($MgSO_4$), and concentrated to afford the crude *cis*-diol (50%–70%). Purification was effected either by distillation or recrystallization.

Experiment 8: $Pd(OAc)_2$-Catalyzed H_2O_2 Oxidation of α-Olefins to Methyl Ketones [Eq. (46)].[136]†

$$RCH{=}CH_2 + H_2O_2 \xrightarrow{Pd(OAc)_2} RCOCH_3 + H_2O$$

Olefins such as 1-octene were passed through a column containing active alumina to remove peroxide impurities and distilled before use. Olefins, glacial acetic acid, and $Pd(OAc)_2$ were placed in a three-necked 1-liter thermostated glass reactor. The ratio of 30% H_2O_2:Olefin:$Pd(OAc)_2$ was $5:1:1\frac{1}{1500}$. The reactor was equipped with a magnetic stirrer, a condenser, and a 100-ml glass funnel (for instroduction of H_2O_2) and connected through a gas counter (for the evaluation of O_2 evolution) to the atmosphere. H_2O_2 solution was introduced dropwise into the mixture of olefin, solvent, and catalyst during 30 min at the reaction temperature of 80°C. The reaction was complete after 6 h.

Then the mixture was cooled and water was added. The yellow upper layer containing

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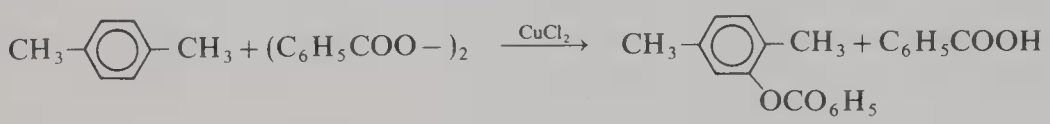
the catalyst was separated and passed through a column of alumina in order to eliminate the catalyst and distilled under reduced pressure.

The yields of methyl ketones (e.g., 2-octanone) were 75%–95% based on the consumed olefins by GLC using a column of DEGS 10% on Chromosorb WHP 80-100 with *o*-dichlorobenzene as an internal standard.

Experiment 9: Benzoyloxylation of p-Xylene with Benzoyl Peroxide/$CuCl_2$ [Eq. (18)].[35b]*



$CuCl_2$ (2.01 g, 0.015 mol) and CuCl (0.099 g, 1 mmol) were quickly weighed and dissolved in acetonitrile (550 ml) while heating and stirring. *p*-Xylene (106 g, 1 mol) was added, and the mixture (in a 1-liter flask equipped with stirrer, condenser, thermometer, gas inlet, and addition funnel) immersed in a constant temperature bath at 60°C. After temperature equilibration under nitrogen, benzoyl peroxide (12.1 g, 0.05 mol) in acetonitrile (150 ml) was added all at once, resulting in a temporary decrease in temperature. Peroxide, detected by iodometry, has disappeared after 24 h. After addition to ice (400 g)/concentrated HCl (100 ml), the separated organic layer was washed with saturated Na_2CO_3 (3×200 ml) and water (200 ml). It was concentrated on a rotary evaporator. Distillation of the residue yielded a clear yellow liquid, b.p. 93–115°C/0.15 mm, which partially solidified on standing. Recrystallization from petroleum ether gave colorless crystals: 2.69 g (24%); m.p. 60–61°C.

Experiment 10: Oxidation of Hexamethylenediamine to Dialdoxime with H_2O_2/Na_2WO_4 [Eqs. (26) and (57a)].[215]†

$$H_2N(CH_2)_6NH_2 + 4H_2O_2 \xrightarrow{Na_2WO_4} HON{=}CH(CH_2)_4CH{=}NOH + 4H_2O$$

To a stirred mixture of hexamethylenediamine (58 g) and Na_2WO_4 (1.66 g) in water (145 ml) was added dropwise 29% H_2O_2 (244 g) at 15°C. The reaction for 3 h gave a precipitate of hexane–dialdoxime, which was filtered, washed with water, and dried to yield the dialdoxime (60%); m.p. 168°C (crystallized from 2 *N* AcOH).

Experiment 11: Oxidation of Aniline to Azoxybenzene with t-BuOOH/Ti^{4+}.[219]§

$$2C_6H_5NH_2 + 3t\text{-BuOOH} \xrightarrow{Ti(OOR)_4} C_6H_5NO{=}NC_6H_5 + 3t\text{-BuOH}$$

123 g (1 mol) of 73% *t*-BuOOH was added dropwise during 30 min to a stirred mixture of aniline (93 g, 1 mol) and tetrastearyl–tetratitanate (1 g) at 70°C. After 15 h stirring at 70°C, iodometric titration indicated the complete consumption of peroxide.

Vacuum distillation (20–0.5 mm Hg) afforded *t*-BuOH, unreacted aniline, and finally 65.6 g (92%) of azoxybenzene, b.p. 121–140°C (0.5 mm), m.p. 36°C.

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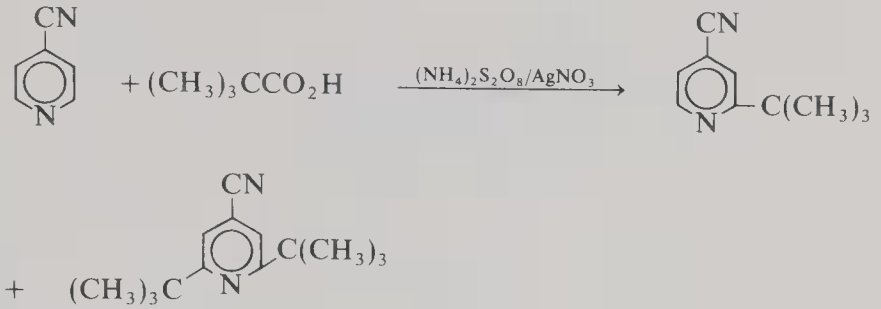
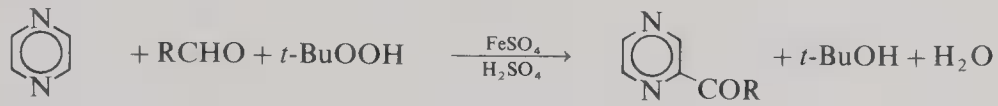
Experiment 12: t-Butylation of 4-Cyanopyridine with Pivalic Acid/$(NH_4)_2S_2O_8/AgNO_3$ [Eq. (64)].[237] *



To a solution of 4-cyanopyridine (0.1 mol) $AgNO_3$ (0.01 mol), pivalic acid (0.5 mol), and H_2SO_4 (0.3 mol) in water (300 ml), heated at 70°C was added, with stirring over a period of 10 min, a saturated aqueous $(NH_4)_2S_2O_8$ (0.1 mol) solution. After the evolution of CO_2 ceased, stirring and heating were continued for an additional 20 min. Then the solution was poured onto ice and the resultant mixture was treated with aqueous ammonia, and extracted with chloroform. The extract was dried with $CaCl_2$, the solvent removed, and the residue analyzed by GLC.

Conversion was 95% and products were 2-*t*-butyl-4-cyanopyridine (85%) and 2,6-di-*t*-buryl-4-cyanopuridine (13%).

Experiment 13: Acylation of Protonated Heteroaromatic Bases with Aldehydes/ t-BuOOH/FeSO₄. Acylation of Quinoxaline.[239a †]



Aldehydes Soluble in Water. Saturated aqueous solutions of $FeSO_4$ (0.06 mol) and *t*-BuOOH (0.06 mol) are simultaneously added dropwise to a stirred and cooled (5–15°C) mixture of aldehyde (0.06 mol), heteroaromatic base (0.02 mol), and 4 *M* H_2SO_4 (0.02 mol). The mixture is then stirred for a further 10 min, neutralized, and extracted with ether. The reaction product is often insoluble in the reaction medium before neutralization and can be collected by direct filtration.

Aldehydes Insoluble in Water. The conditions are essentially the same, but glacial acetic acid (20–40 ml) is added in order to bring the aldehyde into solution. Again, precipitation of the reaction product may occur spontaneously or upon addition of water to the reaction mixture.

2-Acylations of quinoxaline are performed with acetaldehyde (70%), 2-furaldehyde (51%), and benzaldehyde (55%).

The experimental procedures on allylic oxidation of cyclohexene with PhCOO*t*-bu/CuBr,[168] 7-butoxylation of norbornadiene with the same reagent,[171] *t*-butoxylation of 2-bromothiopene Grignard reagent,[274] oxidation of tertamine to N-oxide with *t*-buOOH/$VO(ACAC)_2$[209] and dimerisation of *t*-BuX (X = OH, COOH, CN, NH_2) with $H_2O_2/FeSO_4$[245] are given in detail in *Organic Synthesis*.

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Appendix: Oxidations of Organic Compounds Leading to Specific Oxidation Products

Examples of procedures, which are described in detail at the end of each chapter, have been collected in the following table. Organic compounds are listed vertically, oxidation products horizontally. On the cross sections one can find the page number(s) referring to the experimental procedures. When two or more procedures are available, the reader can make a proper selection. Superscript numbers (e.g., [1]) refer to the extended lists of pages given in the footnotes.

	Aldehydes	Ketones	Benzoquinones	Diphenoquinones	Fuchsones	Carboxylic acids/esters	Diols	Hydroperoxides	Diketones	Lactones	Epoxides	Furans	Dihydrofurans	Tetrahydrofurans	Phenols
Alcohols	[1]	...	...	...	...	...	...	...	...	...	...	802	...	864	...
Primary	30, 416, 601	[2]	...	...	...	...	...	...	...	...	...	...	...	...	...
Secondary	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Tertiary	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Allylic	104, 105, 832	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Benzylic	[3]	...	...	...	...	416	...	...	...	...	...	...	...	...	...
Acetylenic	...	240	...	...	...	...	...	...	...	...	...	...	...	...	...
α-Keto	...	...	...	...	...	...	...	...	416	...	...	...	...	...	...
Steroid	535	535, 830	...	...	...	...	...	...	...	...	...	...	...	...	...
Diols	804, 832, 833	804	...	...	...	...	...	...	...	...	...	...	...	...	...
Polyols	...	...	...	...	...	...	...	...	531	561	...	...	...	...	...
Lactols	...	...	...	...	...	...	...	...	...	528	...	...	...	...	...
Ethers	...	106	106	...	...	106	...	...	618	...	...	499	...	...	...
Phenols	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Monohydric	...	436, 735, 804	364, 437, 735	433, 562	417	...	...	602	...	...	...	...	498	...	...
Polyhydric	...	...	[4]	548	...	436	...	...	...	...	...	...	...	...	...
Hydrocarbons	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Saturated cyclic	...	96, 466	...	...	...	466	...	...	...	...	...	...	...	...	...
Unsaturated	101, 107, 466, 677	[5]	...	...	...	309, 466	659, 676, 867	...	...	308, 309	29, 866	...	311	...	...
Acetylenic	...	...	...	...	...	734	...	...	685, 734	...	...	...	...	...	...
Activated	99	97, 98, 99, 100	...	...	...	98, 360	...	...	...	...	...	...	...	...	...
Aromatic	...	...	618	...	...	...	...	...	...	...	...	...	...	...	842, 843

[1] 102, 236, 240, 561, 830.
[2] 103, 105, 237, 238, 416, 465, 830.
[3] 105, 416, 465, 601, 832.
[4] 364, 433, 545, 616, 735.
[5] 100, 310, 360, 361, 435, 498, 867.

Flavones	Amides	Nitriles	Isocyanates	Azo/azoxy compounds	Aminooxides	Oxazoles	Oxadiazoles	Benzoxazoles	Benzimidazoles	Oximes	Nitrates	Alkylaromatic compounds	C–C dimers	Diynes	Sulfoxides	Sulfones	Disulfides
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
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732	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
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...	...	...	...	...	...	...	...	...	...	...	...	...	418, 434, 499	...	...	...	...
...	...	...	...	...	...	...	...	...	...	...	...	498, 860	...	...	...	...	...

	Aldehydes	Ketones	Benzoquinones	Diphenoquinones	Fuchsones	Carboxylic acids/esters	Diols	Hydroperoxides	Diketones	Lactones	Epoxides	Furans	Dihydrofurans	Tetrahydrofurans	Phenols
Aldehydes	...	435	...	...	...	865	...	...	...	...	...	...	...	...	...
Ketones	...	...	...	...	...	733, 865	...	311, 417, 805, 835	...	...	...	311	...	...	...
Isocyanides	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Carboxylic acids	...	...	...	...	...	805	...	...	...	236, 731	...	...	...	...	...
α-Hydroxy	835	237, 835	...	...	...	...	...	...	...	...	...	...	...	...	...
Hydrazides	...	...	...	...	...	611	...	...	...	...	...	...	...	...	...
Mercaptans	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Sulfides	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Sulfoxides	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Amines, aliphatic	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Primary	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Secondary	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Tertiary	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Amines, aromatic	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Primary	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Secondary	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Tertiary	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Hydroxylamines	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Hydrazines, hydrazones	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Oximes	601, 734	107, 601, 734	...	...	...	...	...	...	...	...	...	...	...	...	...
Enamines	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Imines	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Semicarbazones	...	601	...	...	...	...	...	...	...	...	...	...	...	...	...
Indoles	...	437	...	...	...	...	...	...	...	...	...	...	...	...	...
Dihydro-1,2-oxazoles	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...

Flavones	Amides	Nitriles	Isocyanates	Azo/azoxy compounds	Aminooxides	Oxazoles	Oxadiazoles	Benzoxazoles	Benzimidazoles	Oximes	Nitrates	Alkylaromatic compounds	C–C dimers	Diynes	Sulfoxides	Sulfones	Disulfides
...	...	...	...	...	...	...	...	...	...	...	...	...	236	...	...	...	...
732	...	...	...	...	...	...	...	...	...	...	733	...	...	...	...	...	...
...	...	...	358	...	...	...	...	...	...	...	...	...	...	...	...	...	...
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...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	32, 33, 602	466	...
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	466	...
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...	...	...	...	868	...	...	...	...	...	868	...	..	...	...	...	...	...
...	...	238, 805	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
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...	...	436	...	551	...	...	...	...	238	...	...	...	...	...	...	...	...
...	466	...	...	834	...	...	...	...	...	...	...	...	...	...	...	...	...
...	...	...	...	...	858	...	...	...	...	...	...	...	...	...	...	...	...
...	...	...	...	394, 554	...	...	...	...	...	...	...	...	...	...	...	...	...
...	...	...	...	806, 834	...	...	...	...	...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	562	...	...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	406	406	...	...	...	...	...	...	...	...
...	352	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
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...	437	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
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